EMA/CHMP/457051/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Durysta

International non-proprietary name: bimatoprost

Procedure No. EMEA/H/C/005916/0000

Note

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

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Table of Contents

List of abbreviations

AC	anterior chamber
AE	adverse event
AESI	adverse event of special interest
AGN-191522	bimatoprost acid
AGN-192024	bimatoprost
BCVA	best-corrected visual acuity
BID	twice daily
Bim SR	bimatoprost sustained release
CCT	central corneal thickness
CECD	corneal endothelial cell density
Cmax	maximum plasma concentration
COVID-19	coronavirus disease-2019
CSR	clinical study report
CSS	summary of clinical safety
ECD	endothelial cell density
ECL	endothelial cell loss
eCRF	electronic case report form
EU	European Union
FE	fellow eye
IBD	international birth date
IOP	intraocular pressure
ISS	integrated summary of safety
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
OAG	open-angle glaucoma
OHT	ocular hypertension
PGA	prostaglandin analogue
PRN	pro re nata
PT	preferred term
RMP	risk management plan
SAE	serious adverse event

SAP	statistical analysis plan
SD	standard deviation
SE	study eye
SITA	Swedish interactive thresholding algorithm
SLT	selective laser trabeculoplasty
SOC	system organ class
SR	sustained release
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

1. Joint Rapporteur(s) Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Durysta with the indication "*for the reduction of intraocular pressure (IOP) in adults with open angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medications*" is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

In addition, satisfactory answers must be given to the "other concerns" .

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality:

- P.1: definition of integral medical device / medicinal product;
- P.2.2/P.5.6: comparability of drug release rates of Phase III clinical trial product and commercial product;
- P.2.3/P.5.2/P.5.3/P.5.6: comparability of commercial batches (AOIML) and NC/C batches regarding contamination with foreign/insoluble particles;
- P.2.4/P.2.5/P.3.4/P.5.1/P.5.2/P.5.3/P.7: inadequate control strategy to ensure sterility of the finished product;
- P.3.4: inadequate definition of critical process steps/parameters to ensure consistent quality of the finished product;
- P.1/P.2/P.3.2/P.4/3.2.A.3: Resomer excipients: to be defined and documented as novel excipients;
- P.1/P.2.1/P.2.4/P.7: commercial applicator to be defined according to the NBOp;

Clinical:

- the definition of "unsuitable for topical IOP-lowering medications" and how such patients can be identified should be clarified in the SmPC
- only the patients who show a response to prostaglandins/prostamides should be treated with bimatoprost SR, so this should be indicated in section 4.1 of the SmPC
- retreatment with Durysta is not considered acceptable due to the substantial safety concern and should be removed from the SmPC
- also the safety of a single Durysta administration needs to be further justified (especially for patients with reduced iridocorneal angle [Shaffer grade 3], but also for patients with wider angle [Shaffer grade 4]; measures to mitigate the risk of endothelial cell loss in these patients should be defined)

1.1. Inspection issues

1.1.1. GMP inspection(s)

The requested GMP inspection for the manufacturing process of the finished product Durysta (including automated ocular implant manufacturing line, AOIML) has been performed by HPRA on April 16th-19th, 2024.

The final inspection report was not included in the submission of responses {Confidential information deleted}.

Outcome of the inspection including deficiencies found was considered in the assessment of MOs raised on particulate contamination (former MO 4), microbiological control strategy (former MO 5) and process control (former MO 6) as well as numerous OCs. Reference is made to the corresponding assessment comments and questions raised. As no follow-up inspection is planned according to the GMP inspector, former MO 1 on GMP is considered resolved. Issues relevant for quality assessment will be followed-up in the corresponding quality MOs and OCs.

1.1.2. GCP inspection(s)

A request for GCP inspection is not required.

1.2. New active substance status

Bimatoprost is an already known active substance. Thus, respective section is not applicable.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Durysta (bimatoprost SR) is intended to be used for the reduction of intraocular pressure (IOP) in adults with open angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medications.

2.1.2. Epidemiology and risk factors

Glaucoma is a chronic, sight-threatening disease that affects over 60 million people globally, and these numbers are expected to increase over time. Glaucoma accounts for 12% of all global blindness with 7.7 million people worldwide affected with blindness or moderate/severe vision impairment due to glaucoma. Elevated IOP is the most prominent risk factor for glaucoma, and the only existing factor that ophthalmic intervention can reliably affect. OHT refers to elevated IOP without evidence of glaucomatous optic nerve damage or visual field abnormality. Patients with OHT or those having a suspicious appearance of the optic disc or retinal nerve fibre layer (e.g., enlarged cup-to disc ratio, disc haemorrhage, nerve fibre layer defect) are often referred to as "glaucoma suspects," as patients with these findings have an increased risk of developing OAG. Although these conditions may represent clinical differences in the spectrum of glaucoma, the treatment approach for both is to lower IOP.

2.1.3. Biologic features, aetiology and pathogenesis

Glaucoma is a degenerative optic neuropathy caused by damage and progressive gradual loss of retinal ganglion cell axons, which are located in the inner retina and comprise the optic nerve. The gradual degeneration of retinal ganglion cells and their axons lead to characteristic cupping of the optic nerve seen in ophthalmoscopy and subsequent visual field defects. Treatment can slow the progression of glaucoma, but there is currently no curative treatment. Glaucoma is often associated with increased intraocular pressure (IOP).

The IOP is defined by a balance between the production and the outflow of aqueous humour, which is produced by the ciliary body, located posterior to the iris, which also suspends the intraocular lens. The

secreted aqueous humour flows from behind the iris into the anterior chamber through the pupil and out of the eye via the drainage angle. Drainage of aqueous humour occurs primarily through draining via the trabecular meshwork. Whether this trabecular meshwork is “open”, i.e., physically unobstructed, helps to define the type of glaucoma as open-angle. Open-angle glaucoma occurs when there is increased resistance to the outflow of aqueous humour within the trabecular meshwork itself, but without visible obstruction to the drainage angle. (Hsu and Desai, 2023; Glaucoma and Systemic Disease.)

2.1.4. Clinical presentation, diagnosis

Individuals with open-angle glaucoma rarely experience symptoms. Thus, open-angle glaucoma is generally detected incidentally during comprehensive ophthalmic examination. This is in contrast to angle-closure glaucoma in which patients present with symptoms and signs including loss of visual acuity, pain, conjunctival erythema, and corneal oedema.

High elevations of intraocular pressure (IOP), up to 40 mmHg in patients with open-angle glaucoma, generally cause no pain, redness, or visual symptoms. There is no loss of visual acuity as long as central vision is preserved. Central visual field loss is a late manifestation of open-angle glaucoma, usually preceded by ganglion cell loss and optic nerve damage. Some patients are unaware of field loss even when it has progressed to central "tunnel vision" of 10 to 20 degrees. Visual field loss cannot be recovered once it has occurred.

The mean progression rate from a full field of vision to blindness takes approximately 25 years in untreated patients. However, it is important to note that the median progression rate is much slower (approximately 70 years), since only a small minority of patients progress rapidly to blindness. Nonetheless, in a Swedish study of 592 glaucoma patients who had died between 2006 and 2010, 250 (42 percent) had at least one eye with blindness (as defined by the World Health Organization criteria) and 16.4 percent were bilaterally blind at their last eye visit; the median age for developing bilateral blindness was 86 years. (Jacobs et al., 2022; Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis.)

2.1.5. Management

The goal of glaucoma therapy is to provide consistent, effective control of IOP to reduce the risk of disease progression. Treatment of glaucoma patients is complex and individualized, with treatment options ranging from non-invasive (such as topical drops and procedures that do not enter the eye, such as laser trabeculoplasty), to more invasive surgical interventions (such as minimally invasive glaucoma surgery [MIGS], trabeculectomy, or tube shunts). Topical drops are typically the first line of treatment for patients with glaucoma or OHT because they are non-invasive.

Reasons why patients are unsuitable for topical IOP-lowering medications could include intolerance and nonadherence. With regard to intolerance, ocular surface manifestations, such as dryness, burning, and foreign body sensation, that result from long-term topical administration, can interfere with glaucoma management and outcome. In terms of nonadherence, elevated IOP typically has no obvious signs or symptoms that help to prompt patient adherence, and up to one third of patients prescribed topical drops for the first time discontinue their prescriptions within a year.

Beyond topical IOP-lowering medications, the non-incisional treatment option commonly used before needing to resort to more invasive options is laser trabeculoplasty, a common type of which is selective laser trabeculoplasty (SLT). SLT is recommended for patients with OAG or OHT who have challenges with topical IOP-lowering medication adherence or tolerance. In clinical practice SLT is used both as initial therapy and as adjunctive therapy in combination with topical medications, in some cases to

reduce the number of medications a patient is required to self-administer. In a review article, SLT was shown to be effective at reducing IOP in 58% to 94% of patients after 12 months; however, this IOP-lowering effect tended to decrease over time with a mean survival time (the time at which 50% of eyes fail to meet target IOP) of approximately 2 years. In the recent LiGHT study, newly diagnosed, treatment-naïve OAG and OHT patients were treated with topical medication or SLT followed by topical medication as required. Overall, 95% of eyes (509/536) treated with SLT and 93.1% of the eyes (499/536) treated in the eye drops group were at target IOP at 36 months. Some studies have shown SLT to be less effective when used in patients previously treated with IOP-lowering eye drops.

2.2. About the product

Bimatoprost SR is a biodegradable, sustained-release, preservative-free bimatoprost implant that is preloaded into a single-use applicator for administration into the anterior chamber (AC) via clear cornea adjacent to the corneal limbus. The implant is designed to provide a controlled and sustained release of bimatoprost to the AC of the eye for the reduction of IOP. There is no need to remove the implant once the drug has been released, the implant will biodegrade.

Bimatoprost [(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide] is a member of a series of unique prostanoid compounds that are potent and efficacious ocular antihypertensive agents. Bimatoprost appears to mimic the activity of biologically active prostamides. Chemically, prostamides differ from prostaglandin analogues by being neutral because they lack carboxylic acids (Krauss 2004). Prostamides can be biosynthetically derived from anandamide, an endogenous membrane lipid. The prostamide pathway leads to the biosynthesis of novel lipid amides that lower IOP.

2.3. The development programme/compliance with guidance/scientific advice

The subject of this application is bimatoprost SR, a bimatoprost intracameral implant developed for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT), who are unsuitable for topical IOP-lowering medications. Bimatoprost SR (United States [US] tradename DURYSTA) was approved by the US Food and Drug Administration on 04 March 2020 (NDA 211911); bimatoprost eye drops (tradename Lumigan) were first approved in the European Union in 2002.

The bimatoprost SR use being proposed for this marketing authorisation application (MAA) is up to 2 as needed administrations of the 10 µg bimatoprost SR implant in patients with OAG or OHT who are unsuitable for topical IOP-lowering medications for reasons other than medication efficacy. The proposed as needed regimen can maintain consistent IOP control for months or years without the need for adjunctive topical IOP lowering medication. This extended duration of IOP lowering can slow disease progression and considerably delay further treatment intensification, which have inherently higher risks.

The applicant and marketing authorisation holder in this procedure is or will be Abbvie Deutschland GmbH & Co. KG, located in Ludwigshafen am Rhein, Germany. The manufacturer is Allergan Pharmaceuticals Ireland. This application constitutes a centralised procedure according to Regulation (EC) No 726/2004, whereby the "optional scope" (Article 3(2) of Regulation (EC) No 726/2004) and its Annex 3(2)(b) (Significant innovation or interest of patients at EU level) apply. No orphan medicinal product designation has been applied for this medicinal product. Furthermore, this submission does not apply for a change to existing marketing authorisation (leading to an extension as referred to in Annex I of regulation No 1234/2008 or any national legislation). This application is submitted in accordance with Article 8(3) (i.e. dossier with administrative, quality, pre-clinical and clinical data) in directive

2001/83/EC. The applicant holds other marketing authorisations for medicinal products containing the same active substance in the EEA, specifically the product "Lumigan eye drops, solution" with the marketing authorisation numbers EU/1/02/205/003-004, EU/1/02/205/005-007 and EU/1/02/205/001-002. A PIP compliance verification is not applicable to this application.

The active substance in Durysta is bimatoprost, the strength of one implant is 10 μg of the API. In accordance with Art. 8(3) or Art. 10a of Directive 2001/83/EC, bimatoprost is a known active substance. Its pharmacotherapeutic group is ophthalmological, prostaglandin analogues, whereas its ATC code is S01EE03. Route of administration is intracameral use, and the package size is 1x10 μg in a single use applicator. The needle of this applicator is a small gauge hypodermic needle which conforms to ISO 7864 Sterile Hypodermic Needles for Single Use. The proposed shelf life is 3 years, and after first opening of container this product should be used immediately. Proposed storage conditions are 2°C-8°C.

This application refers to a medical device within the meaning of Article 2(1) of Regulation (EU) 2017/745, which is intended to administer a medicinal product where they form a single integral product which is intended exclusively for use in the given combination and which is not reusable (Art 1(9) second subparagraph of Regulation (EU) 2017/745). Its name is DURYSTA Applicator, it is a sterile, single use disposable injection device, containing a rod-shaped implant which is administered into the anterior chamber via the corneal limbus. It is classified as a Class IIb medicinal device, and its EU manufacturer is Allergan Pharmaceuticals Ireland. It is not to be used with a companion diagnostic within the meaning of Article 2(7) of Regulation 2017/746.

This product will be subject to medical prescription, as specified under Article 1(19) of Directive 2001/83/EC.

Apart from bimatoprost, the excipients in this product are polylactic acid, di-lactide coglycolide polymers and polyethylene glycol 3350 NF. No materials of animal and/or human origin are contained in this product or are used for its manufacturing.

Non-clinical scientific advice has been sought for this product from EMA (EMA/SA/0000047623, 2021-01-29) and from the Danish and Swedish national competent authority (in 2014-07-17 from DHMA and 2014-09-17 from MPA, respectively):

In procedure EMA/SA/0000047623, the applicant asked whether CHMP agrees that the available non-clinical data generated for bimatoprost SR are sufficient to support a MAA of bimatoprost SR for the claimed indication. CHMP responded that it agrees that the available data on bimatoprost and the data obtained with intra-cameral slow-release formulations in dogs should be sufficient to support a MAA, pending evaluation of the data that will actually be submitted. However, CHMP also mentioned that the concentration of bimatoprost in the iris ciliary body seems high and that this needs to be justified in view of the concentration that would be needed to obtain a durable IOP reduction without risk for induction of tachyphylaxis. Furthermore, CHMP mentioned that in the monkey study there was corneal endothelial cell loss and corneal oedema (suggestive of potential problems in human eyes), and it has to be considered that in the monkey model safety signs regarding the reduction of corneal endothelia cell count were observed. Finally, CHMP added that care must be taken to assess the potential effect of continued exposure to bimatoprost SR on corneal safety.

In 2014, the applicant sought advice from DHMA. The Danish HA in principle agreed that the completed and the ongoing toxicology study are adequate to support phase 3 studies and registration. Questions were asked about the difference in generation 1 and 2 implants, about the elimination of the implant, local toxicity and risk of cataracts, the ability of the angle size to accommodate the implant and whether the position of the implant in the anterior chamber angle could influence outflow.

Finally, the applicant sought the same scientific advice at MPA. The Swedish agency answered that Allergan could use the Lumigan data package to support the clinical safety for bimatoprost SR. However, MPA was concerned whether the 18-month dog would be able to capture events related to corneal endothelial safety. The Swedish Agency also noted that the Cynomolgus monkey eyes were too small for the implants (what has subsequently also been confirmed by Allergan). Furthermore, the MPA questioned whether corneal endothelial cells regenerate in dogs as they do not regenerate in humans. Allergan answered to that concern that the cells do not regenerate in adult dogs but that in rabbits, corneal cells do replicate. While Allergan stated that no adverse histological changes have been seen in dogs, reduction of endothelial cells was observed in all Cynomolgus monkey studies due to chronic physical contact of the implant with the corneal endothelium in this species. Then, MPA asked about the potential of debris from biodegradation of the implant clogging the trabecular meshwork (TM) and acute IOP rises, whereby the applicant answered that the polymer erodes and then solubilises and leaves the anterior chamber through the TM. Finally, MPA concluded that the non-clinical package would need to clarify corneal endothelial safety and that there were no concerns regarding plugging of the trabecular meshwork from the biodegradation of the implants.

Clinical development programme

The clinical development programme for bimatoprost SR was initiated in 2010 with the start of Phase I/II Study 192024-041D. Global Phase III Studies 192024-091 and 192024-092, designed as the pivotal trials to support the United States New Drug Application (US NDA), were initiated in 2014. Global Phase III Studies 192024-093 and 192024-095, initially designed as the pivotal trials to support the European Medicines Agency Marketing Authorisation Application (EU MAA), were initiated in 2016. In early 2019, Studies 1698-301-007 and 1698-302-007 were initiated. Study 1698-301-007 was designed to obtain data on as needed (PRN) re-administration of bimatoprost SR, and study 1698-302-007 was designed to evaluate the long-term safety and efficacy of subjects that were enrolled in the previous bimatoprost SR pivotal studies. In March 2020, protocols for studies 192024-095, 1698-301-007, and 1698-302-007 were amended to discontinue administration of the bimatoprost SR 15-µg dose strength in the ongoing studies (the 15-µg dose strength in Study 192024-093 had been previously discontinued and replaced with the 10-µg dose strength in an August 2018 amendment). bimatoprost SR 15 µg was the only dose strength administered in study 192024-095; therefore, enrolment and retreatment of subjects in study 192024-095 was stopped, with continued subject follow up per protocol. In August 2020, study 192024-093 was amended to add flexibility to the timing of re-administration, thereby lengthening the study duration. In addition, there was an update to the retreatment criteria to include an IOP-based criterion to eliminate re-administration to eyes that have a sustained clinical response and may not need additional IOP-lowering treatment.

Scientific Advice/Presubmission Interaction

The Phase III development programme to support the EU MAA was designed based on advice given at the scientific advice meetings, which included meetings with:

- Medicines and Healthcare products Regulatory Agency (MHRA): July 2014
- Danish Health and Medicines Authority (DHMA): July 2014
- Medical Products Agency (MPA): August 2014

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) scientific advice on the modifications to the clinical programme and regulatory strategy was received in January 2021 (EMA/SA/0000047623).

Pre-submission meetings with the EMA, Spanish Agency of Medicines and Medical Devices (AEMPS), and Austrian Agency for Health and Food Safety (AGES) were conducted in December 2021.

GCP Compliance

The applicant confirms that the clinical study reports (study 192024-093, study 1698-301-007, studies 192024-091 and 192024-092) submitted comply with the guidance ICH Topic E 3 (Structure and Content of Clinical Study Reports) as well as the Note for guidance on the inclusion of appendices to clinical study reports in marketing authorisation applications (Module 1, Annex 1).

As per Good Clinical Practice (GCP), an independent ethics committee (IEC) / institutional review board (IRB) ensured the ethical, scientific, and medical appropriateness of the studies (192024-093 and 1698-301-007) before they were conducted and approved all relevant documentation. IEC/IRB approval of the protocol, informed consent, and subject information and/or advertising, as relevant, was obtained prior to the authorisation of drug shipment to a study site. The clinical studies were conducted according to good clinical practice. There were no GCP non-compliance identified (Module 1, Annex 1).

As stated by the applicant in Module 1.9 'Information relating to Clinical Trials', in accordance with Article 8 (ib) of Directive 2001/83/EC, clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

CHMP assessment

The applicant is submitting the initial marketing authorisation application (MAA) for bimatoprost sustained release (SR) 10 µg intracameral implant developed for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medications. In the Dossier, Module 1.0, Annex 5, the applicant provided a justification for a few specific programme decisions and comments from agency correspondence from pre-submission interactions that required further clarification. In principal, most of the advice given was considered and suggestions were implemented. Whenever advice was not followed or the applicant's position not supported, a statement/discussion is provided within the assessment.

2.4. General comments on compliance with GMP, GLP, GCP

The GMP certificate provided was considered acceptable in the context of this procedure. The submitted QP declaration was acceptable.

Relevant non-clinical toxicology studies were conducted in accordance with Good Laboratory Practice.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

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

2.5.2. PRIME

N/A

2.5.3. Accelerated assessment

N/A

2.5.4. Conditional marketing authorisation

N/A

2.5.5. Marketing authorisation under exceptional circumstances

N/A

2.5.6. Biosimilarity

N/A

2.5.7. Additional data exclusivity/ marketing protection

N/A

2.5.8. New active substance status

Not applicable.

2.5.9. Orphan designation

Not Applicable.

2.5.10. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.11. Derogation(s) from orphan market exclusivity

N/A

2.5.12. Information on paediatric requirements

Pursuant to Article 7 and 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) (P/0293/2014) on the granting of a product-specific waiver.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as intracameral implant in an applicator (integral medical device) containing 10 µg bimatoprost as active substance (sustained release).

Other ingredients are: Resomer R 203 S poly (D,L-lactide), Resomer RG 752 S poly (D,L-lactide-co-glycolide), Resomer R 202 H poly (D,L-lactide) acid end and macrogol 3350 (PEG 3350), which form a biodegradable copolymer matrix.

The product is available in a single use pen-shaped applicator with a 28 gauge needle. The implant is retained in the needle. The applicator containing the implant is packaged in a sterile laminated foil pouch (polyethylene/terephthalate/polyethylene aluminium foil/adhesive/sealant) foil pouch containing a desiccant sachet (silica gel). The sterile pouch is packaged in a thermoform tray with lid, which is packaged in a carton box.

3.1.2. Active Substance

3.1.2.1. General Information

In the present MAA dossier, full information of the drug substance is provided by the applicant.

The API of the current MAA, bimatoprost, is a known active substance but not monographed in Ph.Eur.

Nomenclature, structural formula, molecular formula and relative molecular mass of the active substance are provided.

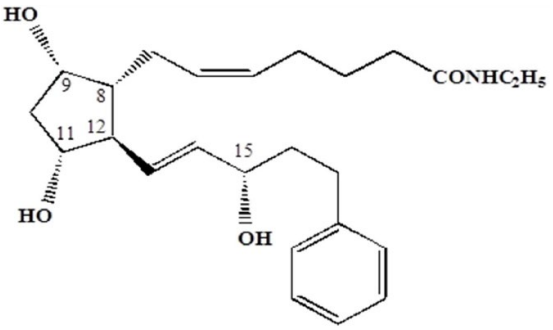


Figure 1: Structural formula of bimatoprost drug substance

An adequate list of physicochemical and other relevant properties is included. Bimatoprost contains five chiral centres. The drug substance is known to exist in two crystalline forms. Further information thereof is provided in section regarding characterisation.

3.1.2.2. Manufacture, process controls and characterisation

The name, address and responsibilities of each manufacturer, including contractor, involved in the manufacturing and testing are provided. Microbial limit test and bacterial endotoxin test was performed. Given information is in general in line with Annex 5.8 and respective section in the eAF.

Description of manufacturing process and process controls

The drug substance bimatoprost is described as a 5-steps manufacturing process comprising four synthetic steps and a subsequent purification step. A chemical synthesis scheme is provided which is regarded as complete and therefore accepted.

The manufacturing steps are described in sufficient detail, including synthesis flow charts, lists of reagents and solvents, input amounts of raw materials, reaction conditions such as temperature, reaction times, pH and in-process controls. The process equipment is briefly listed (material) but size thereof is not described. However, this is accepted.

Reprocessing could be possible if drug substance batches should fail, which is regarded as acceptable.

Control of solvents, reagents and auxiliary materials: the provided specifications for materials used in the synthesis of the drug substance are acceptable and include relevant quality parameters and appropriate limits.

Confirmation is given that none of the materials used in the synthesis of the drug substance are derived from human or animal sources and are thus free of potential TSE/BSE agents.

Control of critical steps are mentioned. The given information is comprehensible and sufficient.

Intermediates: Information on the quality and control of intermediates isolated during the process is provided by submitted specifications. For each intermediates description of analytical methods and brief validation data (summary tables) thereof are provided. Issues regarding specifications and batch data are raised in the LOQ.

The manufacturing process of bimatoprost is a standard manufacturing process and does not involve aseptic processing or sterilisation. Therefore, validation data are in general not assessed from the quality assessor.

Manufacturing process development

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. In total, three processes have been applied where process 3 is the current one. A description and discussion of any significant changes made to the manufacturing process used in producing non-clinical, clinical, scale-up, pilot and production scale batches is provided. However, issues thereof are raised (please refer to LOQ).

Characterisation

The structures of bimatoprost and an intermediate have been confirmed by several analytical methods. Respective data to confirm stereochemistry has been provided.

Polymorphism of the drug substance is described. In all commercial scale batches one form is produced. Discussion regarding polymorphism is suitable for 3.2.S. No discussion regarding particle size is provided.

For elucidation of structure and other characteristics, primary reference standard has been used.

Impurities

Organic impurities in bimatoprost are listed. Their synthesis is described next to characterisation thereof. Fate/Purge/carry over are discussed. All actual impurities are specified on drug substance level.

Several potential organic process-related impurities are discussed. They are described regarding fate and purge. However, they have not been found in drug substance batches of the current process.

bimatoprost has five chiral carbon atoms. Enantiomer of bimatoprost is not specified on DS level, also optical purity is not specified. This is per se accepted. No evaluation regarding mutagenic impurities is provided which is per se in line with ICH M7.

A brief nitrosamine risk assessment on drug substance level is provided. It is concluded that proposed bimatoprost drug substance manufacturing process is not at risk for the formation or introduction of nitrosamine impurities.

The parameter <residue on ignition> in the drug substance specification is considered as an inadequate control of inorganic impurities.

Residual solvents used in the manufacture of bimatoprost are listed comprehensively.

Further, potential and actual impurities on different intermediate levels are discussed regarding potential source, fate and tolerance and synthesis- and characterisation data are provided.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

An in-house specification has been presented as bimatoprost is not monographed in Ph. Eur. The provided drug substance specification contains the following parameters: appearance, identification (IR and HPLC), assay, related compounds, water content, residual solvents, residue on ignition, optical rotation, bacterial endotoxin and microbial enumeration.

The specification parameters, limits and analytical methods for bimatoprost, which is not monographed in the Ph. Eur. were set in accordance with recommendations described in Ph. Eur. general texts and relevant guidelines. Where applicable, Ph. Eur. methods are used.

The chemical names/nomenclature of impurities have been laid down as part of the specification. All specified parameters and respective acceptance criteria except limit for total impurities on drug substance level are accepted – please refer to LOQ.

The following thresholds are applicable according to ICH Q3A: reporting threshold: 0.05%, identification threshold 0.10 %, qualification threshold 0.15%. Limits higher than the qualification threshold have been toxicologically qualified. –

Proposed limit for individual unidentified impurities is accepted as it is in line which the identification threshold.

The set limit for residual solvents (ethyl acetate and heptane) are below respective limits proposed by ICH Q3C and are thus accepted.

No specifications have been set for physicochemical properties, polymorphic forms or particle size, as these attributes are not considered to be relevant to drug product attributes or performance. Reference regarding product attributes or performance is made to 3.2.P.

A risk assessment regarding elemental impurities is provided where three batches of bimatoprost drug substance (namely 1800104, 1800131, 1800036commercial batch size) have been tested for elemental impurities class 1, 2A and selective class 3 elements (Cd, Pb, As, Hg, Co, V, Ni, Li, Sb, Ba, Mo, Cu, Sn and Cr) using ICP-MS. Al was not included in respective studies (reference is made to an issue raised in S.3.2). None of the elements exceeded the 30% control threshold of the respective ICH Q3D parenteral limit. Results are presented in tabular form. No further controls are thus necessary and provided evaluation is accepted for the drug substance.

Analytical procedures and reference standards

The analytical procedures used to test bimatoprost are described in sufficient detail. Calculations are provided where applicable.

Validation for several in-house methods is provided. Where Ph. Eur. methods are used, no validation is needed. For bacterial endotoxin testing and microbial enumeration method, suitability is shown.

Method for assay and related substances (HPLC): provided analytical method validation for related compounds is not acceptable. A thorough clarification should be provided how initially presented LOQs can be revised without a change in the method. The connex between validation data provided in sequence 0000 and sequence 0002 should be thoroughly discussed and comprehensively shown. If this is not justified sufficiently, the issue will be upgraded to a MO. Please refer to LOQ.

Forced degradation studies: have been performed in the course of assay and related substances method validation. Provided summary data are not seen as sufficient. data are not seen as complete. Not only assay degradation, but also impurities increase, mass balance and peak purity (as already requested at d120) should be provided. Up to now, respective forced degradation study is not accepted

and the analytical procedure regarding assay and related substances is not seen as stability-indicating. Please refer to LOQ.

Reference Standards or Materials: information is provided for the primary reference standard of bimatoprost drug substance and specified impurity standards.

Batch analysis

In total, batch data for 8 batches (all in commercial scale) are provided showing compliance with set acceptance criteria.

CoAs for three batches not older than 3 years are now provided in S.4.4 (batches 220248, 2200255, 2200256). However, an issue is raised – please refer to LOQ.

Container closure

LDPE bag inside a second LDPE outer bag (closed with twist tie or suitable device) under argon or nitrogen headspace. As secondary packaging, a laminated aluminium foil bag is used. The secondary packaging container is placed in a HDPE drum (used as tertiary outer container).

Compliance of the primary packaging system with Regulation (EU) 10/2011 is stated. Further, an acceptable specification of the primary packaging material is provided.

3.1.2.4. Stability

Long-term- (-15°C to -25°C, three batches) and accelerated (5°C, one batch) data up to 36M and 6M respectively are provided for the drug substance bimatoprost showing no OOS and no trend. Results of stability studies are presented for batches manufactured between 11/2014 – 06/2018 that were analysed according to the specifications valid at time of analysis and with analytical procedures valid at time of analysis.

In principle, the proposed retest period of 36M when stored at -15°C to -25°C in the recommended container closure system (see S.6) under argon or nitrogen headspace could be accepted provided that issues raised are solved adequately (please see S.4.3 regarding stress studies, S.4.5 regarding specification and respective acceptance criteria).

The effect of short-term excursions during shipping or handling has been evaluated and is accepted. No storage restriction regarding light is necessary.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Description of the product

The drug product should be clearly identified with its new standard term "intracameral implant in applicator" (now given only in brackets). Strength of the product (10 µg) should be indicated in the description.

Dimensions (length 1.1 mm and diameter 0.2 mm) of the rod shaped implant are stated in section P.1 to define the dosage unit. The description of the container closure in section P.1 is regarded as adequate.

Section P.1 was not updated with a clear definition of the applicator. It is noted that omission of identification of the medical device parts is not in line with EMA/CHMP/QWP/BWP/259165/2019.

Section P.1 does not include a clear definition of the applicator, which is an integral medical device part of the medicinal product to be assessed within this procedure for marketing authorisation. According to Annex 1 of Directive 2001/83/EC, details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product should be given in section P.1. Therefore, serial number, product/item code or other indications necessary to delimit precisely the device incorporated in the medicinal product need to be indicated in Section P.1. Section 2.2.4.1 of the Application Form should be updated accordingly**. (MO 1 / former MO 2)**

Pharmaceutical Development:

Components of the drug product

Drug substance bimatoprost: polymorphic form and degradation due to sterilisation are discussed below. Particle size distribution of the drug substance (input material for powder blending) is adequately discussed. Omission of testing of bulk and tapped density of the drug substance is regarded as justified. Microbiological quality of the drug substance is adequately controlled by testing for bacterial endotoxins and microbial enumeration.

Drug product

Brief information on the formulation development is given, e.g. an overview on formulations tested in early development including different combinations of poly (D,L-lactide) (PLA), poly (D,L-lactide-co-glycolide) (PLGA) and polyethylene glycol (PEG) polymers. Several questions on the quality and control of these polymers are still pending (see corresponding MO 6 / former MO 7 in section P.4).

According to the quality target product profile (QTPP) of the finished product submitted, the formulation was designed to release bimatoprost drug substance for at least 3-4 months. An initial formulation ("generation 1") was rejected Information on achievement of these objectives as given in section P.2.2 is generic (e.g. reference to general literature) and not regarded as sufficient. Clinical data on intraocular pharmacokinetics is limited due to small sample size, non-validated assay and issues on mode of analyses (reference is made to NC/C report).
The QTPP submitted is not regarded as sufficient to demonstrate adequate development of the finished product. An updated version of the QTPP covering all quality characteristics of the finished product to ensure the desired quality (accounting for safety and efficacy) should be provided.

Sterilisation of the finished product leads to significant degradation data given on test setup and analytical method are not regarded as sufficient to evaluate the chemical degradation of the drug substance after sterilisation. It is noted that this question is not a safety concern.
Definition of implant size as given in Pharmaceutical Development (approximate dimensions) is not acceptable and should be revised (see also MO 4 / former MO 5).
Physical stability of the finished product was demonstrated. Adequate information on LOD of the XRPD method and overlay diffractograms were provided. Omission of testing of the polymorphic form is accepted.
Influence of sterilisation on the structure of the copolymer matrix as discussed in the response is not regarded as stringent concerning glass transition temperature Tg. Glass transition temperature of the copolymer matrix should be clearly defined in the dossier, including influence of sterilisation.

Drug release method development: test method for clinical phases I and II was changed for clinical phase III based on DoE studies. It is stated that Phase III method has been designed to achieve complete release. This method is also proposed as QC method.

Bridging of commercial batches regarding drug release to clinical batches for which satisfactory efficacy has been demonstrated is regarded as essential. However, discriminatory power of the release method

is pending, and acceptance criteria currently proposed for QC testing are not in line with drug release rates of the Phase III clinical trial product.
(MO 2 / former MO 3)

Manufacturing process development

Development of manufacturing process was performed with DoE experiments. Within the section, final results of development are presented.

A question to clearly describe all changes of the manufacturing process and the applicator used for Phase III clinical batches is still raised as part of MO 3 / former MO 4.

The proposed commercial manufacturing process is different compared to the process used for clinical batches.
Particulate contamination of the ophthalmic implant is not adequately reflected in the dossier (sections P.2.2 and P.2.3). A sound risk evaluation on source and occurrence of particulate contamination should be presented.
Test method and validation should be revised based on the data provided, the proposed limits for foreign/insoluble particles are not accepted. The acceptable control level for foreign/insoluble particles should be derived from batches that can be assigned to clinical trials. Any statistical analysis performed to define acceptance criteria for this CQA should be duly justified and included in the dossier.
Comparison of commercial batches with clinical batches should be made with the commercial process validation batches. Any statistical analysis applied for comparison should be duly justified and included in the dossier.
The comparison table ("batch genealogy") should be updated. Part numbers used during development should be given.). **(MO 3 / former MO 4)**
Polymer retention system: information on definition of specification (viscosity) and shelf-life of the solution has been submitted.

The choice of the sterilisation method is adequately justified in line with the *Guideline on the sterilisation of the medicinal product, active substance, excipient, and primary container (EMA/CHMP/CVMP/QWP/850374/2015).*

Container closure system (CCS)

Description of primary and secondary packaging has been amended as requested. Detailed questions on CCS raised in section P.7 are still pending.
Information on the integral medical device, the applicator, and its development is given.

The rod-shaped implant is preloaded into a single-use applicator to facilitate injection of the implant directly into the anterior chamber of the eye. The applicator contains a 28-gauge ultra-thin wall hypodermic needle lubricated with silicone. The finished product applicator containing the implant is packaged in a laminated aluminium foil pouch with a 3-gram desiccant sachet. The foil pouch serves as the primary container closure for the drug product and provides the moisture and microbial barriers.

Revised overview on changes in applicator during development of the finished product is regarded as adequately detailed (except pending definition of subassembly parts as questioned in the corresponding MO). Actuation force of configurations and ejection distance of configurations can be regarded as similar. Acceptability of corresponding QC limits is pending.

Information given on development of the applicator and changes made is regarded as sufficient. Materials used for individual components are indicated. Information on changes in dimensions is given. For the needle, only change in gauge is indicated. Adaptions made are described, changed dimensions

are not given. On a risk-based approach, no further question is raised. Colour of safety tab was changed, no impact on performance is expected. No changes regarding audible click are described.

Additional information on real time ageing study and results for transit testing of the container closure system were submitted. Summary results transit testing: no issues on damaged foil pouches, as reported as outcome of GMP inspection, were detected within this study. Explanation given on influence of age of applicator components on overall shelf-life of the medicinal product is regarded as sufficient. Information on usability testing in section P.2.4 is still generic and only referencing to 3.2.R . Design elements to confirm satisfactory administration of the finished product is discussed in section P.2.4. SmPC describes an "audible and/or palpable click". Explanation has been given that the snap feature of the lever of the applicator makes an audible and palpable click. Thus, both features are interconnected. It has been confirmed that the polymer retention system was used for Phase 3 clinical trials, and that it is injected in the eye. Section P.2.4 and SmPC were updated accordingly. Clarification regarding function of the housing cap is given (no update of SmPC required).

Microbiological attributes

According to the response given, sterility testing of the finished product is now performed in compliance with Ph. Eur. monograph 1163 on Eye Preparations. However, the test method is not clearly defined in section P.5.2, and only a validation summary is given, which is not regarded as sufficient.
The proposed control strategy for microbiological attributes and corresponding data submitted in the MA dossier do not adequately ensure sterility of the finished product. Sterility is a compendial requirement for all eye preparations, and the integral finished product (intracameral implant in applicator) is labelled to be sterile and delivered in a sterilised pouch. **(part of MO 4 / former MO 5)**
a) Method for sterility testing should be clearly defined in section P.5.2: reference to Ph. Eur. 1163 (drop test) should be given. Sample preparation and test procedure should be described in adequate detail in the section (e.g. if/how applicator parts are separated). The corresponding validation report should be given in section P.5.3. Section P.5.1 needs to be updated to indicate "sterility" as acceptance criterion. **(sub-item a) is part of MO 4 / former MO 5)**
Former MO 5b) and MO 5d) are resolved (see section P.3).
Former MO 5c) on bioburden control is followed-up as MO 4b): see section P.3.
Former sub-item MO 5e) is resolved.
A new issue regarding sterility assurance of the finished product has to be added regarding primary packaging / pouch ensuring sterility: in the course of the recent GMP inspection (see former MO 1), a major issue was brought up.
c) The design of the primary packaging (foil pouch) is not regarded as sufficient to ensure that the sterile barrier of the finished product is maintained. Corresponding dossier sections (P.1, P.2.4, P.2.5, P.7 and P.8) should be updated. **(sub-item c) is part of MO 4 / former MO 5)**

Compatibility

For a solid dosage form risk of interaction is low and interaction studies are not generally required. Regarding leachable study, section P.8.1 was updated with information on sample, analytical methods and AET. Numeric results are given. Section P.2.6 includes a reference to the leachable study in P.8.1. In conclusion, data on leachable testing is regarded as sufficient for the proposed product (solid implant in applicator).

Evaluation of biocompatibility of the applicator (ISO 10993) is not in the merit of the Competent Authority, it should be evaluated by the Notified Body. Accordingly, no comments are made by the Rapporteur on biocompatibility of the CV1B applicator materials and waiving to the CV1C applicator.

3.1.3.2. Manufacture of the product and process controls

The finished product is manufactured by the site responsible for manufacturing, packaging, QC testing and batch release.

Manufacturing process

The manufacturing process has been described.

Batch size is defined. Batch formula was revised in line with validation data and therefore accepted. Process description does not clearly indicate the new unit operation and should be updated accordingly. An additional question is raised on the description of final packaging (section 1.5 in P.3.3).

Equipment used in the manufacturing process (and as applied for validation batches) is described in adequate detail.

Definition of CPPs in the dossier needs to be updated **(MO 5 / former MO 6).**

Time span between bioburden testing and start of sterilisation should be defined in the dossier justified by specific data **(part of MO 4 / former MO 5)**

Process validation

The finished product is a specialised dosage form (modified release, depot preparation based on biodegradable polymers), the manufacturing process includes new and complex technologies and a non-standard sterilisation method is used. Information on process validation, including validation reports, is still not included in eCTD Section P.3.5 Process validation. The approach to give only references to validation data located in section 3.2.R is not accepted. Section P.3.5 should be updated to include all validation data of both manufacturing process and sterilisation required for marketing authorisation.

Initial process validation ("original process validation") applying manufacturing process 2.0 was performed. All results were found as compliant by the applicant. Information has been given regarding the use of applicator parts within process validation. This supplier will be used for the commercial product. For "repeat validation batches" (), revised manufacturing process 2.1 was used. Section P.3.5 should be updated to indicate batch numbers of validation batches, corresponding manufacturing dates and a statement that process validation was performed with consecutive batches. No information or discussion on implant weight is given in P.3.5. Data given in 3.2.R are not adequately clear to allow a conclusion on the interplay of filament composition, implant weight and final assay. Reference is made to the MO on critical process parameters.
A discussion on defect rates and yields has been provided, which is underlining the complexity of the non-standard manufacturing process. Discussion on defect rates and yields - including outcome of process validation and rationale for the definition of commercial yields - should be indicated in section P.3.5. In addition, the section should be updated to give an overview on how hold times were defined (hold times applied to the different validation batches), including the cumulative hold time from the start of date of manufacture to the start of the sterilisation.

Validation reports on sterilisation of the finished product have been submitted as requested, but not included in section P.3.5 (see above). Explanation given on the bioburden recovery efficiency test and the calculation of correction factors is regarded as sufficient. Justification of the bioburden limit based on validation data is accepted. Former MO 5d) is resolved.

Excipients

For compendial excipients: microbiological quality and bacterial endotoxins have been adequately specified. Substitution type of hypromellose is defined. Water used is specified as Water for Injections Ph. Eur

Non-compendial excipients:

Novel excipient status: for the specific non-compendial polymeric excipients only reference to the US product Durysta is made in the response. Further, a general list of drug products using PLA/PLGA polymers is provided (without information on the use of the specific polymers as questioned). Ozurdex is the only ophthalmic product in this list marketed in the EU (intravitreal implant). In conclusion, it was not substantiated that the specific excipients are already used in a drug product authorised in the EU. The non-compendial polymeric excipients form a complex delivery system. Within the copolymer matrix, these excipients have a specific function (controlled degradation, sustained release), and control of these materials is seen as critical for the quality of the finished product.
Specification of residual monomersin resomer should be tightened in line with batch data **(MO 6 / former MO 7)**

3.1.3.3. Product specification, analytical procedures, batch analysis

Release and shelf-life specifications for the finished includes tests for physical appearance (visual), identity (HPLC, TLC), potency (HPLC), impurities (HPLC), insoluble particulate matter (Ph. Eur.), content uniformity (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and drug dissolution (HPLC).

Appearance: implant dimensions (diameter and length) are regarded as stability relevant for the dosage unit and should be controlled throughout shelf-life. Identification of drug substance is performed by combination of two unspecific methods, comparison of retention time (HPLC) and comparison of retention factor (TLC), which is acceptable.
Assay (potency): batch data clearly show that the commercial process is capable to result in a finished product with consistent results. The proposed limit is not regarded as justified and therefore not accepted. In line with Directive 2001/83/EC, assay at release should be specified as 95-105%.
Widening of assay range during shelf-life is not supported by long-term stability data
Related substances: full chemical names of all specified impurities are indicated in the footnote of the specification. Based on a maximum daily dose of 0.35 µg, reporting threshold is 0.1%, identification threshold is 1.0% and qualification threshold is 1.0%. The limits for specified impurities are below the qualification threshold (1.0%) and therefore accepted. The limit for individual unspecified impurities is within identification threshold and therefore accepted. Release and shelf-life limit for total related substances should be tightened in line with batch data and stability data, respectively. A limit of NMT 1.0% total impurities at release would be acceptable without further justification.
Foreign/insoluble particles: Ph. Eur. defines limits for testing of sub-visible particles on a per volume basis, which is not applicable for the proposed product. Actuation force: the proposed specification limit is not accepted based on the data provided in section P.2.4. Pouch integrity creep test: pressure is now specified in SI units Content uniformity: reference to Ph. Eur. monograph 2.9.40 is given.
Finished product specification needs to be updated to indicate "sterility" as acceptance criterion
Bacterial endotoxins: Ph. Eur. does not foresee specific limits for the proposed dosage form. It is, however, stated in Ph. Eur. that a limit for intravitreal preparations is expressed per eye. The proposed approach to specify a combined limit is regarded as acceptable Loss on drying (Ph. Eur. 2.2.32) should be specified at release and during shelf-life as the finished product Information should be given, if and how exhaustion of the desiccant is evaluated during shelf-life.
Omission of testing of polymorphic form of the drug substance has been justified.

Analytical procedures and reference standards

Method numbers have been assigned for in-house methods. Analytical methods have been revised. Information on reference standards is regarded as sufficient (reference is made to the Drug Substance Part 3.2.S).

Batch analyses

Section P.5.4 has been updated to include batch data up to "original process validation batches" and recent "repeat validation batches". Clarification has been given that the "primary stability" batches were not produced with the commercial process as described in section P.3.3

Characterisation of impurities

Related substances: the information provided is still not regarded as sufficient.
Elemental impurities: the risk analysis submitted adequately addresses all potential sources of elemental impurities as outlined in ICH Q3D.
Nitrosamine impurities: the risk evaluation concerning the presence of nitrosamine impurities in the drug product was updated with regards to the questions raised. Synthesis of drug substance, the drug substance itself, excipients used and the drug product manufacturing process are adequately addressed. No risk for the presence of nitrosamine impurities in the drug product was identified. The proposed control strategy for nitrosamine impurities is accepted. Former MO 8 is resolved.

Container closure system

Information provided on the container closure system including the integral medical device (applicator) is not regarded as sufficient.

Desiccant pouch: materials of construction and weight are indicated, resulting in a specified bioburden. Specification should be revised (loss on drying, moisture adsorption capacity). Given that the performance of the desiccant will be affected by the environment, storage conditions and shelf life should be given in the dossier.

Laminated foil pouch: information on the foil pouch should be updated.
The applicator (integral medical device) is assembled in the course of the manufacturing process of the finished product. Information given on subassembly components as supplied and used as input materials for the manufacturing of the finished product does not reflect the complexity of the applicator. It is still not regarded as sufficient.
Full name and address of the supplier of backhalf-subassembly and housing cap and the supplier of needle and plunger should be given in section P.7. Compliance of the silicone oil with Ph. Eur. monograph 3.1.8 "silicone oil used as a lubricant" is regarded as mandatory. Reference to alternative standards (e.g. to ISO standards for medical devices) is not accepted, as a specific Ph. Eur. monograph is available.

Secondary packaging: brief information on thermoform tray and lid material and dimensions is given. Specification includes "QC measurement per drawing" only. No sealing or printing is performed, no label is attached. As the secondary packaging material is non-functional, no further question is raised. Photographs of assembled product (applicator), pouched applicator, thermoform tray with pouch and tray in carton box are given to illustrate packaging of the finished product including labelling.

3.1.3.4. Stability of the product

Stability data submitted comprise data obtained after long-term (5°C) and accelerated storage conditions (25°C/60%RH). Stability batches tested include "primary stability batches" manufactured in 2014-2016, which are not regarded as representative for the finished product to be authorised. The

corresponding change in process (process 1.1 vs. process 2.1) is regarded as significant as several critical manufacturing steps are concerned.
For the commercial product, long-term results of three validation batches covering 24, 18 and 6 months, respectively, are given, as initially submitted. Corresponding accelerated data up to 6 months of two validation batches are available. Details of validation batches are indicated in section 4.3.5.
Both long-term and accelerated results of commercial batches comply with the shelf-life specifications, no trends were observed. Results at accelerated conditions (25°C) are comparable with results at 5°C,.
Sterility was not tested during accelerated study.
Temperature excursion, thermal cycling and photostability studies: confirm that the finished product is not sensitive to low/high temperatures or light.

The stability programme is not fully in line with EMA/ICH storage conditions: the general case (long-term 25°C/60% RH and accelerated 40%/75% RH) has not been tested for representative finished product batches, and no sound justification for storage at 2-8°C has been given. It is noted that precautionary restrictions of the storage temperature are not accepted for finished products, there should be a direct linkage between label statements and demonstrated stability characteristics. Storage restrictions should be based on stringent stability data obtained with a discriminatory method for drug release that is able to detect changes in polymer matrix. Glass transition temperature of the polymer matrix (Tg) and influence on sterilisation on Tg are not adequately characterised. Accordingly, the proposed temperature storage restriction (2-8°C) is currently not accepted, and stability data covering the general case should be presented, if not otherwise justified.

Based on the data available, no shelf-life can be granted yet for the finished product: questions pending on analytical methods should be resolved. Test parameters need to be updated in line with questions raised in Section P.5.6. Stability studies should be performed with commercial primary packaging, i.e. with the final design of the sterile barrier (pouch) including labelling. Stability data should cover a minimum of 6 months duration at long-term and accelerated conditions on at least two production scale batches.
The stability commitment should be updated according to questions raised on the stability programme.

Regional information

Applicator (medical device part) and implant form a single integral product that is not reusable and intended exclusively for use in the given combination. Conformity to the relevant General Requirements as outlined in Chapter I, II and III of Annex I of Regulation (EU) 2017/745 is declared for the medical device part However, the description of the medical device part in the NBOp is not aligned with Module 3 of the dossier, which does not include a corresponding reference. Module 3 (sections P.1, P.2.1, P.2.4 and P.7) and Application Form (section 2.2.4.1) should be revised to indicate the commercial applicator to allow bridging to the NBOp. **(MO 7 / former MO 9).**

Data on usability studies as mentioned in the summary in 3.2.R should be presented in Module 5.

3.1.3.5. Post approval change management protocol(s)

Not applicable.

3.1.3.6. Adventitious agents

No risk regarding TSE/BSE was identified.

3.1.3.7. GMO

Not applicable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The documentation of the drug substance is not approvable as several Other Concerns are still unresolved.
The documentation regarding the drug product is not approvable as seven Major Objections were raised:

- P.1: definition of integral medical device / medicinal product;
- P.2.2/P.5.6: comparability of drug release rates of Phase III clinical trial product and commercial product;
- P.2.3/P.5.2/P.5.3/P.5.6: comparability of commercial batches (AOIML) and NC/C batches regarding contamination with foreign/insoluble particles;
- P.2.4/P.2.5/P.3.4/P.5.1/P.5.2/P.5.3/P.7: inadequate control strategy to ensure sterility of the finished product;
- P.3.4: inadequate definition of critical process steps/parameters to ensure consistent quality of the finished product;
- P.1/P.2/P.3.2/P.4/3.2.A.3: Resomer excipients: to be defined and documented as novel excipients;
- P.1/P.2.1/P.2.4/P.7: commercial applicator to be defined according to the NBOp;

In addition, numerous Other Concerns were identified.

For details, reference to the Quality AR (day 150) is made.

3.2. Non-clinical aspects

3.2.1. Introduction

The scope of the present non-clinical dossier is to delineate the pharmacological, pharmacokinetic and toxicological characteristics of the bimatoprost intracameral drug delivery system (Bim IC DDS) also referred to as Bim sustained-release (Bim SR).
The synthetic prostamide bimatoprost has been used in humans for almost two decades as efficient ocular hypotensive agent in order to mitigate the consequences of increased intraocular pressure (IOP), leading to glaucoma characterized by optic nerve damage and vision loss. Previously, such treatment has been conducted in the form of topical ocular drops (Lumigan). The here presented test article is a rodlike polymer-matrix consisting to 20% of bimatoprost, which is designated to be implanted within the anterior chamber of the eye using a specific applicator. Subsequently, bimatoprost will gradually dissipate into the aqueous humour to locally exert its IOP-lowering action on the structures responsible for aqueous humour outflow (e.g. the trabecular meshwork).
In order to elucidate the aforementioned characteristics of Bim SR in animals, according studies were performed in Beagle dogs and cynomolgus monkeys, by testing different polymer formulations, sizes and dose levels of Bim SR. The following contains a comprehensive overview of the Assessors opinion on the conducted non-clinical studies, with a strong focus on the identified concerns.

3.2.2. Pharmacology

Glaucoma is a worldwide leading cause of irreversible vision loss and improvement of current therapeutic concepts is still needed (Jonas et al., 2017; Kwon et al., 2009). Due to the asymptomatic

progression of the disease until a relatively late stage, diagnosis is frequently delayed and non-adherence of the patients to topical therapy challenge appropriate control of IOP. Treatment is usually initiated with ocular hypotensive drops and may be accompanied by laser trabeculoplasty and surgery, which all together may slow disease progression. Hence, there is an unmet need to control IOP in patients, unsuitable for topical IOP-lowering medications due to intolerance or non-adherence.

Bimatoprost eye drops represent an approved medication, which is locally administrated to lower IOP.

Bimatoprost does not stimulate the PGF2a-sensitive, classical FP receptor, but activates an ill-defined prostamide receptor. The Bim SR formulation is administrated into the anterior chamber, which is clearly a novel compartment within the eye and possibly with different target structures. The Bim SR formulation includes a drug delivery system (DDS) containing polymers like polylactic acid, a lactide-glycolide copolymer and polyethylene glycol 3350 All polymers are widely used in the medical field.

Primary Pharmacodynamics:

The preclinical pharmacology data in monkeys and dogs support a reduction in IOP, however, such an effect is also seen in eyes receiving the DDS implant only. Thus, it is not clear to which extent an installation of the bimatoprost free DDS implant into the anterior chamber contributes to the proposed effects of therapeutic relevance. Moreover, the duration of the effect with respect to the DDS implant is not well described.

Overall the preclinical pharmacology is not in favour of a clear concentration dependent lowering of the IOP in hypertensive animals by IC Bim SR (generation 2). In normotensive animals IOP lowering effects were described but were not corrected for DDS implant effects. Hence, the duration and quantification of the proposed therapeutic effects cannot be estimated. A possible rebound effect indicated by an elevated IOP over basal levels cannot be excluded, particularly in the "wash out phase" of Bim SR.

The final formulation Bim SR Generation 2 was not investigated in animals with elevated IOP, thus no proof of concept is available with the final product.

Secondary Pharmacology:

The IC application of Bim SR represents a locally restricted administration of the therapeutic concept. Thus, systemic plasma concentrations of Bim SR after intraocular application are very low. Consequently, it is not deemed necessary to perform secondary pharmacology for Bim SR.

Safety Pharmacology:

All safety pharmacology studies were done with bimatoprost (AGN-192024) in the absence of the DDS implant. These studies include in vitro and in vivo experiments. It is agreed that the safety pharmacology of bimatoprost is well characterized.

Due to the anatomical restrictions in monkeys the wideness of the anterior chamber parameters was investigated and found to be smallest in monkeys, followed by humans and dogs. The progressive loss of corneal endothelial cells and subsequent cornea thickening in monkey studies is therefore explained and corroborated by fit simulation analyses, which favour the interpretation that the DDS implant has constant contact with the corneal endothelium and thereby promotes inflammatory process. It is therefore clear that the DDS implant, implant swelling, precise position, corneal consequences and at least the adequate species are crucial in the pharmacodynamics study programme. Hence, the applicant states that DDS implant without bimatoprost differs in water absorption, swelling and

degradation profile from Bim SR. Since drug free DDS implant does not act as a true placebo, conclusions have to be handled with caution.

Bim SR generations 2, the final formulation used in humans was not controlled for DDS implants, in particular in dogs or under conditions of pathological IOP models. Thus, it is not possible to evaluate the precise local side effects and possible long term safety issues of Bim SR generations 2.

Pharmacodynamic drug interactions:

Given the clinical experience with bimatoprost (Lumigan) and the studies BIO-99-311 and BIO-99-319 pharmacodynamics drug interactions with bimatoprost are not expected. Bim SR (generation2) or the DDS implant were not tested for possible interactions with other IOP reducing agents. However, due to the locally restricted availability of Bim SR no systemic interactions are expected.

3.2.3. Pharmacokinetics

The applicant submitted an extensive non-clinical pharmacokinetics study programme in Module 4.2. Most of the submitted studies are not relevant to Bim SR. This is because in most of the submitted studies, no Bim SR was administered (e.g. many submitted studies were conducted with the topical bimatoprost solution Lumigan or with oral or intravenous bimatoprost administrations), or because systemic ADME endpoints were studied which bear little relevance for Bim SR due to the very little to negligible bimatoprost exposures after Bim SR administration. Nonetheless, four relevant ocular (and systemic) distribution studies were conducted in which generation 1 and/or 2 Bim SR was intracamerally administered to Beagle dogs. The scope of the submitted non-clinical ocular PK studies is sufficient to allow an adequate assessment of the ocular pharmacokinetics of bimatoprost in Bim SR after intracameral administration.

Regarding the applied methods of analysis, the applicant provided a range of (partial) validation reports on LC-MS/MS based methods in Module 4.2.2.1 to quantify bimatoprost and its main metabolite bimatoprost acid in the blood of dogs (main species in which systemic PK was studied after intracameral administration of Bim SR), monkeys, mice, rats and rabbits. Note that the measurements of bimatoprost and bimatoprost acid in animal tissues such as the aqueous humour, the iris-ciliary body, vitreous humour, retina, choroid, conjunctiva, periorbital fat, eyelid margin, and cornea were not validated. This was the content of a concern discussed in section 3.2.6 of this report.

The applicant validated this LC-MS/MS method for all relevant non-clinical animal blood specimens in terms of linearity, selectivity (including carry over), concentration range, extraction efficacy, sensitivity, precision, accuracy and stability. All validation aspects met the pre-specified acceptance criteria, the used analytics can therefore be regarded to be fit-for-use and reliable for the detection of bimatoprost and bimatoprost acid in blood of the examined animal species. Importantly, the lower limit of quantitation was established down to maximally 0.025 ng/mL for bimatoprost and 0.05 ng/mL bimatoprost acid.

In terms of absorption, no dedicated stand-alone systemic absorption study was submitted in Module 4.2.2.2. However, the applicant measured systemic absorption of bimatoprost and bimatoprost acid after intracameral administration of Bim SR in different dog and monkey PK and/or toxicity studies. Therefore, the scope of the submitted studies is considered sufficient for the non-clinical evaluation of systemic bimatoprost and bimatoprost acid exposures.

Regarding distribution, the applicant submitted three studies in Module 4.2.2.3 in which the ocular pharmacokinetics of Bim SR (generation 1 and the clinical generation 2) were examined after intracameral administration to Beagle dogs. Additionally, one ocular distribution study was submitted after topical administration of bimatoprost ophthalmic solutions in rabbits and monkeys. Finally, an in

vitro albumin and melanin binding study was submitted in Module 4.2.2.3. No concerns were identified on the scope of the submitted studies.

In Study PK11086, the applicant assessed the ocular pharmacokinetics of Bim SR after intracameral administration of different 20 µg new generation (generation 2) implant formulations to Beagle dogs (single bilateral administrations for n=2 dogs per group per formulation, one male and one female dog per group). After administration, aqueous humour was sampled at 1, 2, 4, 6, 8, 10, 12, and 14 weeks post dose from each eye. Ocular tissues (cornea, iris-ciliary body, choroid, retina, vitreous humour) and the remnant implant were harvested 14 weeks post-dose upon euthanasia. In Study PK14025, the applicant compared the ocular pharmacokinetics of bimatoprost and bimatoprost acid after 7 days of consecutive q.d. topical ocular administration of Lumigan (0.03%) and after single intracameral administration of Bim SR (15 µg, generation II implant) in female dogs. Samples were drawn from the Lumigan dogs at Day 7, specifically at 0.5, 1, 2, 4, 9 hr post dose, and from the Bim SR dogs 1, 2, 3, 4.5, 6, ~7 months post dose. In total, 10 female dogs bilaterally received topical Lumigan drops once a day, whereas 14 female dogs bilaterally received Bim SR implants. Bimatoprost and bimatoprost acid concentrations were measured in ocular tissues, aqueous humour, the residual implant and periocular tissues. Finally, in Study PK15022, the ocular pharmacokinetics of bimatoprost and bimatoprost acid after intracameral Bim SR administration (containing 15 µg bimatoprost, n=12 dogs) and topical Lumigan administration (0.03%, q.d. for 7 consecutive days, n=4 dogs) were analysed in female aphakic dogs. The following tissues or compartments were analysed for bimatoprost and bimatoprost acid: corneal endothelium, the remaining cornea, conjunctiva (bulbar and palpebral), upper and lower eyelid margin, periorbital fat, aqueous humour, iris-ciliary body, retina (macula and periphery), vitreous humour, and remnant dose implants. Samples were taken 28, 56, 84 days post-dose (n=4 animals were killed per collection time point), and 2 hours post-dose at Study Day 7 from Lumigan dogs.

In Study PK11086, the highest Cmax and $AUC_{0\text{-last}}$ in aqueous humour were identified with the 026BG formulation (the generation 2 clinical formulation). Bimatoprost acid exposures in aqueous humour were similar among the different formulations. The Tmax of bimatoprost and bimatoprost acid of the 026BG formulation was 8 weeks post-dose. No drug was measured in the retina and the vitreous humour, and bimatoprost acid was not detected in any of the ocular tissues in all groups. Note that 14 weeks post-dose, the administered implants did not contain any measurable amount of bimatoprost, demonstrating that bimatoprost had fully dissolved from the implants by that time.

Study PK14025 demonstrated that exposure of bimatoprost was considerably higher in the target tissues (aqueous humour, iris-ciliary body) when administered as the Bim SR formulation into the anterior eye chamber as when topically administered as an ophthalmic solution. The different exposures between the two routes of administration were extensive. While e.g. in the iris-ciliary body bimatoprost Cmax levels were approximately four orders of magnitude higher in Bim SD dogs compared to Lumigan dogs (Cmax being 18,100 ng/mL in the Bim SD dogs), $AUC_{0\text{-tlast}}$ was even approximately five orders of magnitude higher in Bim SD dogs (486,000 ng*d/g in Bim SD dogs). At the same time, the off-target exposure in periocular tissues such as the upper and lower eyelid margin, periorbital fat and the bulbar conjunctiva were evidently much lower after intracamaral administration compared to topical administration. Interestingly, corneal bimatoprost concentrations were higher in Bim SR dogs than in Lumigan dogs (approximately by three orders of magnitude in terms of Cmax and by four orders of magnitude in terms of $AUC_{0\text{-tlast}}$). Of note, in both groups, bimatoprost partitioning to the retina was below detection. Importantly, already by Day 80, 99.8% of the drug load had been released from the implants in Study PK14025. Even 182 days post-dose, the administered implants had not dissolved in the same study.

The results of Study PK14025 are summarised in the table below:

Table 1: Pharmacokinetic parameters of bimatoprost in ocular tissues following topical once daily (QD) for 7 Days administration of Lumigan 0.03% (bimatoprost ophthalmic solution 0.03%) or administration of a Single Bimatoprost SR (15 µg) implant to Beagle Dogs

LUMIGAN 0.03% Once Daily (QD) for 7 Days					
Ocular Tissue	C_{max} (ng/mL or ng/g)		$AUC_{0\text{-tlast}}$ (ng•hr/mL or ng•hr/g)		T_{max} (hr)
	Mean	SE	Mean	SE	
Cornea	2.90	1.70	15.5	4.8	9
Aqueous Humor	0.285	0.166	1.45	0.41	1
Iris-Ciliary Body	0.825	0.505	5.12	2.30	9
Upper Eyelid Margin	2100	410	8500	1510	2
Lower Eyelid Margin	1160	340	6220	1240	2
Bulbar Conjunctiva	75.4	21.9	517	107	9
Periorbital Fat	36.1	10.8	139	25.6	2
Retina (Macula)	BLQ	NC	NA	NA	NA
Bimatoprost SR (15 µg)					
Ocular Tissue	C_{max} (ng/mL or ng/g)		$AUC_{0\text{-tlast}}$ (ng•day/mL or ng•day/g)		T_{max} (day)
	Mean	SE	Mean	SE	
Cornea	2980	530	93,800	14,900	52
Aqueous Humor	22.9	19.6	727	511	27
Iris-Ciliary Body	18,100	16,700	486,000	441,000	52
Upper Eyelid Margin	BLQ	NC	NA	NA	NA
Lower Eyelid Margin	BLQ	NC	NA	NA	NA
Bulbar Conjunctiva	0.129	0.055	1.62	0.69	52
Periorbital Fat	BLQ	NC	NA	NA	NA
Retina (Macula)	BLQ	NC	NA	NA	NA

[a] Half-life ($T_{1/2}$) was not calculable for any matrix in either study group
SE = standard error; NC = not calculable

Finally, in aphakic dogs that had received a Bim SR implant (Study PK15022), much lower bimatoprost concentrations in the iris-ciliary body and the aqueous humour were measured as compared to the ocular PK measurements in healthy (phakic) dogs in Study PK14025. This is likely because the absence of the lens in aphakic dogs led to an increased release of bimatoprost and bimatoprost acid from the anterior eye chamber into more distal compartments of the eye and ultimately into the systemic circulation. The results of this study suggest that for aphakic or pseudophakic patients the implantation of Bim SR bears a higher risk for off-target retinal interactions of bimatoprost than after topical Lumigan administration.

Apart from ocular distribution studies of bimatoprost and bimatoprost acid after intracameral administration of Bim SR to Beagle dogs, also a plasma protein binding study, ocular and systemic distribution studies in NZW rabbits and cynomolgus monkeys after topical administration of an ophthalmic bimatoprost solution, and a binding study of bimatoprost to synthetic melanin (Study PK-99-045) were submitted in Module 4.2.2.3. As topical administration is not relevant to Bim SR, the rabbit and monkey studies were only rapidly screened (no concerns were identified). Similarly, plasma protein binding of bimatoprost is of little relevance for Bim SR due to the very low to negligible systemic exposures of bimatoprost after instillation of Bim SR into the anterior eye chamber (vide infra). Finally, in Study PK-99-045, the applicant demonstrated that bimatoprost reversibly bound to melanin at a bimatoprost-concentration independent equilibrium of approximately 20%. This suggests that also after Bim SR administration to the anterior chamber, a fraction of the dissolving bimatoprost

will reversibly bind to melanin in the iris-ciliary body. No adverse safety effects or efficacy decrease are expected from this reversible binding to melanin.

Metabolism of bimatoprost after intracameral administration of Bim SR was analysed in Beagle dog ocular distribution studies (vide supra). Of note, metabolism of bimatoprost after topical administration of Lumigan was also studied in rabbits and monkeys. Based on these studies, it can be expected that the major metabolite of bimatoprost after intracameral administration of Bim SR is bimatoprost acid. Also, systemic metabolism studies were submitted in Module 4.2.2.4. As only very low systemic bimatoprost exposures will be realised after intracameral administration of Bim SR, these studies were only broadly screened in the frame of this centralised assessment.

Excretion of bimatoprost was studied after i.v. administration of tritium-labelled bimatoprost to rats, monkeys and humans. No stand-alone excretion studies were submitted after intracameral administration of Bim SR. As systemic bimatoprost concentrations after intracameral Bim SR administration are expected to be very low, this is acceptable.

No pharmacokinetic drug-drug interaction studies were submitted that are specific for the intracameral administration of Bim SR. As the systemic release of bimatoprost from the administered implant is very low, systemic DDIs are very unlikely.

Finally, one other pharmacokinetic study was submitted in Module 4.2.2.7. In this study (Study PK09109-PK), the applicant examined the pharmacokinetics and pharmacodynamics of bimatoprost after intracameral administration of a generation 1 Bim SR implant to normotensive male Beagle dogs. The endpoints of this study were the measurement of IOP and hyperaemia after Bim SR administration, but also on-contact specular microscopy, gonioscopy examinations, pachymetry measurements, pupil diameter and gonioscopy imaging for selected animals. In total, ten groups were used in this study. In study group 1-6, either a sham control or 0, 8, 15, 30 or 60 µg of bimatoprost (contained in the Bim SR implant) were injected into the right eye of the dogs (n=8 per group). No ocular tissue samples were collected from these dogs, and the left eye was used as untreated control. In study groups 7-10, 8, 15, 30 and 60 µg of bimatoprost were administered in both eyes to n=3 dogs per group. In these groups, blood, aqueous humour (at weeks 2, 3, 5, 7, 9, 11, and 14 post-dose) and tissues (approximately 3-month post-dose) were sampled.

Until day 70 of the experiment in Study PK09109-PK, the bimatoprost in the administered generation 1 Bim SR caused an approximately dose-dependent lowering of the measured IOP. Importantly, during this timeframe, all test-article groups showed a significant IOP lowering effect in comparison to the two placebo groups (groups 1 and 2). In the 4th month of the study, an IOP lowering effect was exclusively seen in the 60 µg group. Interestingly, also the placebo implant clearly decreased IOP when compared to the IOPs in the left untreated eyes and the sham-treated eyes in group 1, however, only between 2.5 and 4 months post-dose. This counter-intuitive effect is discussed in much more detail in the non-clinical pharmacodynamics and toxicology assessment. The measured IOPs in Study PK09109-PK are summarised in the Figure below:

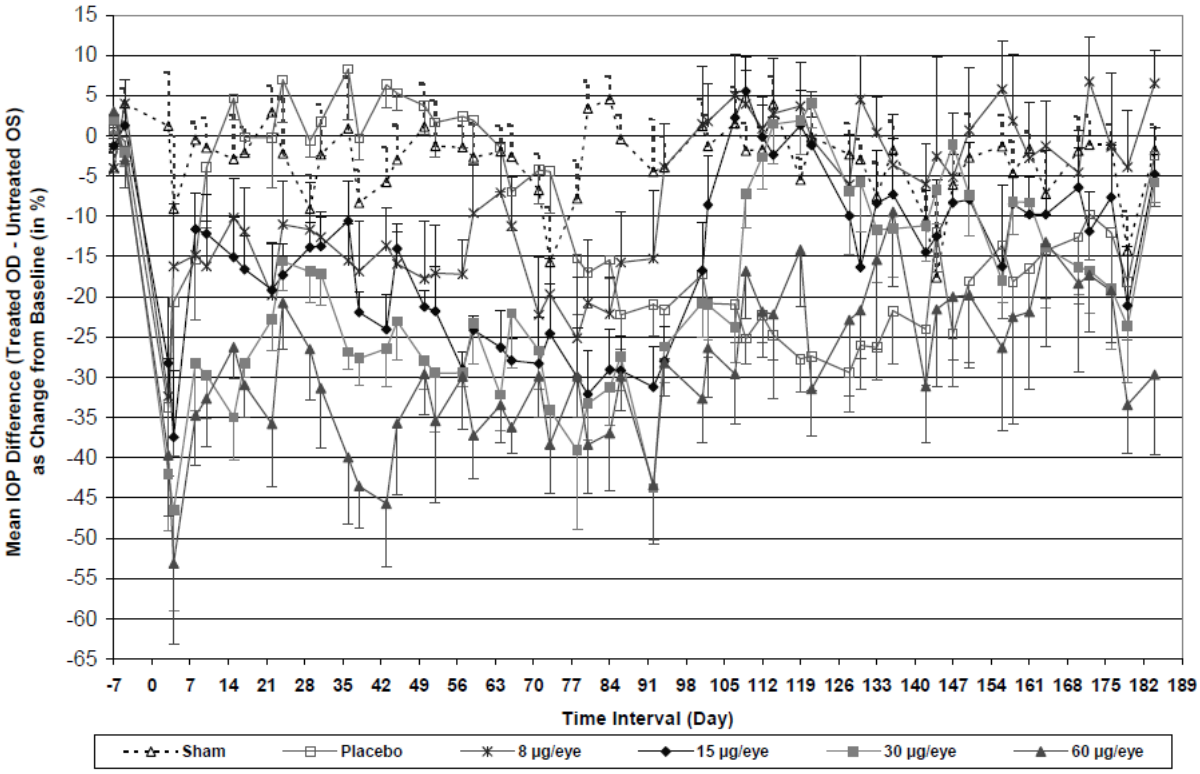


Figure 2: Intraocular pressure (IOP) measurements for male dogs administered bimatoprost to the right eye via Intracameral Drug Delivery System (IC DDS) in Study PK09109-PK

Importantly, in Study PK09109-PK, bimatoprost (and its main metabolite bimatoprost acid) was below the limit of quantitation (0.25 ng/mL) in all harvested samples. This demonstrates that systemic exposure after intracameral administration of generation 1 Bim SR is very low and presumably toxicologically negligible. Bimatoprost concentrations in aqueous humour had a Tmax between week 7 to 11. At 14 weeks post-dose, the mean measured bimatoprost concentration in the aqueous humour, the cornea and the iris-ciliary body ranged between approximately 1 and 23 ng/mL, were lowest in aqueous humour and highest in the iris-ciliary body and were approximately dose dependent (highest measured levels in the 60 µg groups). In terms of safety, the applicant concluded that the administration of the Bim SR implant was generally well tolerated. However, conjunctival hyperaemia (mild to moderate) was observed and was generally most frequent in the highest bimatoprost group, and least frequent in the 0 µg implant group. Apart from IOP lowering, also test-article related and dose-dependent miosis was observed (which is explained by the applicant by an effect of bimatoprost on the iris). However, no other clinically meaningful conditions were recognised.

Furthermore, in Study PK09109-PK, the placebo and bimatoprost implants appeared swollen and/or misshapen between Week 9 and 13, but all apart from one remained intact throughout the study. Furthermore, the remnant implants that were collected 3-month post-dogs from the sacrificed dogs had lost >90% (in the 8 µg group even 100%) of their bimatoprost content in all groups, demonstrating a rapid release of bimatoprost after instillation into the anterior eye chamber. However, this also demonstrates that the bimatoprost content in the implant possesses much faster dissolution kinetics than the implant itself. By that time, biopolymer loss was only 6-20%, demonstrating much slower dissolution kinetics of the implant. After 6 months, no bimatoprost was detected in any of the collected implants. Interestingly, the average polymer weight loss over 6 months was 84% for the placebo implants and 47% for the bimatoprost-loaded implants. Furthermore, the applicant describes that the implants were highly porous and fragile at 6 months post-dose and that the diameters of the bimatoprost-loaded implants increased on average 2.3 times of their original diameters before

implantation. These results demonstrate that the composition and shape of the implants changes over time. The rationale behind these observations might be surface reaction and subsequently surface passivation with e.g. ocular proteins (leading to a passivating protein corona, as observed with other particles in vivo).

3.2.4. Toxicology

In the present non-clinical toxicological dossier, the applicant provides a set of studies in order to examine the toxicological potential of a bimatoprost intracameral drug delivery system (IC DDS), from here on referred to as "Bim SR (sustained release) implants" or just "implants". To this end, several single dose toxicity studies and repeat dose toxicity studies were performed on the actual implant. As the active pharmaceutical ingredient (i.e. bimatoprost; AGN-192024) is identical to the one in registered Lumigan, it is deemed justified to reuse previous Lumigan studies for the present application. These latter studies represent the majority of the present dossier.

In total, four single dose toxicity studies were conducted on Bim SR implants (TX09051, non-GLP; TX09066, GLP; TX10016, GLP; TX11076, non-GLP) which were supplemented by two studies derived from the Lumigan registration procedure. Three of the Bim SR studies were performed on purebred Beagle dogs and one study on cynomolgus monkeys. The preference of dogs over monkeys was rationalized by differences in the anterior chamber size of the eyes between these two species. Specifically, dogs have a wider iridocorneal angle than monkeys allowing for deeper accommodation of the implant within the inferior part of the anterior chamber. This was associated with milder or none of the adverse events, which were seen in monkey studies. In terms of iridocorneal angle size, dog eyes are more comparable to human eyes.
The treatment was performed with either Bim SR Generation 1 (TX09051; TX09066; TX10016) or Generation 2 (TX11076). Generation 2 is characterized by a polymer formulation of optimized biodegradation.
During a GLP-compliant dose-finding study (TX09066, issued March 2011), Beagle dogs (5 groups; 5 males 5 females per group) received a single implant containing 0 (placebo), 20, 30, 40 or 50 µg bimatoprost into the right eye. The left eye remained untreated or was sham injected (needle inserted and withdrawn) in the placebo group. Dogs were subsequently examined for six months. This study defined a no observed effect level (NOAEL) of a single 20 µg implant per eye. Based on this, a GLP-compliant follow-up study (TX10016; issued December 2011) was conducted including two groups of male dogs (n=6 per group) one group receiving two implants at the same time containing a total of 20 µg bimatoprost the other group receiving a sham injection (all left eyes remained untreated; a placebo group was not included). Subsequently, dogs were followed for six months.
As the applicant strived to develop a different polymer formulation for Bim SR to improve its biodegradation characteristics, another non-GLP single dose toxicity study (TX11076; issued March 2013) was conducted in order to compare four different novel Bim SR formulations (4 groups; n=6 male Beagle dogs per group). Dogs were treated as for study TX10016 (i.e., 2 × 10 µg per right eye; left eyes of group 1 sham injected, left eyes of residual groups non-treated; a placebo group was not included). Three animals per group were sacrificed after 17 weeks (interim examination). The remaining animals in Groups 2, 3, and 4 were sacrificed after 35 weeks of observation, and the remaining animals in Group 1 were sacrificed after 52 weeks of observation.

Bim SR-related effects were consistent between the studies, restricted to the eye and generally considered non-adverse. The expected pharmacological ocular effects of bimatoprost were observed, i.e., lower intraocular pressure (IOP) and miosis (constricted pupils). Of which the latter was clearly drug- and not implant-related.
Implant-related events commonly consisted in hyperaemia, corneal vascularisation, corneal oedema, fibrillary matrix deposition and microscopic changes of the endothelium and Schwalbe's line cells

(hypertrophy and hyperplasia). These findings are also recapitulated in the repeat dose toxicity studies discussed below. The observed effects were generally mild and transient and hence rightfully not considered adverse. Only the 50 µg single implant treatment in study TX09066 led to a decrease of corneal endothelial cell density – an event which must be considered adverse. In conclusion of the dog studies, a NOAEL of 20µg (as one or two implants) is agreeable.

As far as the study design is concerned, it was noted that the majority of events (e. g. corneal vascularisation, corneal oedema, reduced corneal endothelial cell density) was presumably caused by the physical presence of the implant (which increased in size according to the dose level) rather than the active pharmaceutical ingredient (API). A clear differentiation between pharmacological and physical effects is difficult, as the placebo control in study TX09066 was run with an implant of one particular size instead of using placebos corresponding to each treatment group. Even more so, studies TX10016 and TX11076 do not include any placebo group but compare implanted right eyes against either non-treated or sham injected left eyes. Hence, these studies do not allow any discrimination between toxicological and physical impacts of the implant.
Of note, the Generation 2 formulation was not placebo-controlled in any toxicology study (as repeat dose toxicity studies – which were conducted with Generation 2 – also did not include appropriate placebo groups). The Assessor wishes to emphasize that for a complete understanding of the toxicological profile of Bim SR in dogs, it would have been necessary to separate the effects of the AIP from the effects of the polymer-matrix. Hence, the applicant was advised to duly justify the methodology based on this concern. By now, this issue is considered resolved.

During the earlier stages of Bim SR development, a non-GLP single dose toxicity study (TX09051; issued August 2010) on cynomolgus monkeys was performed, which prompted the applicant to conclude that dogs are a more suitable model for Bim SR development, mainly because of the space to accommodate the implant within the inferior part of the anterior chamber (which is larger in dogs). This is supported. However, it must be noted that animals which received one or two implants (4 groups; 4 females per group. 2 × 0 µg [placebo]; 1 × 30 µg; 1 × 60 µg; 2 × 60 µg) into the right eye exhibited adverse events not observed in subsequent dog studies. These events included aqueous flare, anterior chamber cells, corneal thickening and endothelial cell loss. As these findings also appeared in the placebo group they must be attributed to the physical presence of the implants. Although it is agreed that these findings are difficult to extrapolate to humans, the study clearly shows that the implant can elicit adverse reactions upon contact with certain eye regions and the occurrence of such events during human use should not be ruled out.

The conducted studies also include measurements of the intraocular pressure (IOP) upon Bim SR treatment. As IOP-decrease is the intended clinical effect of bimatoprost, this activity is not toxicological but pharmacological by definition. Hence, the applicant legitimately refused a formal evaluation of this aspect as part of their toxicological package. However, several studies give cause for concern as to which extent the IOP-lowering effect is based on bimatoprost and not on the physical presence of the implant. Study TX09066 reveals an IOP-lowering effect of the placebo, which is slight but consistent over the observation period (6 months) (see Table 2 below).

Table 2: Summary of IOP percent difference (Right vs. Left, excluding Week 1)

	Interval						
Group (treatment)	Day 15	Week 5	Week 9	Week 13	Week 17	Week 22	Week 27
1 (placebo)	-1.5	-1.9	-1.8	-7.8	-11.2	-13.0	-3.9
2 (20 µg/right eye)	-8.6	-10.0	-15.7	-8.4	2.4	-10.1	-13.5
3 (30 µg/right eye)	-13.8	-22.7	-22.5	-28.9	-9.1	-1.4	2.9
4 (40 µg/right eye)	-19.8	-21.0	-17.5	-20.1	-14.4	-9.3	-5.7
5 (50 µg/right eye)	-17.4	-24.4	-35.9	-25.5	-22.7	-21.5	-17.0

Values indicate combined sex data of the right eye compared to the left eye at the same interval

Furthermore, in study TX09051, which was conducted in cynomolgus monkeys, the placebo implant elicits a decrease in IOP, which is at least equivalent to the decrease observed in the highest dose group which received 120 µg bimatoprost (see Figure 3 below). It is emphasized that the time axis is not linear but segmented in an arbitrary manner (e.g., the distance between week 2 and week 5 is equivalent to the distance between week 17 and 26). This is misleading as in such a way the placebo effect (which is predominant between weeks 5 and 26) is ostensibly underestimated.

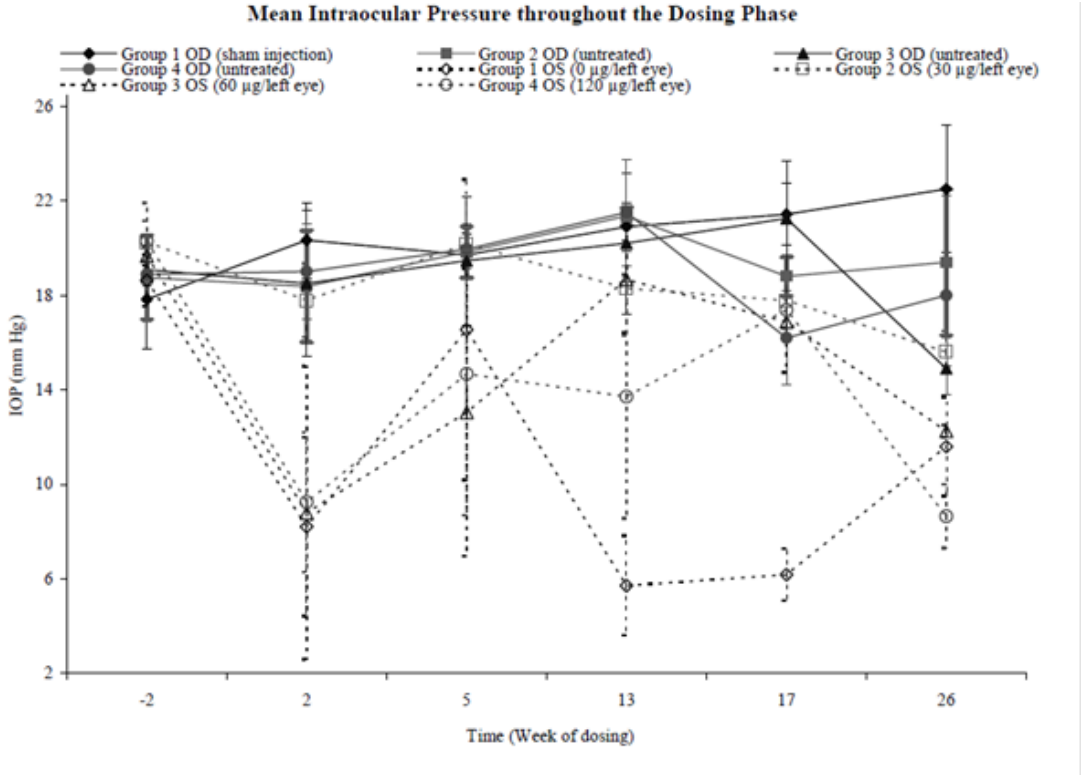


Figure 3: Mean intraocular pressure throughout the dosing phase

Strikingly, in both studies (TX09066 and TX09051) the placebo exerts a robust IOP-lowering effect between three and five months after injection – an observation also made in study PK09109. In study TX09051 it is considered that the placebo's effect on IOP is due to inflammation or even due to chemical results of polymer degradation of the implant. In the latter case, this would suggest a mode of action for IOP-decrease based on polymer degradation and (at least to a certain extent) questions the purpose of the presence of bimatoprost in the implant.

Taken together, the conducted non-clinical placebo-implant controlled studies (TX09051, TX09066, PK09109, BIO-09-803 and BIO-009-787) challenge bimatoprost as the sole cause of the observed IOP-decrease. The applicant is asked to further substantiate that implant-released bimatoprost (at the reached concentrations in the eye) is key for the IOP-lowering effect of Bim SR.

In conclusion, the conducted single dose toxicity implant studies are not conclusive to disentangle the physical and the toxicological/pharmacological effects of Bim SR. Of note, this also applies for the intended clinical effect, which is lowering the IOP.

In addition to the single dose implant studies, the applicant provided two acute single dose injection safety studies (1893-3137-7 and 1012C-2968-59, both GLP-compliant) in mice and rat, which were both conducted in 1995. In these studies, AGN-192024 (this is bimatoprost solution) ophthalmic solution was injected intraperitoneally at a single concentration (0.1%; mouse study) or intravenously at different concentrations (0.001%, 0.01% and 0.1%; rat study) - no adverse effect was reported at any dose level. Although these studies provide evidence for the systemic safety of bimatoprost, they do not sufficiently reflect the chemical complexity of Bim SR implants or the concentrations of the various derivative compounds (including bimatoprost) within the anterior chamber. Hence, these studies are of little value for the characterisation of the toxicological profile of Bim SR.

The applicant provided three repeat dose toxicity studies for the Bim SR implant in Beagle dogs – TX12012; TX12018; TX12102 of which TX12102 is GLP-compliant. Of note, all of these studies address Generation-2 Bim SR and none of these studies were controlled against a placebo implant, making distinctions impossible regarding the physical and pharmacological impact of the implant. The tables below indicate the study design of all three studies.

TX12018

Table 3: Implants were administered two times at 3-month intervals followed by at least 4 months of observation after the second dose

Group	No. of Animals/ Sex	Study Animal Numbers[a]	Anterior Chamber Angle Size[b]	Eye Treatment/Dose		Frequency of Injections
				Right Eye	Left Eye	
1	5F	150, 152-155	<540 µm	One 10 µg Bimatoprost PF IC DDS (0.203 x 1.05 mm)	Sham injection	OD&OS: Days 1 and 92
2	5F	250-254	≥540 µm to 635 µm	One 10 µg Bimatoprost PF IC DDS (0.203 x 1.05 mm)	Not treated	OD: Days 1 and 92
3	5F	350-354	<540 µm	One 15 µg Bimatoprost PF IC DDS (0.254 x 1.15 mm)	Not treated	OD: Days 1 and 92
4	5F	450-454	≥540 µm to 635 µm	One 15 µg Bimatoprost PF IC DDS (0.254 x 1.15 mm)	Not treated	OD: Days 1 and 92

F = Female; OS = Left eye; OD = Right eye
a = All animals were sacrificed after at least 4 months of observation following the second (last) dose (after at least 7 months on study).
b = Anterior chamber angle size measured at pretest post LUMIGAN drop.

TX12012

Table 4: Implants were administered two times at 3-month intervals followed by at least 4 months of observation after the second dose

Group[a]	No. of Animals	Dosing Regimen		Dose Level (µg/right eye/dose)	Dose Concentration (µg/implant)
	Female	Right Eye	Left Eye		
1	12	One 10 µg bimatoprost implant	Sham injection[b]	10	10
2	12	One 15 µg bimatoprost implant	NT	15	15
3	12	Two 10 µg bimatoprost implants	NT	20	10

NT = Not treated.

a Animals were divided into two cohorts (six animals/group/cohort, see Protocol Deviations for exceptions). Day 1 of the dosing phase was designated as the first day of dosing for each cohort.

b Group 1 animals received a sham injection (needle inserted and withdrawn with no implant administered) in the left eye.

TX12102

Table 5: Implants were administered three times at 4-month intervals (days 1, 120, 232) and followed for either 40 weeks (interim sacrifice; 12 animals per group) or 79 weeks

Group	No. of Animals[a,b]	Dosing Regimen		Dose Level (µg/right eye/dose)	Dose Concentration (µg/implant)
	Female	Right Eye	Left Eye		
1	24	One 10-µg Bimatoprost implant	Sham injection[c]	10	10
2	24	One 15-µg Bimatoprost implant	NT	15	15
3	24	Two 10-µg Bimatoprost implants	NT	20	10

NT = Not treated.

a Animals were divided into three cohorts (eight animals/group/cohort). Day 1 of the dosing phase was designated as the first day of dosing for each cohort.

b Animals designated for the interim sacrifice (12 animals/group) were terminated after at least 5 weeks of observation post the third dose (during Week 40). The remaining animals were sacrificed after at least 44 weeks of observation following the third dose (during Week 79).

c Group 1 animals received a sham injection (needle inserted and withdrawn with no implant administered) in the left eye.

Considering the expected relevance of the anterior chamber angle size for implant accommodation, study TX12018 (end date December 2012) investigated implant tolerance in Beagle dogs according to the study design above. Anterior chamber angle size measurements (<540 µm; ⩾540 µm to 635 µm) refer to the maximum phantom circle size (maximum circle fit; maximum implant fit), which was measured by Anterior Segment Optical Coherence Tomography (AS-OCT) and quasi represents the available space for the implant in the inferior part of the anterior chamber.

Regardless of iridocorneal angle size 10 and 15 µg implants were well tolerated and elicited similar main and side effects, including hyperaemia, decreased IOP, miosis, fibrillary matrix deposition, Schwalbe's line cell-hypertrophy and –hyperplasia. These effects were not considered adverse due to their minimal nature, restricted location and the lack of ophthalmic and or gonioscopic findings. The relevance of the anterior chamber angle size therefore appears to be subsidiary.

In study TX12018, an increase in iridocorneal angle size (maximum circle fit) over the observation period is observed. Strikingly, this change affects all eyes (right and left) irrespective of the treatment. On the contrary, other repeat dose toxicity studies (TX12012 and TX12102) report a "narrowing of the approach to the iridocorneal angle" upon Bim SR treatment. The applicant was invited to discuss possible reasons for (i) the general increase of the maximum circle fit over time in all eyes and (ii) the respective discrepancy between the studies. This issue is now considered resolved.

Study TX12012 (issued January 2014) was conducted according to the study design outlined above. Also here, each treatment group was assembled from 3 subsets of animals according to the maximum circle fit: subset A: 343 to 429 µm; subset B: 436 to 479 µm; subset C: 486 to 522 µm. At initiation of the study, each treatment group consisted of 4 animals from each subset. The findings are generally consistent with study TX12018 except for the mentioned discrepancy regarding the implant-effect on the iridocorneal angle. Furthermore, one case of small peripheral anterior synechia and one case of significant iris atrophy (a full thickness iris hole) were identified. A concern was raised on the latter, which is now considered resolved.

Regarding IOP-measurements, the study explains that *"because of the transient reduction observed in the sham-injected left eye of Group 1, it was considered more appropriate to compare the delta% change in IOP of the right eyes of Group 1 (10 µg implant) versus the mean of the untreated left eyes of Groups 2 and 3. When the data were reviewed in this way, the delta% change in IOP of the treated right eyes of the three groups (Groups 1, 2, and 3) showed practically no difference between dose level."* The Assessor disagrees and holds the position that it is more rationale to normalize the IOP in treated eyes of all groups against the sham-injected left eyes of group 1. If all treated eyes are compared with the mean of group 2/3 untreated eyes, the IOP-lowering effect of the actual injection procedure is ignored. Hence, this approach is considered misleading and additionally raises the question of why a sham-injection was conducted at all. Hence, the applicant is encouraged to accordingly re-evaluate all IOP datasets, which use untreated instead of sham-injected for comparison.

The GLP-compliant study TX12102 is the most extensive amongst the repeat dose toxicity studies. The study was performed as outlined in the according study design above. The 72 animals were subdivided (similar to TX12012) to yield 4 subsets (18 animals per subset) with increasing mean maximum circle fits. These subsets were distributed evenly between the treatment groups. In line with studies TX12018 and TX12012, corneal findings were a function of length and number of implants rather than of the maximum phantom implant fit. Hence the latter aspect is confirmed to play a secondary role for implant tolerability (at least within the tested ranges of iridocorneal angle width). The findings in this study are basically consistent with the previous repeat dose toxicity studies. A single case of mild dyscoria (abnormal shape of the pupil) in group 2 (15 µg implant) and one case of anterior synechia in group 2 were identified. As both findings did not affect the optics of the eye, they were not considered adverse.

Notably, intact implants, partially biodegraded implants or implant remnants were found by gonioscopy in each implant toxicity study in a large number of eyes until the very end of the observation period: Single dose toxicity (all times represent end of observation period): In study TX09051 at day 171 (week 26) implants were intact but swollen in all treated eyes but one. Study TX09066 likewise describes swollen implants during week 27 of the dosing phase. In study TX10016 all implants remained visible through week 26 of the dosing phase. Study TX11076 (which, only includes the Generation-2 Bim SR formulation) describes signs of biodegradation for most implants after ~6 months. Nonetheless, implants were visible in one of three remaining animals during weeks 43 and 52 of the dosing phase. Repeat dose toxicity (all times represent end of observation period): In study TX12018 all implants were detectable until the end of the observation period (6 months/day 179) and

often described as bigger than original size. Likewise, study TX12012 identifies implants in the majority of treated eyes by week 31 of the dosing phase. Of note, study TX12102 detects implant remnants in most (if not all eyes) by the end of the dosing phase, which is 18 months (week 78).
Taken together, not even an approximate timescale by which the implant definitely undergoes complete biodegradation could be defined. As a consequence, it is unclear how long residual implant material might reside in the eye and represents a potential safety risk in the long term. In fact, study TX12102 reveals that by the end of the observation period (= 18 months) implant remnants are detectable in most if not all eyes. Importantly, these remnants often deposit within the trabecular meshwork, a structure, which is of fundamental importance for the drainage of the aqueous humour and thus to control the intraocular pressure (IOP). The long-term effect of these deposits (beyond week 78) on the IOP is unclear. Strikingly, right (treated) eyes of dogs in group 3 (treated three times with doses of 20 µg) of study TX12102 show a certain IOP-increase compared to baseline (IOP of the same eyes at study initiation) at the end of the observation period (see Figure 4 below).

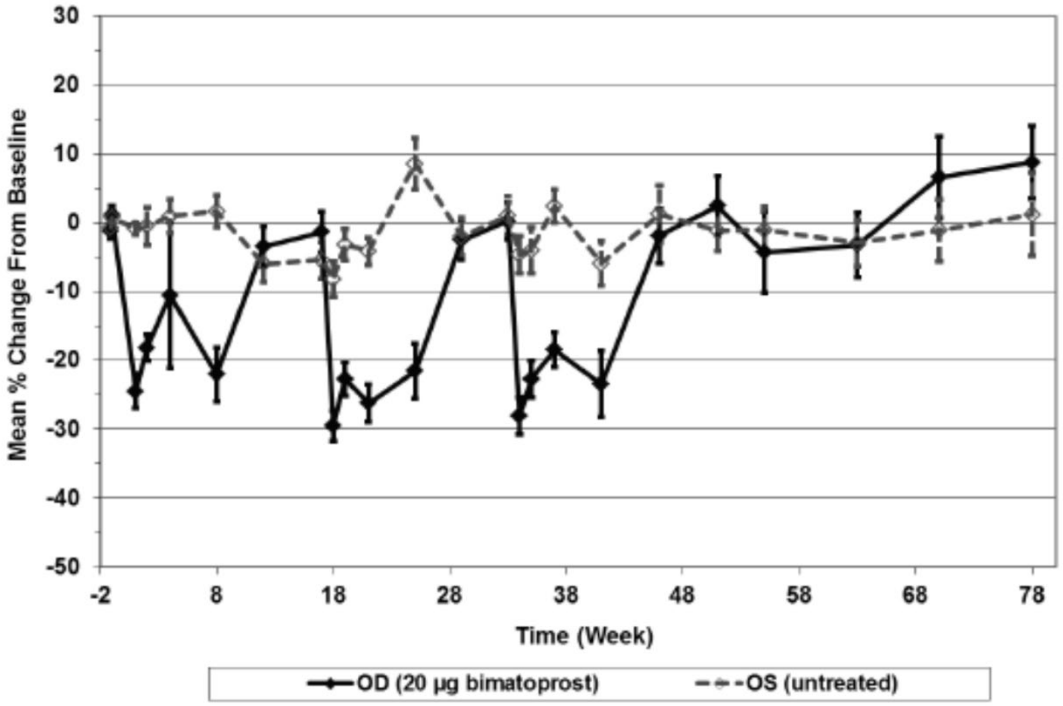


Figure 4: IOP group mean - % change from baseline - group 3

This deposition of implant remnants within the trabecular meshwork seems to be a very late event. Only a single animal (i.e. H09853) from group 3 was described to have an implant located within the trabecular meshwork in week 38. All other cases were described in week 78 at the end of the dosing phase. It is hence reasonable to surmise that the identified deposits resulted from the very first implant injection and more remnants are to accumulate within the trabecular meshwork which belong to the 2nd and 3rd injection.

Three circumstances substantiate the afore-mentioned concern, that the observed IOP-increase could be implant-triggered. (i) Only the group which received the highest load of implants (group 3) is affected by the late apparent IOP-increase. It is very possible that a certain amount of remnants must accumulate to elicit this effect. (ii) The effect is high and robust (similar extent over 2 consecutive timepoints) enough to consider a true IOP-increase. (iii) The depositing implant remnants within the trabecular meshwork are reminiscent of the pathology of pigment dispersion syndrome

(PDS)/pigmentary glaucoma, which is characterized by pigment accumulation within the trabecular meshwork disturbing the aqueous outflow.

In order to refute this concern, the applicant would have had to extend the observation period beyond 78 weeks, to further examine the IOP (or any other parameter). This was not done.

At all events (and irrespective of the specific concern above), the applicant does not provide sufficient data to conclude on the final fate of the implant and on the long-term condition of the test animal's eyes after the implant's entire elimination. As the deposition of implant remnants in the trabecular meshwork appears to be a very late event, it is very possible that other adverse events (including but not limited to increased IOP) occur on a timescale beyond the observation period of study TX-12102. Of note, limited biodegradability of the implant was also observed over the course of clinical studies. The applicant is advised to thoroughly discuss this matter and to comprehensibly rule out that implant-remnants represent a long-term health risk.

With respect to corneal changes (e. g. vascularisation; oedema), the applicant considers transient contact between the (mobile) implant and the corneal endothelium as a cause. Such contacts are possibly the result of postural changes. As humans are presumably more subjected to changes of head orientation (e.g. sleeping position) and lowering their sight (e.g. reading, working or due to frailty), the applicant is encouraged to discuss the probability of such corneal changes based on differences in eye position between dogs and human. In other words, is a higher implant mobility and thus a higher frequency of corneal changes to be expected in humans? Meanwhile, this question is considered answered.

Study TX12012 describes one case of a full thickness iris hole near the pupil margin (iris atrophy) in an eye given 20 µg implants. The applicant considers these findings attributable to intense miosis, an ocular response to prostamides unique to dogs (a statement made several times throughout the dossier). Hence, these adverse events are not expected to occur in humans. Previously, the applicant was encouraged to duly corroborate this statement on a weight-of-evidence basis. Therefore, the applicant was supposed to provide literature that (i) chronic intense miosis can cause such an event and (ii) such intense miosis upon prostamides would not appear in humans. By now, the applicant has provided sufficient literature to corroborate the two points raised above and the concern is considered resolved.

The applicant conducted a total of three GLP-compliant genotoxicity studies, in order to prove the active ingredient (= bimatoprost = AGN-192024) non-genotoxic. Of note, all three studies were completed in the 1990s. Names and completion dates of the studies are listed below:
Study G95BN52.503003: Salmonella/Escherichia Coli mutagenicity assay; completion 1995.
Study G95BN52.702005: Reduced volume L5178Y/TK+/- mouse lymphoma mutagenesis assay, completion 1996.
Study 19471-0-455OECD: in vivo mouse micronucleus assay with AGN-192024; completion 1998.

In addition, two GLP-compliant carcinogenicity studies are provided in the present dossier (ALG 053/984511 in mice and ALG 058/984512 in rats). Both studies are based on oral gavage of AGN-192024 at different dose levels and potential carcinogenicity was followed for two years (104 weeks). Both studies demonstrate this administration of AGN-192024 is non-carcinogenic. Hence, it is not expected that Bim SR implants mediate carcinogenicity, based on the API (= bimatoprost).

In summary, none of the studies listed above indicates a genotoxic or carcinogenic potential for AGN-192024 (or its S9-derived metabolites). It must be stressed, though, that the listed studies merely investigated the genotoxic/carcinogenic potential of the AGN-192024 as well as its (S9-induced or in

vivo) metabolites but none of the other constituents of the implant.
Over the course of implant degradation, certain (undefined) compounds may reach sufficient concentrations inside the anterior chamber to exert a genotoxic/carcinogenic effect. At this point, the Assessor wishes to remind that the applicant considered "chemical results from polymer degradation" as one possible reason for the IOP-lowering effect of the placebo-implant in the monkey-study TX09051 (see report TX09051-TX, p. 26, 3.11 Intraocular Pressure Measurements). Although it is appreciated that this monkey-study was conducted with a different implant formulation (i.e. "Generation 1") than the one designated for the clinics, none of the implant polymer formulations can be considered pharmacologically inert. No genotoxicity studies and no carcinogenicity studies were provided by the applicant, which account for the complex chemistry and pharmacology of the whole implant. Previously, the applicant was asked to discuss this issue and to provide reasonable arguments that no implant-associated compounds are of any genotoxic or carcinogenic concern. This issue is now considered resolved.

With respect to reproductive and developmental toxicity, the following GLP-compliant studies were provided by the applicant:

Fertility and early embryonic development:
Study 1801-013: Oral (gavage) fertility and general reproduction study of AGN-192024 in rats.

Embryo-fetal development:
Study TX 99020: Oral (gavage) dosage-range developmental toxicity study of AGN-192024 in mice.
Study 1801-019: Oral (gavage) developmental toxicity study of AGN-192024 in mice.
Study 1801-013P: Oral (gavage) dosage-range developmental toxicity study of AGN-192024 in rats.
Study 1801-018: Oral (gavage) developmental toxicity study of AGN-192024 in rats.
Study 1801-012P: Oral (stomach tube) dosage-range developmental toxicity study of AGN-192024 in rabbits.

Prenatal and postnatal development, including maternal function:
Study TX99057: Oral (gavage) developmental and perinatal/postnatal reproduction toxicity study of AGN-192024 in rats, including a postnatal behavioural/functional evaluation.

In all of these studies, bimatoprost was administered orally. The studies therefore correspond neither to the route of administration nor to the final formulation of the test article. Thus, the studies are of limited value for the evaluation of the toxicity profile of Bim SR implants. However, as systemic levels of AGN-192024 and its metabolite AGN-191522 during implant studies were usually below the limit of quantitation, it is very unlikely that implant-derived compounds will cause any of the adverse events, which appeared in the studies above (e.g. in rabbit-study 1801-012P no live fetuses were observed in any drug-treated animal). Hence, Bim SR implants are not considered of concern for reproduction and development. No concern was raised.

In addition, the applicant provided GLP-compliant studies on antigenicity (TX99054, TX99053) and immunotoxicity (TX99052). The studies provide evidence that AGN-192024 itself is neither antigenic nor immunotoxic.
As the systemic concentrations of AGN-192024 (and likely all implant components) upon Bim SR implantation are usually below the lower limit of quantitation, Bim SR is very unlikely to have a systemic antigenic or immunotoxic potential. No concern was raised.

As the test article is clearly proposed for ocular use, the applicant is asked to justify the lack of an ocular phototoxicity study.

No dependence studies were conducted as Bim SR does not represent any potential of abuse.
No dedicated metabolite or impurity studies were included in the toxicology package of this dossier.
No other toxicology studies were provided by the applicant.

3.2.5. Ecotoxicity/environmental risk assessment

Table 6: Summary of main study results

Substance (INN/Invented Name): Bimatoprost SR/Durysta			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	**2.4 ± 0.1**	Potential PBT (Y/**N**)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00000165	μg/L	> 0.01 threshold (Y/**N**)
Other concerns (e.g. chemical class)			(Y/**N**)

PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Bimatoprost is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore, bimatoprost is not expected to pose a risk to the environment.

3.2.6. Discussion on non-clinical aspects

Pharmacodynamics:

The preclinical in vivo data in monkeys and dogs support a reduction in IOP, however, such an effect is also seen in eyes receiving the DDS implant only. Thus, it is not clear to which extent an installation of the bimatoprost free DDS implant into the anterior chamber contributes to the proposed effects of therapeutic relevance. Moreover, the duration of the effect with respect to the DDS implant is not well described.

Overall the preclinical pharmacology is not in favour of a clear concentration dependent lowering of the IOP in hypertensive animals by IC Bim SR (generation 2). The main studies were performed in normotensive animals. The IOP lowering effects were described but were not corrected for DDS implant effects. Hence, the duration and quantification of the proposed therapeutic effects cannot be estimated. A possible rebound effect indicated by an elevated IOP over basal levels cannot be excluded, particularly in the "wash out phase" of Bim SR.

Matrix metalloproteases (MMP) might be involved in the protein turnover in the trabecular meshwork and thereby reduce outflow resistance. Thus, an in vitro investigation with human trabecular meshwork

cells showed enhanced expression levels of MMP and TIMP genes and MMP-1 on protein level, when treated with bimatoprost, but not with bimatoprost acid. However, these effects were seen with 1 mM (~416 µg/ml) bimatoprost, a concentration which has not been reached in aqueous humour by a single Bim SR application.

The final formulation Bim SR Generation 2 was not investigated in animals with elevated IOP, thus no proof of concept is available with the final product.

Pharmacokinetics:

The submitted non-clinical PK studies support the notion that ocular tissues in vicinity to the anterior eye chamber receive considerably higher bimatoprost concentrations when intracamerally administered as Bim SD implant than when topically administered as ophthalmic solution (as is e.g. the case with Lumigan). However, important multidisciplinary concerns were identified, specifically that the administered Bim SR implants did not dissolve in any of the in vivo studies submitted in Module 4.2, and that the implant alone also exerts a pharmacological efficacy that is comparable to the efficacy exerted by the bimatoprost content in Bim SR at 20 µg of bimatoprost. These aspects are thoroughly discussed in the non-clinical pharmacology and toxicology assessments or in the clinical assessment of this submission.

Considering the in vivo PK results submitted in Module 4.2, it is uncertain as to whether the Bim SR implant fully degrades after intracameral instillation into the anterior chamber of the treated eye. This results in an important safety concern as the remnant implant or fragments thereof possess very low dissolution kinetics and might consequently lead to adverse local ocular reactions in the long run. These reactions could potentially be irritation of the ocular tissues adjacent to the implants or implant fragments, or mechanical blocking of the trabecular meshwork by implant fragments with a subsequent increase of IOP and its related pathologic sequelae.

Three concerns were originally identified in the submitted non-clinical PK studies:

Originally, it was unclear whether intracameral Bim SR administration may cause relevant ocular DDIs that would agonise or antagonise the (topical) administration of other ophthalmologic products. Therefore, the applicant was expected to broadly discuss whether during the active release period of bimatoprost from intracamerally administered Bim SR pharmacokinetic DDIs with other ophthalmologic products could be relevant. The applicant replied to this concern that due to the low concentrations of bimatoprost achieved in ocular surface tissues after intracameral administration of Bim SR, DDIs in these tissues with topically applied products are unlikely. Vice versa, it can be expected that topically administered products will only achieve lower concentrations in tissues of the anterior eye chamber and that therefore DDIs with the bimatoprost content dissolving from Bim SR are unlikely as well. Apart from other aspects in the applicant's response, this PK aspect indeed renders the ocular DDI potential of Bim SR very low. It was therefore agreed that this original concern can be considered resolved.

Then, the applicant was originally requested to clarify whether the bioanalytical methods for tissue samples (aqueous humour, ICB, vitreous humour, retina, choroid, conjunctiva, periorbital fat, eyelid margin, and cornea) were validated according to adequate guidelines. In their responses, the applicant confirmed that bioanalytical methods for ocular tissue samples were not validated, though the applicant claims that they were demonstrated to be precise and accurate. This is acknowledged; the concern was therefore considered resolved.

Finally, systemic absorption was analysed after intracameral administration of Generation 1 and 2 bimatoprost SR. The applicant concluded a similar systemic exposure between both formulations after intracameral administration. However, the applicant was originally requested to discuss differences in terms of Tmax and Cmax (study report TX9051-TX). In addition, the applicant was requested to

provide local exposure data. In the response to this question, the applicant acknowledges that Cmax values for both bimatoprost and bimatoprost acid were near the assay LLOQs, which makes it challenging to determine any dose response or accurately evaluate differences in terms of Tmax. Both TX09051 TX and TX12102 TX A1 evaluated systemic exposure for toxicokinetic evaluation and did not assess local exposure. Local exposures were reported in Studies PK14025 PK and PK15022 PK. Differences between parameters could not be discussed. It was concluded that this issue is not pursued any further in the frame of this marketing authorisation application.

Toxicology:

In total, several other toxicological concerns were identified that need to be properly addressed by the applicant in order to be resolved. Of note, the following OC, addressing the presence of implant remnants beyond the observation period, strongly supports a related major clinical objection. They should hence be read in conjunction.

Most importantly, intact implants, partially biodegraded implants or implant remnants were found by gonioscopy in each implant toxicity study in a large number of eyes until the very end of the observation period. Taken together, not even an approximate timescale by which the implant definitely undergoes complete biodegradation could be defined. As a consequence, it is unclear how long residual implant material might reside in the eye and represents a potential safety risk in the long term. In fact, study TX12102 reveals that by the end of the observation period (= 18 months) implant remnants are detectable in most if not all eyes. Importantly, these remnants often deposit within the trabecular meshwork, a structure, which is of fundamental importance for the drainage of the aqueous humour and thus to control the intraocular pressure (IOP). The long-term effect of these deposits (beyond week 78) on the IOP is unclear. Strikingly, right (treated) eyes of dogs in group 3 (treated three times with doses of 20 µg) of study TX12102 show a certain IOP-increase compared to baseline (IOP of the same eyes at study initiation) at the end of the observation period. This deposition of implant remnants within the trabecular meshwork seems to be a very late event. Only a single animal (i.e. H09853) from group 3 was described to have an implant located within the trabecular meshwork in week 38. All other cases were described in week 78 at the end of the dosing phase. It is hence reasonable to surmise that the identified deposits resulted from the very first implant injection and more remnants are to accumulate within the trabecular meshwork which belong to the 2nd and 3rd injection.

Three observations constitute a substantial concern, that the mentioned IOP-increase might be implant-triggered. (i) Only the group which received the highest load of implants (group 3) is affected by the late apparent IOP-increase. It is very possible that a certain amount of remnants accumulates to elicit this effect. (ii) The effect is sufficiently high and robust (similar extent over 2 consecutive timepoints) to consider this a true and non-random IOP-increase. (iii) The depositing implant remnants within the trabecular meshwork are reminiscent of the pathology of pigment dispersion syndrome (PDS)/pigmentary glaucoma, which is characterized by pigment accumulation within the trabecular meshwork disturbing the aqueous outflow.

In order to refute this concern, the applicant would have had to extend the observation period beyond 78 weeks, to further examine the IOP (or any other parameter). This was not done.

At all events (and irrespective of the specific concern above), the applicant does not provide sufficient data to conclude on the final fate of the implant and on the long-term condition of the test animal's eyes after the implant's entire elimination. As the deposition of implant remnants in the trabecular meshwork appears to be a very late event, it is very possible that other adverse events (including but not limited to increased IOP) occur on a timescale beyond the observation period of study TX-12102. Of note, limited biodegradability of the implant was also observed over the course of clinical studies. The applicant is advised to thoroughly discuss this matter and to comprehensibly rule out that implant-

remnants represent a long-term health risk.
In response to this question, the applicant points out that the trabecular meshwork extends 360 degrees around the iris and (visible) implant remnants occupied only a small portion of the circumference, unlikely to affect drainage and aqueous humour flow. However, the applicant is again (and as written above) made aware that the present issue of implant remnants is not restricted to humour drainage from the trabecular meshwork. Rather, this would only be one scenario which might require further attention. The actual problem consists in the fact that (any sort of) health risks remain as long as parts of the implant remain. Hence, this issue must be considered unresolved. **(OC)**

Concerning the study design, most of the Bim SR studies in this dossier were not controlled against a placebo implant. Notably, the majority of implant effects (e.g. hyperaemia, corneal oedema, corneal vascularisation, Schwalbe's line cell hypertrophy/hyperplasia, fibrillar matrix deposition) were presumably caused by the physical presence of the implant rather than the active pharmaceutical ingredient (bimatoprost). However, a clear differentiation between pharmacological and physical effects is mostly impossible, because of the frequent aforementioned lack of placebo groups. Furthermore, both toxicity studies, which included a placebo implant (TX09051 and TX09066) were conducted with Bim SR of Generation 1 formulation. In consequence, the Generation 2 formulation was not placebo-controlled throughout the whole toxicological study package.

The Assessor wishes to emphasize that for a complete understanding of the toxicological profile of Bim SR, it would have been necessary to separate the effects of the AIP from the effects of the polymer-matrix. As the implant is a solid foreign body of which independent effects must be expected (in contrast to e.g., vehicle-controls in many other drug development programs), the applicant is supposed to duly justify this choice of methodology.

After subsequent communication between the Agency and the applicant, it is agreed that firstly, Generation 1 and Generation 2 implants differ only in the ratio of matrix components and, secondly, that the nominal weight of the placebo implant used in study TX09066-TX exceeds the weight of implants designated for clinical use. Hence, the used placebo implant suffices to also substantiate the safety of Generation 2 Bim SR implants. Hence, as far as safety aspects are concerned, this issue is considered resolved.

The conducted Bim SR studies also include measurements of the intraocular pressure (IOP) upon Bim SR treatment. As IOP-decrease is the intended clinical effect of bimatoprost, this activity is not toxicological but pharmacological by definition. Hence, the applicant legitimately refused a formal evaluation of this aspect as part of their toxicological package. However, several studies give cause for concern as to which extent the IOP-lowering effect is based on bimatoprost and not on the physical presence of the implant. Study TX09066 reveals an IOP-lowering effect of the placebo, which is slight but consistent over the observation period (6 months) (see report TX09066-TX, p. 34, text table 1). Furthermore, in study TX09051, which was conducted in cynomolgus monkeys, the placebo implant elicits a decrease in IOP, which is at least equivalent to the decrease observed in the highest dose group which received 120 µg bimatoprost (see report TX09051-TX, p.39, figure 2). At first, the Assessor wishes to emphasize that the time axis (on the abscissa) is not linear but segmented in a seemingly arbitrary manner (e.g. the distance between week 2 and week 5 is equivalent to the distance between week 17 and 26). This is misleading as in such a way the placebo effect (which is predominant between weeks 13 and 26) is ostensibly underestimated. Strikingly, in both studies (TX09066 and TX09051) the placebo exerts a robust IOP-lowering effect between three and five months after injection – an observation also made in study PK09109. In study TX09051 it is considered that the placebo's effect on IOP is due to inflammation or even due to chemical results of polymer degradation. In the latter case, this would suggest a mode of action for IOP-decrease based on polymer degradation and (at least to a certain extent) questions the purpose of the presence of bimatoprost in the implant.

Taken together, the conducted non-clinical placebo-implant controlled studies (TX09051, TX09066, PK09109, BIO-09-803 and BIO-009-787) challenge bimatoprost as the sole cause of the observed IOP-decrease. The applicant is asked to further substantiate that implant-released bimatoprost (at the reached concentrations in the eye) is key for the IOP-lowering effect of Bim SR.

In response to this concern, the applicant points out that within the first 3 months upon implantation the main IOP-lowering effect in TX09066-TX seems to derive from released bimatoprost. This is agreed. However, the IOP-lowering effect of the implant clearly exceeds (at least until week 22) the timeframe of bimatoprost release and it must be ruled in that the physical presence of the implant exerts this effect. While the mechanism behind IOP-lowering seen with placebo-implants is currently unknown, this issue remains as a factual observation and is considered to be relevant to be described in the SmPC in order to be resolved.

In study TX12018, an increase in iridocorneal angle size (maximum circle fit) over the observation period is observed. Strikingly, this change affects all eyes (right and left) irrespective of the treatment. In addition, other repeated dose toxicity studies (TX12012 and TX12102) report a "narrowing of the approach to the iridocorneal angle" upon Bim SR treatment. The applicant is invited to discuss possible reasons for (i) the general increase of the maximum circle fit over time in all eyes and (ii) the respective discrepancy between this study and the studies mentioned above.

The applicant comprehensively responded that this discrepancy arises from differences in the way the eyes were treated (with or without Lumigan) before baseline measurements of the iridocorneal angle. This is accepted.

Regarding IOP-measurements, study TX12012 explains that *"because of the transient reduction observed in the sham-injected left eye of Group 1, it was considered more appropriate to compare the delta% change in IOP of the right eyes of Group 1 (10 µg implant) versus the mean of the untreated left eyes of Groups 2 and 3. When the data were reviewed in this way, the delta% change in IOP of the treated right eyes of the three groups (Groups 1, 2, and 3) showed practically no difference between dose level."* The Assessor disagrees and holds the position that it is more rationale to normalize the IOP in treated eyes of all groups against the sham-injected left eyes of group 1. If all treated eyes are compared with the mean of group 2/3 untreated eyes, the IOP-lowering effect of the actual injection procedure is ignored. Hence, this approach is considered misleading and additionally raises the question of why a sham-injection was conducted at all. Hence, the applicant is encouraged to accordingly re-evaluate those IOP datasets, which were evaluated in the criticized way.
In response to this concern the applicant explains that "sham injection"-effect on IOP is immediate and transient returning to baseline within the first two weeks after injection. The Assessor does not consider this explanation sufficient to prefer untreated eyes over sham-injected eyes as the rational control group. Hence this issue remains.

Study TX12012 describes one case of a full thickness iris hole near the pupil margin (iris atrophy) in an eye given 20 µg implants. The applicant considers these findings attributable to intense miosis, an ocular response to prostamides unique to dogs (a statement made several times throughout the dossier). Hence, these adverse events are not expected to occur in humans. The applicant is encouraged to duly corroborate this statement on a weight-of-evidence basis. Therefore, the applicant should provide literature that (i) chronic intense miosis can cause these events and (ii) such intense miosis upon prostamides would not appear in humans.
Upon this request, the applicant provided substantial literature references to consider this issue resolved.

As the test article is clearly proposed for ocular use, the applicant is asked to justify the lack of an ocular phototoxicity study.

In response to this concern, the applicant emphasizes that "according to ICH S10, the initial consideration for assessment of photoreactive potential is whether a compound absorbs photons at any wavelength between 290 and 700 nm. A compound that does not have a Molar Extinction Coefficient (MEC) greater than 1000 L mol 1 cm 1 at any wavelength between 290 and 700 nm is not considered to be sufficiently photoreactive to result in direct phototoxicity. Bimatoprost does not absorb ultraviolet radiation between 280 and 700 nm and therefore possesses negligible phototoxicity or photosensitisation potential." This is uncorroborated. The applicant is requested to provide appropriate data to underpin their statement that bimatoprost does not absorb light within this spectrum.

Although the applicant states that no novel excipients are used with Bim SR, it is noted that resomer-related safety documentation should be provided in module 4.
The applicant responded that resomer related safety documentation (Evonik Resomer Technical Information) has been provided in Module 4.3. This issue is considered resolved.

Finally, two concerns were identified in the submitted ERA:

The applicant has provided an experimentally determined log Kow value. A study protocol for the study procedure was not submitted. According to the CHMP Q&A document on the "Guideline on environmental risk assessment of medicinal products for human use" (EMA/CHMP/SWP/44609/2010 Rev. 1), the log Kow value should be determined experimentally. Studies performed in accordance with OECD Test Guidelines are preferred. A calculated value is generally not acceptable. The applicant is requested to provide a study protocol on an experimentally derived n-octanol/water partition coefficient (log Kow) for bimatoprost.
Following communication between the Agency and the applicant, no respective study protocol has been submitted under eCTD 1.6 Environmental Risk Assessment. Hence this concern remains.

Furthermore, it is noted in the SmPC that, "DURYSTA should be limited to two implants per eye." Therefore, as a worst case, the dosage of 0.04 mg/120 days should be used to determine the daily dose. We kindly ask the applicant to update the ERA accordingly.
Recently, the applicant has provided an updated calculation on this matter. This is acceptable and the ERA has been updated accordingly.

3.2.7. Conclusion on non-clinical aspects

Several other concerns were identified that all need to be adequately addressed in order to be resolved.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Table 7: Tabular listing of clinical studies

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Dose-ranging	192024-041D	5.3.5.1	Evaluate the safety of an intracameral implant of Bimatoprost SR in patients with OAG; Evaluate the IOP-lowering effects of an intracameral implant of Bimatoprost SR in patients with OAG	Phase 1/2, multicenter, dose-ranging (with repeat administration), open-label (with masked efficacy evaluations), randomized, paired-eye comparison Active control: LUMIGAN 0.03% eye drops, once daily	Bimatoprost SR; 6, 10, 15, and 20 µg (2 × 10 µg); intracameral implant	Enrolled: 109 (34 Gen 1 Bimatoprost SR; 18 Gen 2 Bimatoprost SR 6 µg; 21 Gen 2 Bimatoprost SR 10 µg; 21 Gen 2 Bimatoprost SR 15 µg; 15 Gen 2 Bimatoprost SR 20 µg)	Patients with OAG and Grade ≥ 3 iridocorneal angle inferiorly by gonioscopy in the study eye, and OAG or OHT in the fellow eye; both eyes required IOP-lowering treatment	Approx. 24 months	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	192024-091	5.3.5.1	Evaluate the IOP-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR in patients with OAG or OHT after initial and repeated administrations	Phase 3, multicenter, randomized, patient- and efficacy evaluator masked, parallel-group, repeat administration Active control: timolol 0.5% eye drops, twice daily	Bimatoprost SR; 10 and 15 µg; intracameral implant	Enrolled: 594 (198 Bimatoprost SR 10 µg; 198 Bimatoprost SR 15 µg; 198 timolol eye drops)	Patients with OAG or OHT and open iridocorneal angle inferiorly by clinical gonioscopy in the study eye, and OAG or OHT in the fellow eye; both eyes required IOP-lowering treatment	Approx. 20 months	Complete; Full
Efficacy and safety	192024-092	5.3.5.1	Evaluate the IOP-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR in patients with OAG or OHT after initial and repeated administrations	Phase 3, multicenter, randomized, patient- and efficacy evaluator masked, parallel-group, repeat administration Active control: timolol 0.5% eye drops, twice daily	Bimatoprost SR; 10 and 15 µg; intracameral implant	Enrolled: 528 (176 Bimatoprost SR 10 µg; 176 Bimatoprost SR 15 µg; 176 timolol eye drops)	Patients with OAG or OHT and open iridocorneal angle inferiorly by clinical gonioscopy in the study eye, and OAG or OHT in the fellow eye; both eyes required IOP-lowering treatment	Approx. 20 months	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	192024-093	5.3.5.1	Evaluate the IOP-lowering effect and safety of Bimatoprost SR compared with SLT in patients with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence)	Phase 3, multicenter, paired-eye, randomized, efficacy evaluator masked, 2-stage Active control: SLT	Bimatoprost SR; 10 and 15 µg; intracameral implant	**Stage 1** Enrolled: 57 (28 Bimatoprost SR 15 µg/ SLT; 29 SLT / Bimatoprost SR 15 µg) **Stage 2** Enrolled: 183 (91 Bimatoprost SR 10 µg/ SLT; 92 SLT / Bimatoprost SR 10 µg)	Patients with OAG or OHT in each eye; both eyes required IOP-lowering treatment	Approx. 12-24 months	Ongoing; Interim

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	192024-095	5.3.5.1	Evaluate the IOP-lowering effect and safety of Bimatoprost SR compared with SLT in patients with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence)	Phase 3, multicenter, paired-eye, randomized, efficacy evaluator masked, 2-stage Active control: SLT	Bimatoprost SR; 15 µg; intracameral implant	**Stages 1 and 2** Enrolled: 144 (72 Bimatoprost SR 15 µg / SLT; 72 SLT / Bimatoprost SR 15 µg)	Patients with OAG or OHT in each eye; both eyes required IOP-lowering treatment	Approx. 12 months	Complete; Full

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	1698-301-007	5.3.5.2	Evaluate the duration of IOP-lowering effect and safety of Bimatoprost SR in patients with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence)	Phase 3b, multicenter, open-label[a] Control: none	Bimatoprost SR; 10 and 15 µg; intracameral implant	Enrolled: 381 (62 Bimatoprost SR 15 µg; 319 Bimatoprost SR 10 µg)	Patients with OAG or OHT and an open iridocorneal angle inferiorly by clinical gonioscopy in the study eye, requiring IOP-lowering treatment	At least 30-48 months	Ongoing; Interim

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	1698-304-007	5.3.5.4	Evaluate the 24-hour IOP-lowering effect and the safety of Bimatoprost SR in subjects with OAG or OHT	Phase 3b, multicenter, open-label Control: none Reference cohort: LUMIGAN 0.01% eye drops, once daily	Bimatoprost SR; 10 µg; intracameral implant	Enrolled[b]: 37 (31 Bimatoprost SR; 6 LUMIGAN 0.01%)	Patients with OAG or OHT in at least 1 eye that requires IOP-lowering treatment and has an open iridocorneal angle inferiorly by clinical gonioscopy	Approx. 12 months	Complete; Full

Gen = generation; IOP = intraocular pressure; NA = not applicable; OAG = open-angle glaucoma; OHT = ocular hypertension; PRN = as needed; SLT = selective laser trabeculoplasty; SR = sustained release; US = United States

a. For subjects enrolled prior to Amendment 1, this was a dual arm study in which subjects were randomized using a 1:1 ratio to either receive 10 µg or 15 µg Bimatoprost SR in the study eye. The subject, investigator, and the site staff were masked to the study treatment dose strength assignment. For subjects enrolled after Amendment 1, all subjects received 10 µg Bimatoprost SR open-label, and no randomization, masking, or stratification were performed.

b. Enrollment as of the data cutoff date for the first database lock. The first database lock occurred when 100% of subjects had completed the primary visit (i.e., the Week 8 Sleep Lab visit) or prematurely discontinued prior to the Week 8 Sleep Lab visit.

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

For the characterisation of bimatoprost, the applicant provided historical data from their initial MAA of Lumigan ophthalmic solution, which shares the same active ingredient – bimatoprost – and has been approved as a topical therapy for IOP-lowering since 2002 in the EU. The provided data and legacy reports inform about the clinical pharmacology of bimatoprost following both the intravenous as well as

the intraocular route of administration. In the scope of the current MAA for Durysta, newly generated data on the systemic exposure of bimatoprost and its primary metabolite bimatoprost acid following intracameral administration of the bimatoprost SR implant in patients with open angle glaucoma or ocular hypertension were provided. These systemic PK data were evaluated in the Phase 1/2 dose-ranging study 192024-041D.

Absorption

The absorption of bimatoprost was characterised during the clinical programme of Lumigan. In the current MAA for bimatoprost SR, data from the initial Lumigan MAA were provided as legacy protocols. Data on absorption following intravenous administration were provided with legacy study 192024-005, data on absorption following single and multiple ocular doses of bimatoprost 0.03% solution were provided with legacy study 192024-006. In the scope of the current MAA for Durysta, systemic PK data were provided.

Ocular bimatoprost (Lumigan)

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

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

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

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

Intravenous bimatoprost

The PK of radioactively labelled bimatoprost following intravenous administration was investigated during the clinical programme of Lumigan in a small single-site (US), open-label study (study 192024-

005). The study objectives included the characterisation of a) blood and plasma radioactivity of 3H-AGN 192024, b) blood PK of AGN 192024 and its human metabolite AGN 191522, and c) urinary and fecal excretion of radioactivity. In this study, six healthy male volunteers received a single bolus intravenous dose of 0.01% (100 µCi/mL) 3H-bimatoprost solution at a mean (± SD) dosage of 3.12 ± 0.12 µg/kg (3.28 ± 0.12 µCi/kg). Blood, plasma, urine, feces, and fecal wipe samples were collected up to 168 hours (four subjects had additional fecal and fecal wipe samples collected up to 192 hours). Samples were analysed for total radioactivity. Blood samples were analysed for intact bimatoprost and bimatoprost acid concentrations. A summary of the mean (± SD) pharmacokinetic parameters is listed in below Table 8.

Table 8: Mean PK parameters in healthy male volunteers following a single intravenous administration of ^{3}H-bimatoprost

Pharmacokinetic Parameter	Radioactivity		Bimatoprost in Blood
	Blood	Plasma	
$AUC_{0\text{-}TLDC}$ (ng·hr/mL)[a]	6.22 ± 0.45	11.2 ± 0.73	2.14 ± 0.51
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	-	-	2.18 ± 0.51
K (hr^{-1})	0.3983 ± 0.05	0.3386 ± 0.09	0.8985 ± 0.33
$T_{1/2}$ (hr)	1.74 ± 0.21	2.05 ± 0.55	0.771 ± 0.32
CL (L/hr)	-	-	118 ± 15.8
CL (L/hr/kg)	-	-	1.50 ± 0.33
V_{ss} (L)	-	-	52.6 ± 18.3
V_{ss} (L/kg)	-	-	0.670 ± 0.27

a – blood and plasma radioactivity, ng equivalents·hour/mL
- – Not applicable
$AUC_{0\text{-}TLDC}$ = area under the concentration-time curve to the last measurable concentration; $AUC_{0\text{-}\infty}$ = area under the concentration-time curve to infinity; CL = total clearance; K = elimination rate constant; $T_{1/2}$ = terminal half-life (harmonic mean); V_{ss} = volume of distribution at steady state

Maximum concentrations of radioactivity in both blood and plasma were reached at the first collection time point, 2 minutes postdose, with mean values of 14.5 and 23.6 ng equivalents/mL, respectively. For blood and plasma, mean concentrations steadily declined with time to below quantifiable limits (0.107 to 0.206 ng equivalents/mL for blood and 0.107 to 0.145 ng equivalents/mL for plasma) by 9 and 12 hours postdose, respectively.

The multi-exponential concentration-time profiles suggest a rapid distribution phase followed by gradual elimination of radioactivity. The mean radioactivity $T_{1/2}$ values in blood and plasma were 1.74 and 2.05 hours, respectively. Based on the blood-to-plasma ratio at 4 hours postdose, there was little transfer of radioactivity into the cellular fraction.

Blood concentrations of intact bimatoprost declined rapidly, with a mean terminal $T_{1/2}$ of 0.771 hours and declined to below the lower limit of quantitation (0.025 ng/mL) by approximately 3 to 6 hours postdose. The systemic blood clearance of bimatoprost was high, averaging 1.50 L/hr/kg. The mean steady-state volume of distribution (V_{ss}) was 0.670 L/kg, indicating that bimatoprost is moderately distributed into tissues.

Concentrations of bimatoprost acid in blood were detected in only 4 of the 6 subjects and only between 0.083 and 1.5 hours postdose. The maximum mean concentration, 0.120 ng/mL, was reached at 0.5 hours postdose. At each time point, concentrations of bimatoprost acid were lower than those of bimatoprost.

The main route of excretion of ^{3}H-bimatoprost derived radioactivity following the intravenous dose was via the urine. A mean of 67.0% of the dose was excreted via the urine through 168

hours postdose, and 24.9% was excreted in the feces by 192 hours postdose. The mean 0- to 192-hour recovery of radioactivity in excreta, including fecal wipes, was 92.0%.

Overall, drug-derived radioactivity and bimatoprost blood concentrations declined rapidly with a mean $T_{1/2}$ of less than 1 hour for bimatoprost. At each time point, concentrations of bimatoprost acid were lower than those of bimatoprost. Renal excretion was the prevalent route of elimination of radioactivity, with approximately 67% of the administered dose excreted in urine and approximately 25% of the dose recovered in feces.

Newly generated data with the intracameral implant Bimatoprost SR

During the clinical programme of Durysta, systemic exposure data were generated in the Phase 1/2 dose ranging study 192024-041D. This was a 24-Month, multicentre, open-label, paired-eye comparison in successive cohorts of patients with OAG. Supporting information assuring GCP compliance was collected from sites outside the United States in compliance with 21 CFR 312.120. For study details compare section *3.2 Dose response study(ies)*.

Drug concentration measurements

Therapeutic drug monitoring was performed at selected sites only. Blood samples were collected at the study site, and the processed plasma samples were sent to the central laboratory (Covance Central Laboratory Services, Indianapolis, IN, or a designated regional facility) for storage. Samples were stored at the central laboratory until subsequent forwarding to a vendor for bioanalysis. Plasma concentrations of bimatoprost and AGN-191522 from patients who had received bimatoprost preservative-free intracameral drug delivery system treatment were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Blood samples for drug concentration measurement were collected at Baseline, Weeks 4, 8, 12, 16, and 20; and Months 6, 12, and 24/Early Exit. Some patients also had blood samples collected at Day 2, Day 8, and Week 2. Blood sample collections for drug concentration measurement were discontinued after the Week 16 visit if there was at least 1 below the limit of quantitation (BLQ) reading at Week 16 or later visits.

For patients who received a second administration of bimatoprost preservative-free intracameral drug delivery system, starting after the second administration, blood samples for drug concentration measurement were collected only at the following times: 4, 8, 12, 16, and 20 weeks after the second administration, 6 and 12 months after the second administration, and at study exit. Blood sample collections for drug concentration measurement were discontinued after the Week 16 visit (16 weeks after the second administration) if there was at least 1 BLQ reading at that or later visits.

Because of the use of Lumigan in the fellow eye, blood samples were collected the morning after the daily topical dose that was administered the prior evening. Plasma samples were analysed at Covance (formerly Tandem Labs, Salt Lake City, UT).

Results

Following administration of up to 2 doses of the same strength of bimatoprost SR (6, 10, or 15 µg) after a minimum of 90 days and up to 12 months following the first administration, or one 20 µg dose, plasma concentrations of bimatoprost and its primary metabolite, bimatoprost acid, were below the lower limit of quantitation (0.001 to 0.005 ng/mL and 0.01 to 0.05 ng/mL, respectively) in the majority of the samples (Module 5.3.5.1, Study 192024-041D). All observed bimatoprost concentrations were at least 14-fold lower than the maximum mean blood concentration reported after topical administration of LUMIGAN 0.3 mg/mL (0.08 ng/mL; Module 5.3.3.1, Study 192024-006 and Report PK-98-119).

Plasma samples from patients who received 6, 10, 15, or 20 µg of bimatoprost preservative-free intracameral drug delivery system were analysed for concentrations of bimatoprost and its metabolite, AGN-151922. A total of 722 samples were received for analysis, of which 44 were not analysed per protocol since concentrations were BLQ at the Week 16 visit or later. There were 43 deviations related to PK blood draws outside the visit window indicated in the protocol and these deviations ranged from 1 to 16 days. Given that bimatoprost and AGN-151922 were measurable above the lower limit of quantitation (LLOQ) only sporadically, these time deviations did not affect the interpretation of the PK results.

Of the 678 samples available for bimatoprost analysis per protocol, 25 samples had insufficient volume for analysis, were haemolysed, or were collected as whole blood rather than plasma and thus were not analysed. An additional 5 samples were analysed for bimatoprost concentrations, but the results were not reportable due to unacceptable response of the internal standard. Of the 653 samples with reportable bimatoprost concentrations, 55 (8.4%) had measurable plasma concentrations while the remaining (91.6%) were BLQ. Bimatoprost was measured sporadically in plasma samples obtained from patients receiving 6, 10, 15, or 20 µg implants with no obvious correlation between dose strength or implant generation (Gen 1 or 2) and plasma concentrations. As a result, no PK parameters for bimatoprost could be calculated. The highest concentration of bimatoprost observed after a single implant administration was 5.02 pg/mL (15 µg Gen 2 implant). No patient had measurable bimatoprost concentrations following repeat administration of bimatoprost preservative-free intracameral drug delivery system.

Of the 678 samples available for bimatoprost acid analysis per protocol, 19 samples had insufficient volume for analysis, were haemolysed, or were collected as whole blood rather than plasma and thus were not analysed. An additional 1 sample was analysed for bimatoprost acid concentrations, but the result was not reportable due to unacceptable response of the internal standard. Of the 659 samples with reportable bimatoprost acid concentrations, 7 (1.1%) had measurable plasma concentrations while the remaining (98.9%) were BLQ. Because bimatoprost acid was measured only sporadically, no PK parameters could be calculated. Those patients with measurable bimatoprost acid concentrations were all treated with Gen 2 implants, and the concentrations of bimatoprost acid ranged from 10.5 to 24.5 pg/mL. Two patients had measurable bimatoprost acid concentrations at Baseline. These concentrations were near the limit of detection and may represent variability in the assay. No patient had measurable bimatoprost acid concentrations following repeat administration of bimatoprost preservative-free intracameral drug delivery system.

The maximal bimatoprost plasma concentration observed following administration of up to 20 µg bimatoprost preservative-free intracameral drug delivery system was 5.02 pg/mL. Using an average blood-to-plasma partition ratio of 0.858 for bimatoprost (Report CPQS-11-004), this concentration was 14-fold lower than the mean blood C_{max} observed previously following once daily bilateral ocular dosing of 0.03% Lumigan for 14 days in healthy volunteers (Study 192024-006; Report PK-98-119). The maximal bimatoprost acid concentration observed following administration of up to 20 µg bimatoprost preservative-free intracameral drug delivery system was 24.5 pg/mL whereas bimatoprost acid was BLQ following ocular dosing of 0.03% Lumigan. It should be noted that the LLOQ for bimatoprost acid in Study 192024-006 was 50.0 pg/mL, while the LLOQ for most samples (> 99%) in the present study 192024-041D was 10.0 pg/mL.

Distribution

Distribution of bimatoprost was characterised during the clinical programme of Lumigan:

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of

bimatoprost remains unbound in human plasma. The in vitro binding of bimatoprost to synthetic melanin was ~20% at concentrations of 0.21 to 104 µg/mL. The overall extent of melanin binding was not dependent on concentration, and the binding was reversible.

Elimination/ Biodegradation

Data on the size of the bimatoprost SR implant over time was provided with the study reports of certain studies, including studies 091, 092, 093, 095, 041D.

The following information on implant size analysis was provided by the applicant with the study report for study 041D:

Implant size and degradation were assessed by the reading centre using OCT and the investigator using gonioscopy. Implant size was assessed by measuring the cross-sectional diameter of the implant.

Overall, implants swelled (increased in diameter) from Week 12 to Month 6. By Month 12, the average implant diameter had decreased from that at Baseline because of ongoing degradation of the implant matrix.

For the clinical assessment using gonioscopy, investigators were asked to assess whether the implants were visible and to estimate the size of the implant relative to the original implant size. In the Gen 2, 20 µg group, the percentage of patients with 2 visible implants was > 70% through Month 12 and had decreased to 50% by Month 24 of Cycle 1. In the Gen 2, 15 and 10 µg groups, the number of patients with a visible implant remained high throughout the study (> 85% at Month 24 of Cycle 1), and in the Gen 2, 6 µg group, the number of patients with a visible implant was 80% at Month 12 and had decreased to 50% at Month 24 of Cycle 1.

Overall, similar to the assessment from the OCT, implants swelled after administration then gradually decreased in size. For Gen 2 implants, approximately 50% of visible implants had decreased to 0% to 25% of the original size by Month 12. At Month 24, 70% of visible implants have decreased to 0% to 25% of the original size.

Dose proportionality and time dependencies

N/A

Special populations

No studies investigating intrinsic factor PK, extrinsic factor PK, or population PK were performed since systemic exposure to bimatoprost following intracameral administration of bimatoprost SR in humans was low and therefore considered negligible by the applicant.

Pharmacokinetic interaction studies

No data were provided.

Pharmacokinetics using human biomaterials

Plasma Protein Binding

The in vitro plasma protein binding of bimatoprost was determined by an ultrafiltration method (Module 5.3.2.1 Study PK-99-121). The extent of drug binding was measured in human plasma, 4.5% human serum albumin and 0.75% α1-acid glycoprotein. Plasma, glycoprotein, and albumin samples were spiked with 3H-bimatoprost at concentrations of 1, 2, 5, 10, and 250 ng/mL. Samples underwent

ultrafiltration for 12 minutes at 37°C and radioactivity was measured in the ultrafiltrate and protein samples by liquid scintillation counting.

Table 9: Percent unbound bimatoprost in human plasma, human serum albumin and α1-acid glycoprotein

Media	Concentration range (ng/mL)	Percent Unbound (Mean ± SD)[a]
Human Plasma	1 – 250	12.2 ± 0.7
4.5% Human Serum Albumin	1 – 250	43.9 ± 1.7
0.75% α1-Acid Glycoprotein	1 – 250	56.5 ± 3.7

a – n = 8 at each concentration

Overall, the unbound fraction of bimatoprost in human plasma was approximately 12%. The extent of binding did not change over a wide range of plasma bimatoprost concentrations. Bimatoprost was moderately unbound to human serum albumin and α1-acid glycoprotein, indicating it is a poor ligand for these plasma proteins.

Blood-to-Plasma Partitioning

The in vitro blood-to-plasma partitioning ratio of bimatoprost and bimatoprost acid was determined by liquid chromatography-tandem mass spectrometry following incubation of bimatoprost (1, 2, and 10 pg/mL) or bimatoprost acid (10, 15, and 30 pg/mL) in human whole blood at 37oC for 0, 10 and 60 minutes (Module 5.3.1.4 Study CPQS-11-004). No results were available for samples spiked with 1 pg/mL bimatoprost and 10 pg/mL bimatoprost acid due to inadequate analytical sensitivity. The results from 2 and 10 pg/mL bimatoprost and 15 and 30 pg/mL bimatoprost acid showed that bimatoprost and bimatoprost acid do not preferentially partition into blood cells. The average blood-to- plasma ratios were 0.858 and 0.788 for bimatoprost and bimatoprost acid, respectively.

Melanin Binding

Bimatoprost melanin binding was determined using ultracentrifugation. Binding was measured in synthetic melanin suspensions spiked with 0.5, 1, 2, 5, 50, and 250 µM 3H-bimatoprost (0.21, 0.42, 0.83, 2.1, 21, or 104 µg/mL) (Module 4.2.2.3 Report PK-99-045). Drug-melanin suspensions were incubated for up to 6 hours at 37°C. Samples were taken at 0, 4 and 6 hours, and underwent ultracentrifugation at 4°C for 30 minutes. Radioactivity was measured in the supernatant (free) and melanin suspension (total) by liquid scintillation counting.

The in-vitro binding of 3H-bimatoprost to synthetic melanin was approximately 20% at concentrations of 0.21 to 104 µg/mL. The overall extent of melanin binding was not dependent on concentration and the binding was reversible.

In Vitro Metabolism

The metabolism of bimatoprost was investigated in human ocular tissue homogenates (corneal epithelium, corneal stroma/endothelium, conjunctiva, iris-ciliary body and sclera; Module 4.2.2.4 Report BIO-95-087). Bimatoprost was not extensively metabolized in the human eye. No metabolism was observed in corneal epithelium, corneal stroma/endothelium, conjunctiva or sclera and minimal metabolism was observed in human iris-ciliary body where the rate of disappearance for bimatoprost was 0.6 nmol/mg protein/hr. There is evidence that hydrolysis of bimatoprost to bimatoprost acid is not a prerequisite for its ocular hypotensive activity (Cantor 2007; Krauss 2004).

The in vitro metabolism of bimatoprost was evaluated by incubating 200 µg of bimatoprost for 24 hours at 37°C in 1.7 mL of Waymouth's media containing human liver slices (Module 5.3.2.2 Study PK-

95-013). A total of 37.8 ± 14.5% of bimatoprost was hydroxylated and conjugated to a glucuronide over a 24-hour incubation. In a second study, the in vitro metabolism of radiolabelled 3H-bimatoprost was investigated in rat, monkey, and human liver slices (Module 4.2.2.4 Study PK-97-004). 3H-bimatoprost (1 µCi/100 µg) in 1.7 mL of Waymouth's buffer was incubated with both male and female cynomolgus monkey and female human liver slices (2 slices/vial) for 18 hours. The percentage of the 3H-bimatoprost that was metabolized by the slices over the 18 hr incubation was 76.8 ± 5.9% in female human liver. An average of 13.3 ± 1.8% of bimatoprost acid was formed in female human liver slices. Bimatoprost was metabolized by deamidation (bimatoprost acid) and glucuronidation in the liver slices of both the species.

The metabolite profile of bimatoprost in human liver microsomes was compared to those of mouse, rat, rabbit and monkey (Module 5.3.2.2 Study PK-99-047). Bimatoprost (1 µCi/28.8 nM 3H-bimatoprost) was incubated with 0.25 mg/mL microsomal protein in 100 mM potassium phosphate buffer (pH 7.4) at 37°C over a period of 10 or 60 minutes. The reaction was initiated by the addition of NADPH regenerating system. Bimatoprost was extensively metabolized by human liver microsomes to three major metabolites (HM4, HM6 and HM11) and several minor metabolites. Based on HPLC retention times, the metabolites of bimatoprost in human liver microsomes were also observed in mouse, rat, rabbit, and monkey. The results of the current study indicate that bimatoprost undergoes P450 mediated oxidative metabolism in all species tested. The metabolite profile was similar across all five species examined with the exception that only rabbit produced significant amount of bimatoprost acid.

CYP Enzymes Involved in the Metabolism of Bimatoprost

In order to identify the specific cytochrome P-450 isoform(s) responsible for the metabolism of bimatoprost in vitro, 3H-bimatoprost was incubated with human liver microsomes from 16 donors in 100 mM potassium phosphate buffer (pH 7.4) using 0.25 mg/mL microsomal protein and 1 µCi/28.8 nM 3H-bimatoprost (Module 4.2.2.6 Study PK-99-037). The reaction was initiated by the addition of NADPH regenerating system. Each incubation was performed at 37°C over a period of 5 or 10 minutes.

Reversed-phase HPLC coupled with radioisotopic detection was used to quantify the metabolites of bimatoprost. Bimatoprost was extensively metabolized by human liver microsomes to three major and three minor metabolites. The structures of the three major metabolites were identified by LC-MS/MS as the hydroxylated analogues of bimatoprost. The formation rate of the three oxidative metabolites from bimatoprost correlated best with the activity of CYP3A4/5 isozyme. The involvement of CYP3A4/5 in bimatoprost metabolism was further confirmed by inhibition of metabolite formation by troleandomycin, a specific mechanism-based inhibitor of CYP3A4/5. Bimatoprost metabolism was also inhibited by ketoconazole, a specific competitive inhibitor of CYP3A4/5. Involvement of CYP3A4/5 in bimatoprost metabolism was further confirmed by the use of cloned human cytochrome P450 isozymes. Marked increases in the formation rates of the three oxidative metabolites were only observed when bimatoprost was incubated in the presence of cDNA expressed CYP3A4. In conclusion, by correlation analysis, chemical inhibition studies and the use of cDNA expressed P-450 isozymes, hydroxylation of bimatoprost to its three oxidative metabolites in human liver microsomes appears to be catalysed by CYP3A4/5. However, due to extremely low drug concentrations of bimatoprost (≤0.00224 ng/mL; Module 5.3.5.1 Study 192024-041D) following intracameral dosing of bimatoprost SR (10 µg/eye), no drug-drug interactions are anticipated.

3.3.1.2. Pharmacodynamics

No PD studies were provided with this application.

Mechanism of action

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

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

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

Primary and Secondary pharmacology

Provided information on pharmacodynamics are limited to the IOP lowering effect of bimatoprost, which were evaluated in the Phase 1 study 192024-041D and the Phase 3 studies 192024-091, 192024-092, and 192024-095.

3.3.2. Discussion on clinical pharmacology

The clinical pharmacology programme for Durysta comprises systemic PK data from a phase 1/2 dose ranging study (192024-041D) supplemented with legacy reports from the original MAA for Lumigan bimatoprost eye drop solution, which has been approved as a topical therapy for IOP-lowering since 2002 in the EU. Provided data on Lumigan include pharmacological characterisation of bimatoprost following intravenous and intraocular administration. The newly generated data for Durysta bimatoprost SR provided for this procedure aim to characterise the systemic PK over a duration of 24 months following intracameral implantation.

Generally, the pharmacological data provided for bimatoprost (from Lumigan MAA) do not give rise to concern. Lumigan has been approved throughout the European Union for more than 20 years and the pharmacological profile is well established.

Data on the systemic exposure following intracameral implantation of bimatoprost SR show that bimatoprost was only detected in 8.4% of evaluable samples (55/653; remaining samples were below the limit of quantification). In these samples only low levels of bimatoprost were reached in the serum. The highest serum concentration of bimatoprost detected in the 24 months follow up duration after implantation of a single bimatoprost SR implant (study 041D) was 5.02 pg/mL (15 µg implant), which is approximately 16-fold lower than the mean c_{max} reached after once daily ocular administration of one drop of 0.3 mg/ml bimatoprost (0.08 ng/ml). Bimatoprost acid, the primary metabolite of bimatoprost, was only detected in 1.1% of evaluable samples (7/659; remaining samples were below the limit of quantification), also at low concentrations (maximum serum concentration detected was 24.5 pg/ml in a patient with a 20 µg implant). These newly generated data on the systemic PK of bimatoprost following intracameral implantation do not give rise to concern.

No data on intraocular pharmacology (apart from data from one aqueous humour sample) were provided in the dossier at submission. Therefore, **the bimatoprost release profile was unknown** and it was **unclear whether the active substance is evenly released from the implant**. The characterisation of the intraocular pharmacology of bimatoprost SR in aqueous humour samples would have been informative. In addition, this would have potentially also provided information on the currently missing section on special populations (e.g. a statistically significant age effect of bimatoprost AUC was reported for Lumigan eye drops). However, no concern is raised due to the well-established bimatoprost PK profile and the low systemic exposure detected following intracameral implantation.

With their responses, the applicant provided additional information on residual bimatoprost concentrations in aqueous humour collected from patients whose implants were removed for various reasons. The provided study had clear limitations, including very low sample number (n=18) and use of a non-validated assay for the determination of residual bimatoprost concentrations in the aqueous humour. Bimatoprost and bimatoprost acid were detected in 5/18 samples, all of which were samples taken from eyes treated with 15µg implants. No active substance was detected in samples taken beyond 100 days post administration (last positive sample taken on day 97 post implantation), including samples treated with BIM SR 10 µg implants.

Given the route of administration, characterisation of the biodegradation of the implant is considered to be of high relevance. According to the provided data at submission, **in a large proportion of patients the implant was still visible 24 months post-implantation**. From the long-term follow up data provided for patients from studies 091, 092, 093, 095, it seemed that visible implants were detected for even longer periods of time and it was **unclear for how long (residual) implants actually remain in the eye**. These results were in accordance with pre-clinical findings from dogs, where implant residues were still detected 18 months post-implantation (see non-clinical section). Long-term data on biodegradation across studies were requested.

In extended follow-up data provided with responses, first cycle implants administered in studies 091 and 092 were still visible in more than 50% of eyes 5 years post implantation (n=68, of which 52.9% were assessed as >0-25% implant size, 47.1% not visible). Compared to this, both second and third cycle implants showed even lower rates of biodegradation, with more than 60% of eyes evaluated positive for remaining implants of varying sizes (cycle 2: n=74, of which 1.4% were assessed as 26-75% implant size, 60.8% >0-25%, 37.8% not visible). In line with these reports, more than 60% of eyes showed visible implants after 3 years of follow-up from study 192024-093 (n=66, 63.6% evaluated as >0-25%, 36.4% not visible). Follow-up data for Month 48 showed even higher rates for incomplete biodegradation (first cycle: 84.6%, second cycle: 85.7%), sample sizes were however small (n=13, n=7, respectively), hampering interpretation. From the provided update on biodegradation with a maximum follow-up time of 60 months in studies 091/092, it is currently unclear how long complete biodegradation of implants takes.

No newly generated data on the PD of bimatoprost were provided with this MAA. Given that the pharmacodynamic properties and the mechanism of action of bimatoprost were established in the original Lumigan MAA, the provided Lumigan legacy reports are considered sufficient to inform the MAA for Durysta.

Given the low systemic exposure observed following intracameral implantation of bimatoprost SR, the omission to further study pharmacodynamics interactions is considered acceptable.

3.3.3. Conclusions on clinical pharmacology

The clinical pharmacology programme has been only superficially described by the applicant and limited PK data on systemic exposure are available. Robust data on intraocular PK are not available. Incomplete implant biodegradation was reported from the majority of patient eyes after a follow-up duration of 60 months. This issue is raised as part of a major objection in the safety section.

3.3.4. Clinical efficacy

The main evidence for the efficacy of a single, flexible or PRN (pro re nata, as needed) re-administration of 10µg Bimatoprost SR for the reduction of IOP in patients with OAG or OHT comes from the Phase III Study 192024-093 and ongoing Phase IIIb Study 1698-301-007. Due to differences in study design and primary efficacy endpoints, these studies were not pooled. Efficacy data are also available from completed Phase III Studies 192024-091, 192024-092, and 192024-095, as well as Phase I/II Study 192024-041D and Phase IIIb Study 1698-304-007.

3.3.4.1. Dose-response studies

Phase I/II study 192024-041D: An open-label (Stage 1) and randomized (Stage 2), dose ranging (with repeat administration), paired-eye comparison, 24-month study to evaluate the safety and efficacy of an intracameral implant of bimatoprost SR in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Stage 1 was an open-label, paired-eye comparison in successive cohorts of patients with OAG. A second stage was planned to be a randomized, masked, parallel-group comparison in patients with OAG or ocular hypertension (OHT). Stage 2 was not conducted, as sufficient information from Stage 1 provided an informed choice of dose strengths for the Phase 3 programme.

This study was conducted in patients with OAG and Grade ≥ 3 iridocorneal angle inferiorly by gonioscopy in the study eye, and OAG or OHT in the fellow eye; both eyes required IOP-lowering treatment. The objectives were to evaluate the safety of an intracameral implant of bimatoprost preservative-free intracameral drug delivery system (Bim PF IC DDS) in patients with open-angle glaucoma (OAG). To evaluate the intraocular pressure (IOP) lowering effects of an intracameral implant of Bim PF IC DDS in patients with OAG. The primary endpoint was time-matched IOP change from study baseline. The secondary endpoints were IOP raw values, mean diurnal IOP, time to IOP-lowering rescue treatment/second administration.

Each patient received an intracameral administration of Bim PF IC DDS in the study eye and topical Lumigan 0.03% eye drops in the fellow eye, once daily in the evening. Cohort 1 received a 10 µg implant and was followed until at least the Month 2 visit, after which time a data review committee (DRC) reviewed the available patient safety and efficacy data and decided whether to stop or delay enrolling additional patients in the study, or progress to Cohort 2. The DRC also decided the dose strengths (6, 10, 15, and/or 20 µg) to be used and number of patients to be enrolled in Cohort 2. A similar process was followed for enrolling patients in Cohort 3.

Overall, 109 patients enrolled in the study. Cohort 1 enrolled 2 patients, Cohort 2 enrolled 25 patients, and Cohort 3 enrolled 82 patients.

Bimatoprost preservative-free intracameral drug delivery system (Bim PF IC DDS), sustained-release biodegradable implants administered intracamerally on Day 1. Dose groups: Generation (Gen) 1 (10 or 15 µg) or Gen 2 (6, 10, 15 µg, or 20 µg [2 × 10 µg]). Patients who received a single administration of an implant with a dose strength of ≤ 15 µg were eligible to receive a repeat administration of Bim PF IC DDS after a minimum of 90 days and up to 12 months following the first administration of a Gen 2 implant if they had not had received rescue treatment in either eye; their IOP in the study eye at Hour 0 represented < 20% change from Baseline Hour 0 at 2 consecutive visits at least 1 week apart; clinical examinations with the first implant indicated adequate safety and the implant did not contact the corneal endothelium (as seen during gonioscopic examinations); and the study eye met anterior chamber (AC) angle requirements using the optical coherence tomography (OCT) measurements performed at screening.

Results: For all Gen 2 dose strengths, Bim PF IC DDS had a similar IOP-lowering effect as topical Lumigan for 12 weeks. For patients with only 1 Bim PF IC DDS treatment who did not require any additional IOP-lowering treatment at Month 24, the IOP reductions at Hour 0 ranged from 5.70 to 7.40 mm Hg, with greater IOP reduction observed with the dose strengths selected for the Phase 3 studies (7.30 and 7.40 mm Hg for Gen 2, 15 and 10 µg, respectively). By Month 6, most patients (> 66%) were still maintained on monotherapy with Bim PF IC DDS. At least 33% and 23% of the Bim PF IC DDS eyes among all Gen 2 dose strengths at Months 12 and 24, respectively, did not require rescue or a second Bim PF IC DDS treatment. For the Gen 2, 15 and 10 µg groups, there were no observable diurnal differences in IOP reduction compared with Lumigan through Week 12. Hour 0 IOP reduction with the second Bim PF IC DDS implant was comparable to that observed with the first implant through Week 16. At Week 16, the retreatment interval selected for the Phase III studies, over 90% of the Bim PF IC DDS eyes did not require rescue or a second implant for the Gen 2, 15 and 10 µg groups. For the efficacy analysis of time to rescue treatment or second implant administration in the Bim PF IC DDS eye, the median time to rescue or retreatment ranged from 38 to 56 weeks in the Gen 2 groups.

Conclusions: In this 24-month study, all dose strengths of Bim PF IC DDS showed IOP-lowering effects similar to that of topical Lumigan for at least 12 weeks in patients with OAG. Over 90% of patients in the Gen 2, 10 and 15 µg treatment groups did not require rescue or second treatment within the first 16 weeks following administration. The majority of the patients by Month 6 and approximately one-fourth of the patients by Month 24 were still on monotherapy with the first Bim PF IC DDS treatment without additional IOP-lowering treatment. In addition, similar IOP-lowering effects were observed in the first 16 weeks following both the first and second treatments.

3.3.4.2. Main study(ies)

3.3.4.2.1. Study 192024-093: A Comparison of Bimatoprost SR to Selective Laser Trabeculoplasty in Patients With Open-Angle Glaucoma or Ocular Hypertension

Methods

Study 192024-093 was a multicentre, randomized, subject and efficacy evaluator-masked 26-month study conducted in 2 stages and evaluating 2 different dose strengths of bimatoprost SR (Stage 1: 15µg; Stage 2: 10µg) administered intracamerally. The safety and IOP-lowering effect of bimatoprost SR were compared to SLT. The study was conducted in 2 stages because the protocol was amended (Amendment 3) to reduce the dose strength administered for newly enrolled subjects to 10 µg. Additionally, the number of administration cycles was reduced from 3 to 2. The primary efficacy analysis was performed for subjects in Stage 2 (10µg bimatoprost) only.

For all subjects who were enrolled and reached the Week 16 visit prior to implementation of Amendment 6, retreatment with bimatoprost SR was fixed at Week 16. With Amendment 6, the dosing schedule was changed from fixed to a more flexible regimen. For subjects who had not yet been retreated at Week 16 after implementation of Amendment 6 and did not meet retreatment criteria at Week 16, Cycle 2 may have been performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria were met.

Approximately 160 patients were planned to be enrolled and treated with bimatoprost SR 10 µg at approximately 70 sites. Approximately 50 patients enrolled before implementation of Amendment 3 and received bimatoprost SR 15 µg.

Study Participants

The study population consisted of patients with bilateral OAG or OHT who are not adequately managed with topical medication for reasons other than medication efficacy (e.g. due to intolerance or nonadherence). Both eyes must require IOP-lowering treatment, must be able to be adequately managed on SLT monotherapy, and must meet study entry criteria.

Key Inclusion criteria

1. Male or female, 18 years of age or older
2. Patient is willing to withhold his/her IOP treatments according to the study requirements, and in the opinion of the investigator, can do so without significant risk.
3. In the investigator’s opinion, patient’s IOP is not adequately managed with topical medication for reasons other than medication efficacy (e.g. due to intolerance or nonadherence)
4. Negative pregnancy test at Baseline for females of childbearing potential

<u>Ocular Inclusion Criteria for Both Eyes:</u>

5. In the investigator’s opinion, both eyes can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analogue (eg, Lumigan, Xalatan, Travatan) eye drops as the sole therapy if medication was taken as directed
6. In the investigator’s opinion, patient’s IOP can be adequately managed with SLT monotherapy
7. In the investigator’s opinion, patient is a suitable candidate for SLT
8. Diagnosis of either OAG (i.e., primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in each eye, requiring bilateral IOP-lowering treatment. (Note: diagnosis does not have to be the same in both eyes)
9. Central endothelial cell density by specular microscopy confirmed as being qualified by Reading Centre assessment prior to beginning Washout
10. The iridocorneal angle must be independently confirmed as being qualified by 2 ophthalmologists using the following criteria:

    a) Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle

    b) Peripheral anterior chamber depth by Van Herick examination ≥ 1/2 corneal thickness

    Note: The independent eligibility assessments must both agree that the Shaffer grade is ≥ 3 and the Van Herick grade is ≥ 1/2 corneal thickness

11. At the Baseline visit (8:00 am ± 1 hour), IOP of ≥ 22 and ≤ 34 mm Hg, with difference between eyes of ≤ 5 mm Hg

12. At the Screening and Baseline (Day -3 to -1) visits, Best-Corrected Visual Acuity (Snellen equivalent, by manifest refraction) of 20/50 or better in each eye

Key exclusion criteria

1. Females who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not using a reliable means of contraception during the study

2. Previous use of commercially available bimatoprost SR; concurrent enrolment in another Allergan bimatoprost SR study; or previous enrolment in which an implant was received. Patients enrolled in the 192024-091/092 studies who were randomized to the control treatment and never received an implant may be considered for enrolment at the investigator's discretion.

Ocular Exclusion Criteria for Both Eyes:

3. History of previous laser trabeculoplasty

4. History or evidence of clinically relevant, substantial ocular trauma (eg, a traumatic cataract, traumatic angle recession, etc)

5. The following surgical history:

    a. History or evidence of complicated cataract surgery: eg, surgery resulting in complicated lens placement (such as anterior chamber intraocular lens implant [IOL], sulcus IOL, aphakia, etc) or intraoperative complications (such as a posterior capsular tear [with or without vitreous loss], substantial iris trauma, etc).

1. Note: history of uncomplicated cataract surgery is not an exclusion.

    b. History of phakic IOL insertion for refractive error correction

6. Intraocular surgery (including cataract surgery) and/or any ocular laser surgery within the 6 months prior to treatment (Day 1)

7. Any history of corneal graft, including partial grafts (eg, Descemet's Stripping Endothelial Keratoplasty [DSEK], Descemet's Membrane Endothelial Keratoplasty [DMEK]); or incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions

8. Corneal or other ocular abnormalities that would preclude accurate readings with an applanation tonometer, anterior segment-optical coherence tomography, specular microscope, and/or a contact pachymeter, or could confound study results, eg, moderate to severe corneal dystrophy, including Anterior Basement Membrane Disease (ABMD; i.e., Map-Dot-Fingerprint [MDF]) and guttata. Mild ABMD or mild guttata are not exclusionary by clinical examination if, in the opinion of the investigator, the condition is stable and not likely to cause corneal changes during the course of the study.

9. Active or recurrent ocular disease (eg, uveitis, ocular infection, chronic moderate to severe blepharitis or severe dry eye, severe ocular seasonal allergies) or sight threatening diseases (eg, neovascular age-related macular degeneration [ARMD], diabetic macular oedema) that, in the opinion of the investigator, would put the patient at a significant risk or would interfere with the interpretation of the study data. Patients with slowly progressive eye diseases (i.e., mild cataracts, nonneovascular ARMD) can be enrolled at the discretion of the investigator

10. Any history of external ocular or intraocular malignancy, and/or any history of benign ocular neoplasia that in the investigator's opinion resulted in clinically significant ocular morbidity
11. History of herpetic ocular diseases (including herpes simplex virus and varicella zoster virus)
12. The following ocular surface findings:
    a. Bulbar conjunctival hyperaemia, on either macroscopic or slit-lamp examination, > +1 (mild) at baseline
    b. Active ocular surface findings other than bulbar conjunctival hyperaemia, on either macroscopic or slit-lamp examination, > +1 (mild) at Baseline
13. History of moderate or worse (≥ +2) bulbar conjunctival hyperaemia due to marketed prostaglandin, prostamide, or prostaglandin analogue use
14. Central corneal thickness of < 480 or > 620 micrometres
15. Anticipated need for any incisional or laser ocular surgery during the study
16. History of anatomically narrow angle resulting in evidence of angle changes or any history of closed angle glaucoma. Note: historically narrow angled patients whose angle has been opened by cataract surgery or peripheral iridotomy may be eligible for enrolment if they have no evidence of angle abnormalities.
17. History or evidence of a peripheral iridotomy/iridectomy in the inferior iris
18. Any history of trabeculectomy or other types of glaucoma surgery, including a glaucoma seton or aqueous bypass stents
19. Peripheral anterior synechiae (PAS) in the inferior iridocorneal angle on gonioscopic examination at Screening
20. Visual field loss that, in the opinion of the investigator, is functionally significant (eg, split fixation, field defect within the central 10 degrees that is visually significant or likely to cause central visual impairment upon progression) or shows evidence of progressive visual field loss within the year prior to baseline (Note: Two visual fields are required for qualification, 1 performed within the 10 months prior to or at Screening, and 1 performed at baseline or during the washout period using the protocol-required testing method. The same test methodology should be used for all historical and study-related examination for a given patient.)
21. Evidence of macular oedema during screening or in patient's medical history

Permissible Concomitant Medications/Treatments

Subjects were allowed to use the following concomitant medications during the study:

Ophthalmic Medications/Treatments: Intermittent use of artificial tear products is allowed if they are taken > 15 minutes before any study procedure or if they are required for a study procedure. Intermittent use of ocular decongestants or antihistamines is allowed if not taken within 2 days prior to a scheduled visit. Use of artificial tear products and ocular decongestants or antihistamines may be restarted 3 days after any study administration (bimatoprost SR, Sham bimatoprost SR, SLT, or Sham SLT) procedure. Use of post-bimatoprost SR administration topical ocular antibiotics for 3 days, and corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) for up to 7 days following the administration days is permissible. Use of immediate pre- and post-SLT topical ocular antihypertensive medication (i.e., brimonidine or apraclonidine) is permissible. Post-SLT topical NSAIDS are also permissible for 3 days following the procedure.

Systemic Medications: Systemic beta-blocker containing medications are permitted, provided that the dose/dosing regimen has remained stable for at least 2 months prior to screening and is not anticipated to change during the duration of the study.

In the unlikely event that the bimatoprost SR implant requires removal for significant safety reasons, this may be performed at the discretion of the investigator following a discussion with the medical safety physician at Allergan as needed. In the event that the investigator performs an unanticipated incisional surgical procedure on the bimatoprost SR implanted eye during which ocular fluid is to be removed, ocular fluid/implant samples may be collected for analysis at the investigator's discretion.

Prohibited Concomitant Medications/Treatments

Non-study IOP-lowering Treatments: Any concurrent non-study IOP-lowering treatment (eg, topical ophthalmic medication containing an ocular antihypertensive, LT) is prohibited in either eye during the study (through Month 24), *unless necessary for the safety of the patient due to inadequate control of IOP as determined by the investigator*. Inadequate control of IOP should be confirmed at a subsequent visit (scheduled or unscheduled visit). Initiation of treatment in one eye should not automatically lead to initiation of treatment in the contralateral eye. Each eye should be evaluated on an individual basis when determining the need for additional non-study IOP lowering treatments. If non-study IOP-lowering treatment is initiated, the investigator will be expected to attest to the need for additional non-study IOP-lowering treatment for safety reasons for each eye individually. Use of any concurrent non-study IOP-lowering treatment with any known effect on study outcomes (eg, crossover effect on the contralateral eye) is prohibited during the study.

Treatments

The eye with the higher IOP at baseline was assigned as the primary eye. If baseline IOP was the same in both eyes, the right eye was the primary eye. The primary eye was randomized to receive either bimatoprost SR or SLT using a 1:1 ratio, stratified by primary eye baseline IOP (≤ 25 vs > 25 mmHg) and between-eye baseline IOP difference (0 to 2 mmHg vs 3 to 5 mmHg). If the primary eye received bimatoprost SR, the contralateral eye received SLT. If the primary eye received SLT, the contralateral eye received bimatoprost SR. Subjects received a 360° administration of SLT in 1 eye on Day 1, and administration of bimatoprost SR in the contralateral eye on Day 4, with a repeat administration of bimatoprost SR at Week 16 for all subjects who met retreatment criteria. For all subjects who were enrolled and reached the Week 16 visit prior to implementation of Amendment 6, retreatment with bimatoprost SR was fixed at Week 16. For subjects who had not yet been retreated at Week 16 after implementation of Amendment 6 and did not meet retreatment criteria at Week 16, Cycle 2 may have been performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria were met.

In order to mask the patient to the treatment assigned to each eye, on Day 1, a sham SLT procedure was performed in the eye that received bimatoprost SR administrations (hereafter referred to as the "bimatoprost SR eye"). Similarly, a sham needleless bimatoprost SR administration (hereafter referred to as the "Sham bimatoprost SR administration") that involved touching the eye at the area of insertion with a needleless applicator that does not deliver an implant into the anterior chamber, was performed on the SLT-treated eye (hereafter referred to as the "SLT eye") on bimatoprost SR administration visits.

Table 10: Study treatment

Study Treatment	Dosage Form	Dose Strength	Bulk Lot
Bimatoprost SR 15 µg	Intraocular implant	15 µg	E80446; E83298; E75845
Bimatoprost SR 10 µg	Intraocular implant	10 µg	E89124; E84330; E83014; E87173
Bimatoprost SR sham	Sham	Not applicable	E87547; E81066; E76003; E90640; 14177P1
Duration of Treatment: 24 months of follow-up after initial Bimatoprost SR and SLT administration.			
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Control treatment: one 360° administration of SLT.			

Table 11: Treatment schedule by eye

Treatment Visit	Bimatoprost SR Eye	SLT Eye
SLT administration (Day 1)	Sham SLT	360° SLT
Bimatoprost SR Cycle 1 administration (Day 4)	Bimatoprost SR	Sham Bimatoprost SR
Bimatoprost SR Cycle 2 administration (Week 16)[a]	Bimatoprost SR	Sham Bimatoprost SR

SLT = selective laser trabeculoplasty; SR = sustained release

[a] Cycle 2 administration of Bimatoprost SR is performed at Week 16 for all patients who meet retreatment criteria. For those patients not meeting retreatment criteria at Week 16, Cycle 2 may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met.

Retreatment with Bimatoprost SR

For all patients who met retreatment criteria at Week 16, Cycle 2 bimatoprost SR administration occurred at Week 16. Retreatment of an eligible implanted eye was permitted if the following criteria were met in that eye:

- IOP > 17 mm Hg
- There is no evidence of any of the following:
    - Significant corneal findings related to presence of the implant (including corneal oedema, peripherally adjacent to the implant location and/or central) at any visit
    - Endothelial cell density less than 1800 cells/mm2 by specular microscopy, confirmed at 2 consecutive visits on separate days
    - Persistent and progressive corneal endothelial cell density decrease ≥ 15% from baseline confirmed at 2 consecutive visits on separate days (scheduled or unscheduled)
    - Remaining implant size or position from prior administration that, based on the investigator's evaluation, precludes placement of another implant (eg, may cause chronic contact of the implants with the corneal endothelium)
    - Clinically significant intraocular inflammatory findings (eg, PAS, uveitis, iridocyclitis, macular oedema, etc) at any visit. Note: mild AC cells/iritis related to the administration procedure itself that resolves rapidly (with or without NSAIDs or steroids) is not prohibitive

Intracameral administration technique

Intracameral administration of bimatoprost SR must be performed by an ophthalmologist who has had adequate training and has been approved by Allergan to perform the procedure. The procedure is described in detail in the Procedure Manual. In brief, following the sterile preparation and sterile field setup, an appropriately sized sterile lid speculum should be placed between the eyelids of the patient. The entrance site for the applicator needle is just anterior to the insertion of the conjunctiva through the clear cornea in the superior or temporal quadrant. The trajectory of the needle should be parallel to the iris plane. The eye is stabilized by either counter traction with a sterile toothed forceps or counter pressure with a cotton tipped applicator as the needle is advanced through the cornea. The actuator button is depressed until an audible and/or palpable click is heard. The bimatoprost SR implant should be visible exiting the needle bevel into the aqueous humour. The needle is then immediately removed from the AC, and the wound is checked for aqueous leakage. Following removal of the lid speculum and sterile drape, additional drops of broad-spectrum antibiotics should be applied.

The procedure for the second administration of bimatoprost SR is the same.

The preparation and procedure for all sham administrations is the same; however, the sham applicator has no needle and thus does not enter the AC (but should touch the eye at the area of recommended insertion).

SLT and Sham SLT Procedure

Pre SLT: 1 drop of apraclonidine or brimonidine (see Procedure Manual) is instilled into each eye 30 minutes to 1 hour prior to SLT (or Sham SLT). Topical anaesthetic drop (eg, proparacaine hydrochloride or equivalent) should be administered to each eye approximately every 5 minutes beginning approximately 15 minutes prior to the procedure.

SLT must be performed by an ophthalmologist who has had adequate training and has been approved by Allergan. The investigator performs 360 degrees of SLT using the standardized method that is detailed in the Procedure Manual. Sham SLT is then performed on the contralateral eye using the same method, with the exception that the laser is not switched to the active state.

Post SLT: 1 drop of apraclonidine or brimonidine is administered into each eye and the IOP is rechecked 1 hour after SLT and Sham SLT administration; because this is a postoperative measurement and not used for efficacy analyses, this measurement does not need to be masked and only 1 measurement needs to be performed. If an IOP spike is observed, the investigator should treat using his/her standard of practice.

Objectives

The primary objective of this study was to evaluate the IOP-lowering effect and safety of bimatoprost SR compared with SLT in patients with OAG or OHT, who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

The primary efficacy analysis (ITT population) uses a mixed effect model for repeated measurement (MMRM) to establish noninferiority of bimatoprost SR 10 µg to SLT in Hour 0 IOP change from baseline at 3 visits: Weeks 4, 12, and 24:

- Statistical noninferiority: meeting non-inferiority margin of 1.5 mmHg at all 3 visits
- Clinical noninferiority: meeting noninferiority margin of 1.0 mmHg at 2 out of 3 visits

The study success requires both criteria for noninferiority to be met.

Regarding statistical hypotheses and more information on the statistical non-inferiority margin, please refer to statistical methods section in this report.

Outcomes/endpoints

Primary efficacy variable

The primary efficacy variable is IOP change from baseline (follow up value minus baseline value) and the primary time period is 24 weeks. Measurements for the primary analysis are designated for the following timepoints: Hour 0 at weeks 4, 12, and 24.

The primary efficacy measure, IOP, is measured using a Goldmann applanation tonometer. Examiners masked to the treatment assignment should perform all efficacy IOP measurements at approximately the same time of day for a given patient throughout the study whenever possible.

A 2-person reading method is used for all efficacy IOP measurements, wherein 1 person adjusts the dial in a masked fashion and a second person reads and records the value. The right eye is to be measured first and the left eye measured second. Two consecutive measurements are taken of each eye. If the first 2 measurements differ by > 1 mm Hg, a third measurement should be taken. If the first 2 measurements differ by ≤ 1 mm Hg, the IOP for the given eye is the average of the 2 readings. If the difference between the first 2 measurements is > 1 mm Hg, the IOP for the given eye is the median of the 3 readings.

All Hour 0 IOP examinations should be scheduled at 08:00 AM ± 1 hour. As scheduling permits, the patient should have approximately the same Hour 0 time of day throughout the study. At selected sites in consenting patients, additional IOP measurements are performed at Hour 2 (Hour 0 + 2 hours [± 30 minutes]) and Hour 8 (Hour 0 + 8 hours [± 30 minutes]).

Secondary Efficacy Variables

- Time to initial use of nonstudy IOP-lowering treatment (as determined by the investigator)
- Percentage of eyes achieving ≥ 20% reduction in IOP from baseline at each postbaseline visit
- IOP changes from baseline at Hour 0 of Weeks 8, 15, and 20

Other efficacy variables

- Time-weighted IOP change from baseline average through Week 24
- Raw IOP at each visit
- Time to onset of effect (time to first achieving ≥ 20% IOP reduction from baseline)
- Percentage of bimatoprost SR and SLT eyes achieving 15% and 30% reductions in IOP from baseline

Sample size

The sample size calculation was based on paired-eye differences using a normal approximation with a 2-sided significance level of 0.05, assuming that there is no difference in mean IOP change from baseline between Bim SR 10 µg eyes and SLT eyes, and that change from baseline in IOP has a standard deviation of 4 mmHg. A sample size of 144 patients with eyes treated with Bim SR 10 µg and SLT provided approximately 98% power in showing noninferiority in 3 out of 3 time points with a noninferiority margin of 1.5 mm Hg, and 90% power in showing noninferiority in 2 out of 3 time points with a noninferiority margin of 1.0 mmHg, assuming that both the between-eyes and the within-patient correlation coefficients are 0.5.

Assuming a premature discontinuation rate of 10%, approximately 160 patients were to be enrolled into this study and treated with Bim SR 10 µg. Additionally, there were 55 Bim SR 15 µg treated patients who were enrolled before implementation of Amendment 3 and treated with the 15 µg Bim SR dose strength.

Randomisation and blinding (masking)

Randomisation

The eye with the higher IOP at Baseline was to be assigned as the primary eye. If baseline IOP was the same in both eyes, the right eye was the primary eye. The primary eye was randomized to receive either bimatoprost SR or SLT using a 1:1 ratio, stratified by primary eye baseline IOP (≤ 25 versus > 25 mm Hg) and between-eye baseline IOP difference (0 to 2 mm Hg versus 3 to 5 mm Hg). If the primary eye received bimatoprost SR, the contralateral eye was to receive SLT. If the primary eye received SLT, the contralateral eye was to receive bimatoprost SR.

Blinding (masking)

A sham SLT procedure was to be performed in the bimatoprost SR eye and a sham bimatoprost SR administration was to be performed in the SLT eye to ensure masking of the study treatments. The Sham bimatoprost SR administration involved touching of the eye at the area of insertion with an Allergan-provided needleless applicator that did not deliver an implant into the AC.

The patient and the site staff were to be masked to the treatment assignment for each eye. Only the site coordinator and designated staff were to be unmasked to the patient's treatment assignment for each eye. Efficacy IOP measurements were to be masked using a 2-person reading method, wherein 1 person adjusted the dial in a masked fashion and a second person read and recorded the value.

The site staff who performed IOP readings were to be masked to the treatment assignment for each eye. Site personnel and patients were to be instructed and reminded throughout the study not to discuss study medication assignments to ensure masking was maintained. In the event that the patient required postoperative topical eyedrops in only 1 eye following a bimatoprost SR administration (eg, topical corticosteroids or anti-inflammatory eyedrops) or SLT administration (eg, treatment of acute post-SLT IOP spike), in order to maintain masking of the eye receiving study treatment, the investigator was to be instructed to dispense the required medication without disclosing which eye was the bimatoprost SR or SLT eye or the aetiology of the signs/symptoms that required the medication.

Statistical methods

Analysis sets

Intention-to-treat population: Patients whose primary eyes were randomized to receive either Bim SR or SLT treatment were referred to as randomized patients. The intent-to-treat (ITT) population was defined as all randomized patients. Analyses using the ITT population were to be based on the randomized treatment assigned to each eye.

Per-protocol population: The per-protocol (PP) population was defined as all patients in the ITT population who had no protocol deviations affecting the data for the primary efficacy analysis for all primary analysis visits (Week 4, Week 12, and Week 24). Since the primary eye and contralateral eye of a patient contributed data separately for the two different treatments in the study, the data from one eye could be excluded from PP analysis due to a protocol deviation, but the patient could still be included in PP population because of valid data from the other eye.

Safety population: The safety population was defined as all patients who had received at least one study treatment (regardless of whether it was the randomized treatment or not) and were used for the safety analyses. Both eyes in the safety population were included in the ocular safety analyses. Ocular safety assessments were based on the treatment received in each eye at the first administration. If a patient received both SLT and Bim SR in the same eye, safety assessment for this patient was summarized under the Bim SR treatment group.

Analysis of baseline characteristics

Demographics and other baseline characteristics were to be summarized descriptively for the ITT population.

Analysis of the primary endpoint

The primary efficacy analysis was performed with patients treated with bimatoprost SR 10 µg in the ITT population. The primary efficacy variable was IOP change from baseline Hour 0 assessed at Weeks 4, 12, and 24. The null and alternative hypotheses for the comparison between bimatoprost SR 10 µg treated eyes and SLT-treated eyes at each visit of Weeks 4, 12, and 24 were:

Null hypothesis: the difference in mean IOP change from baseline between the bimatoprost SR 10 µg eye and SLT eye (bimatoprost SR 10 µg minus SLT) is > 1.5 mm Hg.

Alternative hypothesis: the difference in mean IOP change from baseline between the bimatoprost SR 10 µg eye and SLT eye (bimatoprost SR 10 µg minus SLT) is ≤ 1.5 mm Hg.

IOP change from baseline was analysed using a mixed effect model for repeated measures (MMRM). The model included Hour 0 IOP change from baseline as the response variable and treatment, visit, eye, baseline Hour 0 IOP, treatment-by-visit, visit-by-baseline, and visit-by-eyes interactions as fixed effects. Unstructured correlation for study visits and eyes were used for repeated measures on the same patient. IOP measurements obtained after initiating the use of nonstudy IOP-lowering medication or procedure in an eye were treated as missing. This corresponds to the hypothetical strategy defined in ICH E9 addendum.

If the model failed to converge, multiple imputation (MI) was to be implemented for missing data before applying MMRM.

The mean difference between the bimatoprost SR 10 µg eyes and SLT eyes and the corresponding 95% confidence interval (CI) were constructed at each visit from MMRM analysis. Noninferiority of bimatoprost SR 10 µg was demonstrated, if the upper limit of the 95% CI was ≤ 1.5 mm Hg at all 3 visits. For additional clinical consideration, Bim SR 10 µg was considered clinically noninferior to SLT if the upper limit of the 95% CI is ≤ 1.0 mmHg at 2 out of the 3 visits.

Sensitivity analyses

Several sensitivity analyses were conducted and are described in the following.

PP analysis:

The same analysis as described above for the primary analysis was also conducted in the PP population.

Analysis of covariance:

Analysis of Covariance (ANCOVA) including within-patient correlation at each visit was conducted for IOP change from baseline at Weeks 4, 12, and 24 in the ITT population. In this analysis, missing data were imputed using the last observation carried forward. At each visit, the model for IOP change from baseline was specified as: IOP Change from Baseline = Treatment + Eye + Baseline IOP, where Eye is

a primary eye or a contralateral eye. Unstructured covariance matrix was used for between eye correlation.

Treatment Effect Regardless of Non-Study IOP Treatment Use:

To evaluate the treatment effect regardless of whether there is any use of non-study IOP lowering treatment, the MMRM analysis for primary analysis was performed in the ITT population using all available Hour 0 IOP data. In this analysis, data after the use of non-study IOP lowering treatment was not excluded.

Tipping Point Analysis: A tipping-point was used to assess the robustness of the primary efficacy analysis with respect to possible deviations from missing at random (MAR) assumption in MMRM model. This analysis evaluated the sensitivity of study results under the missing not at random (MNAR) assumption.

Tipping point analysis was based on multiple imputed (MI) datasets for IOP data while applying a shift parameter to imputed IOP data for Bim SR 10 µg treated eyes. Specifically, missing IOP data was calculated by adding a positive shift value to the imputed data to discount the treatment effect for Bim SR 10 µg. This shift essentially made the IOP data higher than imputed for Bim SR 10 µg treated eyes. Note that there was no shift applied to SLT treated eyes. Starting from a shift of 0 mmHg (i.e., no shift), the above procedures was repeated with incremental shift values of 1 mmHg. The shift values were adjusted with unmasked data. The tipping point was reached when the analysis result being switched from positive (i.e., Bim SR 10 µg is non-inferior to SLT) to negative (i.e., Bim SR 10 µg is no longer non-inferior to SLT). The corresponding shift value was defined as the tipping point. If the IOP value at the tipping point was clinically implausible, the primary analysis results was considered as robust.

Impact of Receiving the 2nd Bim SR After Week 16 and Prior to Week 24

Some patients received the second Bim SR 10 µg administration after Week 16 and prior to Week 24, thus the time interval between the second Bim SR 10 µg administration and the primary analysis endpoint at Week 24 was shorter for these patients as compared with patients who received the second Bim SR 10 µg at Week 16. To evaluate any potential impact of this difference in timing of the second administration on Week 24 IOP data from these patients in the primary analysis, additional sensitivity analysis was conducted by excluding the IOP data at Week 24 for these patients. More specifically, for patients who received flexible administration of the second Bim SR 10 µg beyond the Week 16 visit, the Week 24 IOP assessment was excluded from the current sensitivity analysis if the second administration date was in the analysis windows for Week 20 or Week 24 and prior to the Week 24 IOP assessment. The MMRM model for the primary efficacy analysis was used.

Analysis of the primary efficacy endpoint in the context of the estimand framework

The most relevant ICEs that have an impact on efficacy outcome are rescue medications or nonstudy IOP-lowering treatment received by patients during the study. The primary analysis of the primary estimand was an MMRM where data after the first nonstudy IOP-lowering treatment were excluded. This analysis would correspond to the Hypothetical Strategy, which assumed data were missing at random. A sensitivity analysis was performed to include all IOP data regardless of use of nonstudy IOP-lowering treatment. This would correspond to Treatment Policy Strategy in accordance with ITT principle.

Secondary efficacy analyses

Superiority Test of Bim SR 10 µg versus SLT: As the secondary efficacy analysis, a superiority test of Bim SR 10 µg versus SLT was performed if the statistical noninferiority was demonstrated in the primary efficacy analysis for the ITT population as the gatekeeping procedure to control overall type I

error rate at the 0.05 level. Superiority of Bim SR 10 µg versus SLT was considered achieved if the upper limit of the 95% CI is < 0 mmHg at Weeks 4, 12, and 24.

Time to Initial Use of Non-study IOP-lowering Treatment: Time to the initial use of non-study IOP-lowering treatment from the Date of the First Treatment as defined below was analysed using Kaplan-Meier (KM) method with graphical displays. If a patient did not use any non-study IOP-lowering treatment in an eye, then the event time was censored at the study exit date or the last visit date if the study exit date was not available.

Additionally, for Bim SR 10 µg, the time to non-study IOP-lowering treatment from the second injection was to be summarized by time to initial use of non-study IOP-lowering treatment from the second Bim SR 10 µg administration. For this analysis, patients with at least two Bim SR 10 µg administrations were to be used, and the event was to be censored at the last available visit date or exit date if the patients did not use any non-study IOP-lowering treatment.

Percentage of Bim SR and SLT Eyes Achieving ≥ 20% Reduction by Visit: Number and percent of eyes that had achieved a ≥ 20% reduction in IOP at each postbaseline visit was summarized by treatment.

IOP Changes from Baseline at Weeks 8, 15, and 20: IOP values at Week 8, 15 and 20 and the changes from baseline was descriptively summarized for Bim SR 10 µg and SLT at each timepoint for the ITT population.

Other efficacy analyses

Other efficacy analyses comparing Bim SR 10 µg and SLT included:

- IOP change from baseline as time-weighted average through Week 24
- Post-baseline IOP as time-weighted average through Week 24
- Time to first achieving ≥ 20% IOP reduction
- Percentage of eyes achieving ≥ 15% and ≥ 30% reductions from baseline IOP by visit
- Diurnal IOP

Analyses were performed for the ITT population. KM methods were used for time to event analysis.

For patients treated with Bim SR 15 µg, descriptive statistics for baseline and change from baseline IOP were summarized for each eye (SLT and Bim SR 15 µg) and visits in the ITT population.

Safety analysis

All safety analyses were performed using the safety population. Unless otherwise stated, the last non-missing safety assessment before the SLT treatment (Day 1) was used as the baseline for all analyses of that safety parameter. All safety analyses were performed for Bim SR 10 µg and Bim SR 15 µg.

Ocular safety was evaluated through ocular AEs, best corrected visual acuity, visual field examination, specular microscopy, macroscopic iris colour assessment, macroscopic conjunctival hyperaemia assessment, gonioscopy/angle assessment, biomicroscopy (using a slit lamp), lens assessment, optic disc examination, dilated ophthalmoscopy, pachymetry, and anterior segment-optical coherence tomography. Non-ocular safety analysis included non-ocular adverse events (AEs), clinical laboratory results, vital signs (blood pressure, pulse rate and temperature), and pregnancy test results.

Safety analyses were summarized by different study periods. All analyses were based on the first treatment received in each eye (Bim SR or SLT). If a patient who received both SLT and Bim SR in the same eye, safety assessments was summarized in Bim SR. For non-ocular safety measures, overall summaries were presented regardless of study treatment.

Results

Participant flow

Subject Disposition

Study completers are defined as subjects who received at least 1 study treatment administration (bimatoprost SR or SLT) and completed the study per the eCRF disposition page. A subject who received study treatment in a particular cycle was considered to have completed that analysis cycle, if (a) the subject was a study completer or (b) the subject received the subsequent bimatoprost SR administration.

A total of 240 subjects (n=57 Bim 15µg, n=183 Bim 10µg) were randomized.

Of the 183 subjects in the ITT population for bimatoprost 10 µg, 155 completed the study and 28 discontinued prematurely from the study. The most common reason for study discontinuation was withdrawal of consent. Of the 4 subjects who discontinued from the study due to adverse events, all subjects discontinued due to non-ocular adverse events.

Of the 180 subjects who entered Cycle 1, 169 completed Cycle 1. Of the subjects who completed Cycle 1, 126 subjects entered Cycle 2, and 112 subjects completed Cycle 2.

Of the 57 subjects in the ITT population for bimatoprost 15 µg, 46 completed the study and 11 discontinued prematurely from the study. 56 subjects entered Cycle 1, 49 subjects entered Cycle 2, and 21 entered Cycle 3. The most common reasons for study discontinuation were withdrawal of consent and adverse event.

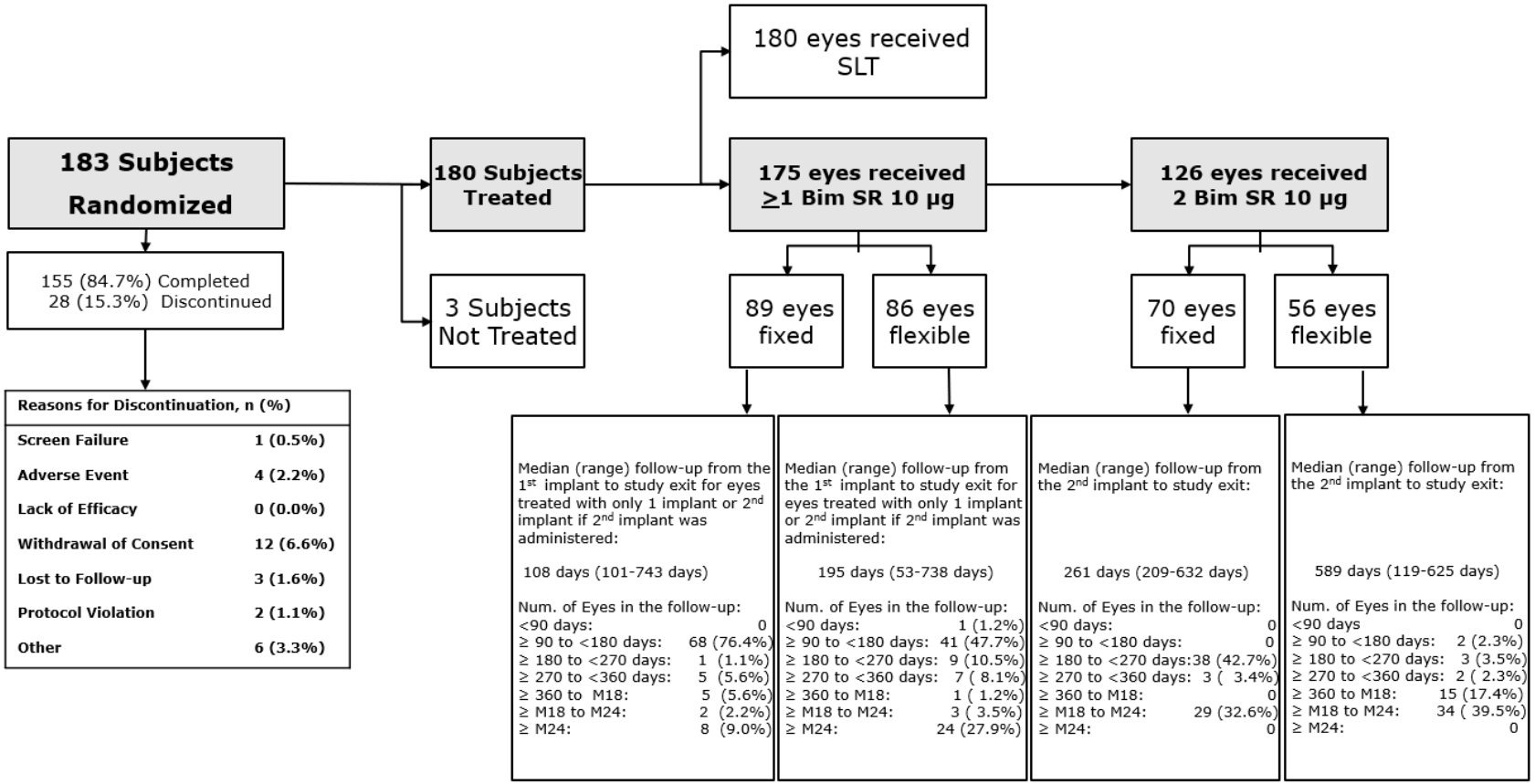


Figure 5: Study 192024-093 participant flow diagram

The flexible administration regimen shows a longer follow-up compared to the fixed administration regimen. The median follow-up of flexible versus fixed administration regimens in each cycle are 195 days vs 108 days in Cycle 1; and 589 days vs 261 days in Cycle 2, respectively. This difference is due to the earlier-enrolled subjects that followed the fixed administration regimen, with a study duration of 12 months. A later protocol amendment revised the administration regimen to be flexible with a longer study duration of 24 months.

Table 12: Disposition of subjects – bimatoprost SR 10 µg/SLT (ITT Population)

	SLT (Primary Eye)/ Bim SR 10 ug (Contralateral Eye) n (%)	Bim SR 10 ug (Primary Eye) / SLT (Contralateral Eye) n (%)	Total n (%)
Number of Subjects Randomized	92	91	183
Number of Subjects Treated [1]	90 (97.8)	90 (98.9)	180 (98.4)
Number of Subjects Randomized but Not Treated [2]	2 (2.2)	1 (1.1)	3 (1.6)
Number of Subjects Completed Study	77 (83.7)	78 (85.7)	155 (84.7)
Number of Subjects Discontinued from Study	15 (16.3)	13 (14.3)	28 (15.3)
Reasons for Discontinuation from Study			
Screen Failure	1 (1.1)	0	1 (0.5)
Adverse Event	2 (2.2)	2 (2.2)	4 (2.2)
Ocular Adverse Event	0	0	0
Non-ocular Adverse Event	2 (2.2)	2 (2.2)	4 (2.2)
Lack of Efficacy	0	0	0
Withdrawal of Consent	6 (6.5)	6 (6.6)	12 (6.6)
Lost to Follow-Up	2 (2.2)	1 (1.1)	3 (1.6)
Pregnancy	0	0	0
Protocol Violation	2 (2.2)	0	2 (1.1)
Study Terminated by Sponsor	0	0	0
Site Terminated by Sponsor	0	0	0
Other	2 (2.2)	4 (4.4)	6 (3.3)

	SLT (Primary Eye)/ Bim SR 10 ug (Contralateral Eye) n (%)	Bim SR 10 ug (Primary Eye) / SLT (Contralateral Eye) n (%)	Total n (%)
Number of Subjects Entered Analysis Cycle 1	90	90	180
Number of Subjects Completed Analysis Cycle 1	84 (93.3)	85 (94.4)	169 (93.9)
Number of Subjects Discontinued during Analysis Cycle 1	6 (6.7)	5 (5.6)	11 (6.1)
Reasons for Discontinuation during Analysis Cycle 1			
Screen Failure	0	0	0
Adverse Event	0	1 (1.1)	1 (0.6)
Ocular Adverse Event	0	0	0
Non-ocular Adverse Event	0	1 (1.1)	1 (0.6)
Lack of Efficacy	0	0	0
Withdrawal of Consent	2 (2.2)	3 (3.3)	5 (2.8)
Lost to Follow-Up	1 (1.1)	0	1 (0.6)
Pregnancy	0	0	0
Protocol Violation	2 (2.2)	0	2 (1.1)
Study Terminated by Sponsor	0	0	0
Site Terminated by Sponsor	0	0	0
Other	1 (1.1)	1 (1.1)	2 (1.1)
Number of Subjects Entered Analysis Cycle 2	65	61	126
Number of Subjects Completed Analysis Cycle 2	58 (89.2)	54 (88.5)	112 (88.9)
Number of Subjects Discontinued during Analysis Cycle 2	7 (10.8)	7 (11.5)	14 (11.1)
Reasons for Discontinuation during Analysis Cycle 2			
Screen Failure	0	0	0
Adverse Event	2 (3.1)	1 (1.6)	3 (2.4)
Ocular Adverse Event	0	0	0
Non-ocular Adverse Event	2 (3.1)	1 (1.6)	3 (2.4)
Lack of Efficacy	0	0	0
Withdrawal of Consent	4 (6.2)	3 (4.9)	7 (5.6)
Lost to Follow-Up	1 (1.5)	1 (1.6)	2 (1.6)
Pregnancy	0	0	0
Protocol Violation	0	0	0
Study Terminated by Sponsor	0	0	0
Site Terminated by Sponsor	0	0	0
Other	0	2 (3.3)	2 (1.6)

[1] Subjects were counted as treated if either eye received study treatment.
[2] Subjects who did not receive study treatment in either eye.
Cross reference: Table 14.1-1.2

Protocol Deviations

Protocol deviations were defined in accordance with the ICH guidelines and included but were not limited to the following: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. Deviations were assessed for their impact on analyses and data integrity or subject safety. Significant protocol deviations are summarized in the table below. In the ITT population, 43 of 183 subjects had significant protocol deviations. Of the 43 subjects with deviations defined as significant, all the data from both eyes of 13 subjects were excluded from the PP population because the protocol deviations affected the primary efficacy analysis. Reasons for exclusion from the PP analysis for the 13 excluded subjects were following: inclusion criteria were not met, no study treatment was given, no post-baseline IOP data were available, and/or baseline IOP was < 20 mmHg.

Per protocol analysis exclusion was applied for each eye (SLT or bimatoprost SR 10 µg). If one eye was eligible for the per-protocol analysis, the subject was counted in the per-protocol population summary.

Table 13: Number (%) of subjects with significant protocol deviations (ITT Population)

Protocol Deviation Category	Protocol Deviation Code	Bim SR 10 ug (N=183) n (%)
Overall		42 (23.0)
Dosed using wrong route of administration (ICH)		3 (1.6)
	SI-03	3 (1.6)
Exclusion criteria met (ICH)		2 (1.1)
	EC-01	2 (1.1)
Inclusion criteria not met (ICH)		4 (2.2)
	IC-01	1 (0.5)
	WO-100	3 (1.6)
Initial informed consent not signed (ICH)		1 (0.5)
	ICF-01	1 (0.5)
Prohibited concomitant medication taken (ICH)		7 (3.8)
	CM-01	7 (3.8)
Study Procedure - not performed		13 (7.1)
	SP-500	13 (7.1)
Study Procedure - not performed in protocol-defined time period		1 (0.5)
	SP-200	1 (0.5)
Study Procedure - not performed per protocol		1 (0.5)
	SP-100	1 (0.5)
	SP-101	0
Unblinded study intervention		0
	UNM-01	0
Visit Schedule - missed visit		6 (3.3)
	VSH-100	6 (3.3)
Visit not performed within defined visit window		10 (5.5)
	VSH-200	10 (5.5)
Wrong study eye chosen based on inclusion/exclusion criteria		2 (1.1)
	RAN-100	2 (1.1)

Subjects were counted only once under each protocol deviation category.
Protocol deviations designated as significant (Code=SD, Code Sequence=01) in the system report were summarized in the table.
Protocol deviation categories with 0 counts are not presented. PDs are reported at the subject level rather than eye level.
"Dosed using the wrong route of administration (ICH)" refers to treatments that were administered/performed on the wrong eye of a subject (Listing 16.2.2-1.1).
The majority of "Study Procedure - not performed" deviations were related to ocular exams not performed at screening or baseline visits (Listing 16.2.2-1.1).
Cross reference: Table 14.1-2.1

Recruitment

A total of 240 subjects were randomized (n= 57 Bim 15µg, n= 183 Bim 10µg,) at 61 sites in 11 countries (Australia, Canada, Germany, Denmark, France, Great Britain, Israel, New Zealand, Philippines, Poland, and the US).

First patient, First Visit: 27 August 2015; Last patient, Last Visit: 31 May 2023

Conduct of the study

Protocol Compliance

The original protocol was approved on 21 May 2015. The protocol was amended 7 times (Protocol Amendment 1, dated 01 October 2015; Protocol Amendment 2, dated 01 May2017; Protocol Amendment 3, dated 05 September 2018; Protocol Amendment 4, dated 31 January 2020; Protocol Amendment 5, dated 21 April 2020; Protocol Amendment 6, dated 28 August 2020; Protocol Amendment 7, dated 29 September 2021). The major changes to the original protocol are summarized below.

- Protocol Amendment 1, 01 October 2015: AM 1 was implemented to clarify some sections, to modify the inclusion/exclusion criteria and to remove the Lumigan challenge.
- Protocol Amendment 2, 01 May 2017: AM 2 was implemented to change the screening requirement for angle eligibility confirmation, modify/clarify the inclusion/exclusion criteria, and change additional procedures for patients with sickle cell disease from required to optional.
- **Protocol Amendment 3, 05 September 2018**: AM 3 was implemented to change the bimatoprost SR dose strength under study from 15 µg to 10 µg, and to reduce the number of administration cycles from 3 to 2.
- Protocol Amendment 4, 31 January 2020: AM 4 was implemented to extend the washout period and update the list of medications requiring washout, allow patients enrolled in the 192024-091/092 studies who were randomized to the control treatment and never received an implant to be considered for enrolment at the investigator's discretion, and revise the statistical methods.
- Protocol Amendment 5, 21 April 2020: AM 5 was implemented to add additional detail regarding bimatoprost SR retreatment criteria.
- **Protocol Amendment 6, 28 August 2020:** AM 6 was implemented to lengthen the study duration, to update retreatment criteria, and to add flexibility in the timing of Cycle 2 bimatoprost SR administration for patients not meeting the retreatment criteria at Week 16.
- Protocol Amendment 7, 29 September 2021: AM 7 was implemented to update the covariates in the primary analysis model, add a subgroup analysis for the flexible administration and clarify the differences in the analyses to be done for bimatoprost SR 10 µg and bimatoprost SR 15 µg.

The progression of protocol amendments relative to Stage 1 (Bim 15µg) and Stage 2 (Bim 10µg) as well as to the number of administrations (fixed and flexible) and number of subjects enrolled is presented in the figure below. With the changes made from Stage 1 to Stage 2 (see below), and from fixed to flexible re-administration, masking was maintained throughout the study, consistent with the masking requirements of the original protocol. Approximately 160 subjects were planned for enrolment in Stage 2(Bim 10µg) to maintain the power for the primary efficacy analysis. Additionally, there were 57 subjects who were enrolled in Stage 1 (15 µg) before implementation of protocol Amendment 3. Implemented in protocol Amendment 6, study duration was increased to approximately 26 months, which includes a screening period of up to 28 days before washout, a washout period of up to 56 days before initial study treatment, plus 24 months of follow-up after initial bimatoprost SR and SLT administration. Prior to protocol Amendment 6, subjects were followed for 52 weeks after initial administration, making the overall study duration approximately 14 months.

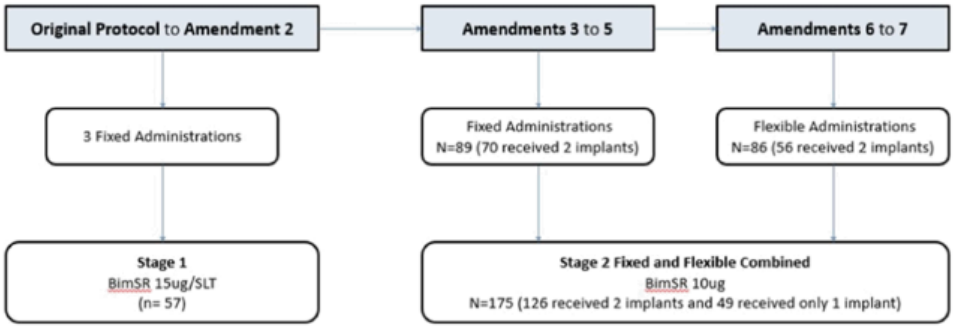


Figure 6: Study 192024-093 protocol amendment progression

GCP Inspections

No GCP inspection have been requested nor taken place.

Baseline data

Demographics

Overall, the mean (SD) age of subjects was 62.4 (11.16) years. The majority of subjects were female, were white, and were non-Hispanic.

Table 14: Demographic (ITT Population)

	SLT (Primary Eye)/ Bim SR 10 ug (Contralateral Eye) (N=92)	Bim SR 10 ug (Primary Eye) / SLT (Contralateral Eye) (N=91)	Total (N=183)
Age (years)			
Mean (SD)	62.6 (11.61)	62.1 (10.74)	62.4 (11.16)
Median	64.0	63.0	64.0
Q1, Q3	56.0, 70.0	57.0, 69.0	56.0, 69.0
Min, Max	29, 86	25, 88	25, 88
n	92	91	183
Age Group, n (%)			
< 45	8 (8.7)	5 (5.5)	13 (7.1)
>= 45 and <= 65	40 (43.5)	53 (58.2)	93 (50.8)
> 65	44 (47.8)	33 (36.3)	77 (42.1)
Sex, n (%)			
Male	46 (50.0)	43 (47.3)	89 (48.6)
Female	46 (50.0)	48 (52.7)	94 (51.4)
Race, n (%)			
White	58 (63.0)	69 (75.8)	127 (69.4)
Black or African American	27 (29.3)	14 (15.4)	41 (22.4)
Asian	4 (4.3)	6 (6.6)	10 (5.5)
American Indian or Alaska Native	0	2 (2.2)	2 (1.1)
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple [1]	0	0	0
Not reported	3 (3.3)	0	3 (1.6)
Race Group, n (%)			
White	58 (63.0)	69 (75.8)	127 (69.4)
Non-White	31 (33.7)	22 (24.2)	53 (29.0)
Not reported	3 (3.3)	0	3 (1.6)
Ethnicity, n (%)			
Hispanic	6 (6.5)	10 (11.0)	16 (8.7)
Non-Hispanic	86 (93.5)	81 (89.0)	167 (91.3)
Not reported	0	0	0
Weight (kg)			
Mean (SD)	85.66 (18.628)	88.40 (21.759)	87.02 (20.236)
Median	82.60	86.20	84.00
Q1, Q3	73.35, 96.00	72.60, 101.20	72.60, 98.40
Min, Max	43.4, 152.0	47.2, 145.2	43.4, 152.0
n	92	91	183
Height (cm)			
Mean (SD)	167.90 (11.049)	169.59 (11.841)	168.74 (11.449)
Median	167.60	169.00	167.60
Q1, Q3	159.40, 175.65	162.60, 177.80	160.00, 177.80
Min, Max	144.8, 190.5	129.5, 196.0	129.5, 196.0
n	92	91	183

Age is based on informed consent date.
[1] Subjects who reported multiple races are only included in 'Multiple' category.
Cross reference: Table 14.1-4.1.1

Ocular Baseline Characteristics

Ocular baseline characteristics were generally comparable between eyes randomized to receive bimatoprost SR 10 µg and eyes randomized to receive SLT. The most common reason for not being adequately managed with topical IOP-lowering medication was memory loss, followed by tolerability/fear of potential side effects.

Table 15: Baseline characteristics (ITT Population)

	SLT (N=183)	Bim SR 10 ug (N=183)
Primary Eye, N1 (%) [1]	92 (50.3)	91 (49.7)
Contralateral Eye, N2 (%)[1]	91 (49.7)	92 (50.3)
Primary Eye IOP Category [2]		
<= 25 mmHg, n (%)	49 (53.3)	48 (52.7)
> 25 mmHg, n (%)	43 (46.7)	43 (47.3)
Overall IOP Category [3]		
<= 25 mmHg, n (%)	115 (62.8)	112 (61.2)
> 25 mmHg, n (%)	68 (37.2)	71 (38.8)
Between Eye IOP Difference [4]		
0-2 mmHg, n (%)	147 (80.3)	
3-5 mmHg, n (%)	36 (19.7)	
Diagnosis, n (%)		
Ocular Hypertension	39 (21.3)	40 (21.9)
Open-Angle Glaucoma	144 (78.7)	143 (78.1)
Primary	142 (77.6)	141 (77.0)
Pseudoexfoliation	0	0
Pigmentary	2 (1.1)	2 (1.1)
Iridocorneal Angle Shaffer Grade, n (%)		
3	78 (42.6)	79 (43.2)
4	105 (57.4)	104 (56.8)
Central Corneal Endothelial Cell Density (cells/mm2)		
Mean (SD)	2517.7 (310.21)	2507.8 (320.73)
Median	2518.0	2493.0
Q1, Q3	2320.0, 2747.0	2309.0, 2733.0
Min, Max	1804, 3256	1817, 3359
n	183	183
Lens Status, n (%)		
Phakic	160 (87.4)	162 (88.5)
Pseudophakic	23 (12.6)	21 (11.5)
Aphakic	0	0
Corneal Thickness (um)		
Mean (SD)	551.3 (31.66)	550.8 (31.77)
Median	549.0	548.2
Q1, Q3	529.0, 573.0	527.0, 574.0
Min, Max	482, 620	481, 625
n	181	182
Iris Color, n (%)		
Monochromic	171 (93.4)	171 (93.4)
Brown	90 (49.2)	90 (49.2)
Dark Brown	17 (9.3)	17 (9.3)
Hazel	14 (7.7)	14 (7.7)
Green	6 (3.3)	6 (3.3)
Blue	42 (23.0)	42 (23.0)
Grey	2 (1.1)	2 (1.1)
Other	0	0
Heterochromic - Peripupillary	7 (3.8)	7 (3.8)
Brown-Green	2 (1.1)	2 (1.1)
Green-Brown	1 (0.5)	1 (0.5)
Blue-Brown	1 (0.5)	1 (0.5)
Brown-Blue	2 (1.1)	2 (1.1)
Other	1 (0.5)	1 (0.5)
Heterochromic - Diffuse	4 (2.2)	4 (2.2)
Brown-Green	1 (0.5)	1 (0.5)
Green-Brown	0	0
Blue-Brown	2 (1.1)	2 (1.1)
Brown-Blue	1 (0.5)	1 (0.5)
Other	0	0
Reasons for Not Being Managed with Topical IOP-lowering Medications, n (%)		
Memory Loss	81 (44.3)	81 (44.3)
Physical Inability to Administer Medication	11 (6.0)	11 (6.0)
Tolerability/Fear of Potential Side Effects	70 (38.3)	70 (38.3)
Other	21 (11.5)	21 (11.5)

Summary of primary eye is based on the randomization visit.
For Shaffer grade, the minimum of measurement from two assessors were used for each eye.
[1] N1: the number of primary eyes randomized to SLT or Bim SR 10 ug. N2: the number of contralateral eyes. Percentages are based on the Ns in the column headings (i.e., the numbers of eyes in the ITT population).
[2] Percentages are based on N1, the number of primary eyes randomized to SLT or Bim SR 10 ug.
[3] Percentages are based on N, the number of eyes randomized to SLT or Bim SR 10 ug.
[4] Between eye IOP difference is calculated as higher IOP minus lower IOP and summarized in the SLT column.
Cross reference: Table 14.1-4.1.2

Prior and Concomitant Medications

In the ITT population, the majority of subjects overall reported use of nonophthalmic prior (83.1% and concomitant (91.8%) medications. Ophthalmic concomitant medications were reported for 96.7% of eyes (177/183) randomized to receive SLT and 97.3% of eyes (178/183) randomized to receive bimatoprost SR 10 µg.

Concomitant nonstudy IOP-lowering medications were reported for 36.7% of eyes randomized to receive SLT and 43.9% of eyes randomized to receive bimatoprost SR 10 µg.

Table 16: Duration of permanent non-study IOP-lowering medications (Concomitant Use)

Intent-to-Treat Population
Study 192024-093: Bim SR 10ug

Treatment Period		SLT (N=183)	Bim SR 10ug Flex (N=88)	Bim SR 10ug Fixed (N=95)	Bim SR 10ug Total (N=183)
Overall	Duration of Rescue Med.(Days)				
	N1 [1]	180	88	92	180
	N2 [2]	66 (36.7)	43 (48.9)	36 (39.1)	79 (43.9)
	Mean (SD)	257 (214.3)	286 (227.6)	220 (173.5)	257 (206.9)
	Median	200	238	178	193
	Min, Max	1, 727	1, 713	1, 668	1, 713
Cycle 1	Duration of Rescue Med.(Days) in Cycle 1				
	N1 [1]	180	88	92	180
	N2 [2]	32 (17.8)	16 (18.2)	13 (14.1)	29 (16.1)
	Mean (SD)	249 (249.6)	318 (275.7)	254 (198.5)	288 (242.9)
	Median	148	313	236	241
	Min, Max	1, 727	1, 713	2, 668	1, 713
Cycle 2	Duration of Rescue Med.(Days) in Cycle 2				
	N1 [1]	126	56	70	126
	N2 [2]	40 (31.7)	27 (48.2)	23 (32.9)	50 (39.7)
	Mean (SD)	222 (171.5)	262 (180.9)	182 (147.3)	226 (170.3)
	Median	174	238	169	183
	Min, Max	1, 584	7, 562	1, 491	1, 562

[1] N1: Number of eyes in the treatment period and used for denominators of percentages.
[2] N2: Number of eyes received non-study IOP-lowering medication as concomitant use in the treatment period.

Treatment compliance

Not applicable; SLT and bimatoprost SR were administered by the investigator.

Numbers analysed

Table 17: Analysis populations

	SLT [1]	Bim SR 10 ug [2]	Total [3]
Intent-to-Treat Population, N	183	183	183
Per-Protocol Population, N	167	169	170
Safety Population, N	180	175	180

[1] Subjects contributed data to SLT
[2] Subjects contributed data to Bim SR 10 ug
[3] Subjects contributed data to either SLT or Bim SR 10 ug
Cross reference: Table 14.1-3.1

All baseline and efficacy analyses were based on the ITT population and all safety analyses were based on the safety population. Additional analysis of the primary efficacy endpoint was conducted on the PP population. Thirteen subjects in the ITT population were excluded from the PP population due to protocol deviations affecting the primary analysis (please refer to section 3.3.2.1. 'Protocol Deviations' for more details).

Outcomes and estimation

Unless the re-administration regimen is specifically stated (i.e., flexible or fixed), the data presented include combined fixed and flexible re-administration regimens. The results are shown only for 10µg strength, as only this strength is applied for.

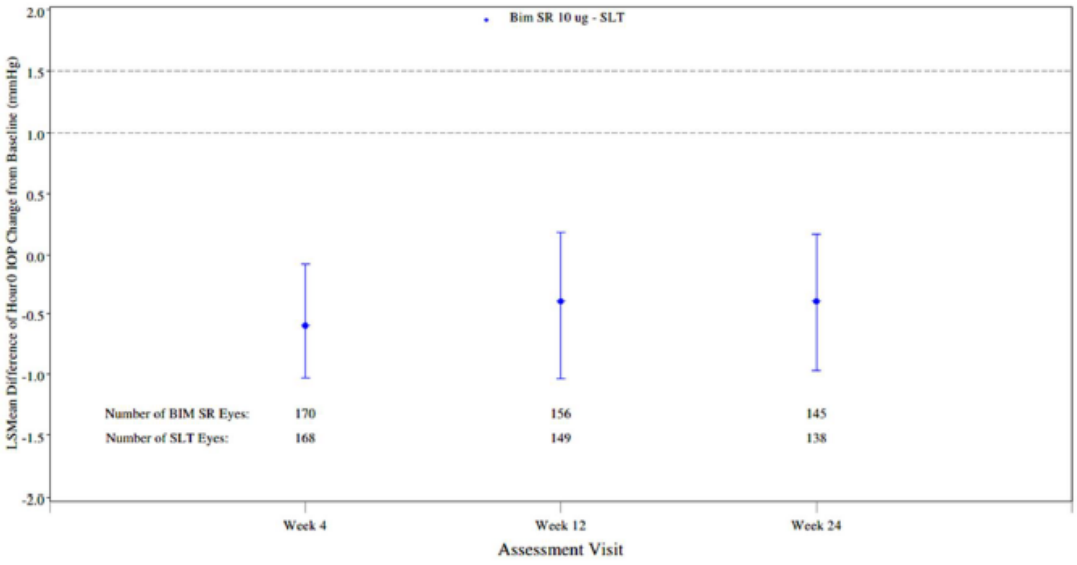
Primary Efficacy Endpoint

Hour 0 IOP change from baseline assessed at Weeks 4, 12, and 24 with comparisons between bimatoprost SR 10 µg and SLT analysed using MMRM (ITT population)

Table 18: Hour 0 IOP (mmHg): Summary of baseline. Postbaseline, and analysis of change from baseline – primary efficacy analysis using MMRM – bimatoprost SR 10 µg/SLT (ITT Population)

	SLT (N=183)	Bim SR 10 ug (N=183)
Baseline		
Mean (SD)	25.1 (3.00)	25.2 (2.99)
Median	24.0	24.0
Q1, Q3	23.0, 26.0	23.0, 27.0
Min, Max	16.0, 34.0	15.0, 34.0
n	183	183
Week 4		
Mean (SD)	18.8 (4.07)	18.3 (4.05)
Median	18.0	18.0
Q1, Q3	16.0, 21.0	15.0, 20.5
Min, Max	11.5, 32.0	11.5, 33.0
n	168	170
Change from baseline		
Mean (SD)	-6.3 (3.69)	-6.9 (3.73)
Median	-6.5	-7.0
Q1, Q3	-8.8, -4.0	-9.5, -4.5
Min, Max	-16.5, 5.0	-19.5, 5.0
n	168	170
Model [1]		
Least Square Mean (SE)	-6.2 (0.28)	-6.8 (0.28)
Difference vs. SLT (SE)		-0.6 (0.24)
95% CI		(-1.03, -0.08)
P-value		0.0231
Week 12		
Mean (SD)	18.1 (3.85)	17.9 (4.29)
Median	18.0	18.0
Q1, Q3	16.0, 20.0	15.0, 20.0
Min, Max	10.5, 30.0	9.0, 37.0
n	149	156
Change from baseline		
Mean (SD)	-6.5 (3.52)	-7.1 (3.98)
Median	-6.5	-7.3
Q1, Q3	-9.0, -4.0	-9.5, -4.0
Min, Max	-16.0, 7.0	-19.5, 7.0
n	149	156
Model [1]		
Least Square Mean (SE)	-6.4 (0.30)	-6.9 (0.30)
Difference vs. SLT (SE)		-0.4 (0.31)
95% CI		(-1.04, 0.18)
P-value		0.1615
Week 24		
Mean (SD)	18.0 (3.40)	17.7 (3.74)
Median	17.5	17.5
Q1, Q3	16.0, 20.0	15.5, 20.0
Min, Max	10.0, 29.0	7.0, 31.0
n	138	145
Change from baseline		
Mean (SD)	-6.5 (3.02)	-7.1 (3.81)
Median	-6.0	-7.0
Q1, Q3	-8.5, -4.5	-9.0, -5.0
Min, Max	-14.0, 3.0	-22.5, 1.0
n	138	145
Model [1]		
Least Square Mean (SE)	-6.5 (0.28)	-6.9 (0.27)
Difference vs. SLT (SE)		-0.4 (0.29)
95% CI		(-0.97, 0.17)
P-value		0.1673

[1] A mixed model repeated measures (MMRM) analysis was performed to compare IOP change from baseline between SLT and Bim SR 10 ug. In the model IOP change from baseline is the response variable, baseline IOP is the covariate, and treatment, visit, eye, and treatment-by-visit, visit-by-baseline IOP, and visit-by-eye interactions are factors in the model. An unstructured covariance matrix for study visit and eyes were used for the analysis.



Bim SR = Bimatoprost Sustained Release; CI = confidence interval; IOP = intraocular pressure; ITT = intent-to-treat; LS = least squares; MMRM = mixed model repeated measures; SLT = selective laser trabeculoplasty

An MMRM analysis was performed to compare IOP change from baseline between SLT and Bimatoprost SR 10 ug. In the model, IOP change from baseline is the response variable, baseline IOP is the covariate, and treatment, visit, eye, and treatment-by-visit, visit-by-baseline IOP, and visit-by-eye interactions are factors in the model. An unstructured covariance matrix for study visit and eyes were used for the analysis.

Cross reference: Study 192024-093 Month 12 CSR Figure 14.2-1.1

Figure 7: LS mean and 95% CI for the difference between bimatoprost SR 10 µg and SLT in the change in hour 0 IOP from baseline at week 4, week 12, and week 24 – bimatoprost SR 10 µg/SLT (ITT Population)

Summary of IOP Baseline, Post-baseline and Change from Baseline by Analysis Cycle (1, 2), ITT

Table 19: Hour 0 IOP (mmHg): Summary of baseline, post-baseline and change from baseline by analysis cycle

Intent-to-Treat Population
Bim SR 10 ug/SLT

Analysis Cycle	SLT (N=183)	Bim SR 10 ug (N=183)
Cycle 1 Week 4		
Mean (SD)	18.8 (4.07)	18.3 (4.05)
Median	18.0	18.0
Q1, Q3	16.0, 21.0	15.0, 20.5
Min, Max	11.5, 32.0	11.5, 33.0
n	168	170
Change from baseline		
Mean (SD)	-6.3 (3.69)	-6.9 (3.73)
Median	-6.5	-7.0
Q1, Q3	-8.8, -4.0	-9.5, -4.5
Min, Max	-16.5, 5.0	-19.5, 5.0
n	168	170
Cycle 1 Week 12		
Mean (SD)	18.1 (3.85)	17.9 (4.29)
Median	18.0	18.0
Q1, Q3	16.0, 20.0	15.0, 20.0
Min, Max	10.5, 30.0	9.0, 37.0
n	149	156
Change from baseline		
Mean (SD)	-6.5 (3.52)	-7.1 (3.98)
Median	-6.5	-7.3
Q1, Q3	-9.0, -4.0	-9.5, -4.0
Min, Max	-16.0, 7.0	-19.5, 7.0
n	149	156

Cycle 1 Week 24		
Mean (SD)	16.8 (3.18)	17.4 (3.94)
Median	17.3	17.5
Q1, Q3	15.0, 19.0	14.5, 20.0
Min, Max	10.0, 24.0	10.0, 28.0
n	46	45
Change from baseline		
Mean (SD)	-7.3 (2.99)	-6.9 (4.35)
Median	-7.0	-7.0
Q1, Q3	-9.0, -5.0	-9.0, -4.0
Min, Max	-13.0, -1.0	-21.0, 3.5
n	46	45
Cycle 1 Month 13		
Mean (SD)	16.6 (3.02)	16.9 (4.09)
Median	16.0	16.5
Q1, Q3	14.8, 19.3	14.5, 18.0
Min, Max	10.0, 23.0	11.5, 26.0
n	20	15
Change from baseline		
Mean (SD)	-7.3 (3.65)	-6.7 (4.31)
Median	-7.3	-7.0
Q1, Q3	-9.3, -4.8	-10.0, -6.5
Min, Max	-17.0, -1.0	-11.5, 4.0
n	20	15
Cycle 2 Week 4		
Mean (SD)	18.8 (3.97)	18.0 (3.82)
Median	18.0	18.0
Q1, Q3	16.0, 21.5	15.0, 20.5
Min, Max	8.5, 30.0	10.0, 27.0
n	114	124
Change from baseline		
Mean (SD)	-6.1 (3.66)	-6.9 (3.66)
Median	-6.0	-7.0
Q1, Q3	-8.0, -3.5	-9.0, -5.0
Min, Max	-17.0, 3.0	-16.0, 2.0
n	114	124
Cycle 2 Week 12		
Mean (SD)	18.9 (3.95)	18.3 (4.18)
Median	18.5	18.0
Q1, Q3	16.5, 20.0	15.0, 20.0
Min, Max	10.5, 36.5	10.5, 29.0
n	95	105
Change from baseline		
Mean (SD)	-6.0 (3.70)	-6.7 (4.14)
Median	-6.0	-6.5
Q1, Q3	-8.0, -4.0	-9.0, -4.5
Min, Max	-18.0, 6.5	-17.5, 2.0
n	95	105
Cycle 2 Week 24		
Mean (SD)	18.4 (3.78)	19.5 (4.04)
Median	18.0	19.0
Q1, Q3	16.0, 20.0	16.5, 22.0
Min, Max	12.0, 31.5	10.0, 32.0
n	83	87
Change from baseline		
Mean (SD)	-6.3 (3.76)	-5.4 (4.06)
Median	-6.5	-5.5
Q1, Q3	-9.0, -4.5	-7.5, -3.0
Min, Max	-17.0, 6.5	-16.0, 9.5
n	83	87
Cycle 2 Month 13		
Mean (SD)	17.4 (2.74)	19.6 (3.22)
Median	18.0	19.5
Q1, Q3	14.5, 20.0	17.0, 22.5
Min, Max	13.5, 22.0	14.0, 24.0
n	18	14
Change from baseline		
Mean (SD)	-6.9 (2.16)	-5.2 (2.37)
Median	-7.0	-5.5
Q1, Q3	-8.5, -5.5	-7.5, -2.5
Min, Max	-10.0, -2.5	-8.0, -1.5
n	18	14

Each analysis cycle starts from the respective Bim SR administration date.

Sensitivity Analyses

Sensitivity analyses were performed for the comparison of bimatoprost SR 10 µg vs SLT for the primary efficacy endpoint, as follows:

- PP population
- ANCOVA based on last observation carried forward
- Tipping point method that penalized the bimatoprost SR 10 ug-treated eyes by adding shifts to the change from baseline.
- Including all IOP data regardless of nonstudy IOP treatment use.
- Excluding IOP after the second bimatoprost SR implant in the flexible re-administration group (see Table below).

Excluding IOP after the second bimatoprost SR implant in the flexible re-administration group

Table 20: Hour 0 IOP (mmHg): Summary of baseline, post-baseline and analysis of change from baseline sensitivity analysis: excluding IOP after the second Bim SR implant treated after week 16 and prior to week 24 in the flexible dosing regiment

Intent-to-Treat Population
Bim SR 10 ug/SLT

Visit	SLT (N=183)	Bim SR 10 ug (N=183)
Baseline		
Mean (SD)	25.1 (3.00)	25.2 (2.99)
Median	24.0	24.0
Q1, Q3	23.0, 26.0	23.0, 27.0
Min, Max	16.0, 34.0	15.0, 34.0
n	183	183
Week 4		
Mean (SD)	18.8 (4.07)	18.3 (4.05)
Median	18.0	18.0
Q1, Q3	16.0, 21.0	15.0, 20.5
Min, Max	11.5, 32.0	11.5, 33.0
n	168	170
Change from baseline		
Mean (SD)	-6.3 (3.69)	-6.9 (3.73)
Median	-6.5	-7.0
Q1, Q3	-8.8, -4.0	-9.5, -4.5
Min, Max	-16.5, 5.0	-19.5, 5.0
n	168	170
Model [1]		
Least Square Mean (SE)	-6.2 (0.28)	-6.8 (0.28)
Difference vs. SLT (SE)		-0.6 (0.24)
95% CI		(-1.06, -0.10)
P-value		0.0175
Week 12		
Mean (SD)	18.1 (3.85)	17.9 (4.29)
Median	18.0	18.0
Q1, Q3	16.0, 20.0	15.0, 20.0
Min, Max	10.5, 30.0	9.0, 37.0
n	149	156
Change from baseline		
Mean (SD)	-6.5 (3.52)	-7.1 (3.98)
Median	-6.5	-7.3
Q1, Q3	-9.0, -4.0	-9.5, -4.0
Min, Max	-16.0, 7.0	-19.5, 7.0
n	149	156
Model [1]		
Least Square Mean (SE)	-6.4 (0.30)	-6.9 (0.30)
Difference vs. SLT (SE)		-0.4 (0.30)
95% CI		(-1.05, 0.15)
P-value		0.1436
Week 24		
Mean (SD)	18.0 (3.40)	17.9 (3.68)
Median	17.5	17.5
Q1, Q3	16.0, 20.0	15.5, 20.0
Min, Max	10.0, 29.0	10.0, 31.0
n	138	133
Change from baseline		
Mean (SD)	-6.5 (3.02)	-6.9 (3.59)
Median	-6.0	-7.0
Q1, Q3	-8.5, -4.5	-9.0, -4.5
Min, Max	-14.0, 3.0	-21.0, 1.0
n	138	133
Model [1]		
Least Square Mean (SE)	-6.5 (0.27)	-6.7 (0.27)
Difference vs. SLT (SE)		-0.2 (0.28)
95% CI		(-0.78, 0.32)
P-value		0.4109

IOP values after week 16 and prior to week 24 in the flexible dosing regimen after the Bim SR second implant treated were excluded for the analysis.
[1] A mixed model repeated measures (MMRM) analysis was performed to compare IOP change from baseline between SLT and Bim SR 10 ug. In the model IOP change from baseline is the response variable, baseline IOP is the covariate, and treatment, visit, eye, and treatment-by-visit, visit-by-baseline IOP, and visit-by-eye interactions are factors in the model. An unstructured covariance matrix for study visit and eyes were used for the analysis.

In addition, the applicant was asked to rerun primary efficacy analysis using a sparse model, which can still be assumed to deliver an unbiased estimate for the treatment effect of bimatoprost. An MMRM with treatment, visit, baseline Hour 0 IOP, between-eye baseline IOP difference, and treatment by-visit as fixed effects had to be performed. The unstructured covariance matrix for study visits and eye (primary [with higher IOP at baseline] vs. contralateral) for repeated measures on the same patient had to be kept. To complement this analysis with some sensitivity analyses, the Tipping Point Analysis and the analysis to estimate the Treatment Effect regardless of Non-Study IOP Treatment Use had to be repeated with this simplified model. Bonferroni-corrected confidence intervals had to be provided also. The results are presented below:

Table 21: Primary efficacy analysis for IOP changes from baseline using the simplified model with or without IOP data after non-study IOP treatment use

Visit	Primary Efficacy Result (full model; excluded IOP data after receiving non-Study treatment)	Simplified Model Excluding IOP Data After Non-Study IOP Treatment Use	Simplified Model Including all IOP Data Regardless of Non-Study IOP Treatment Use
Week 4			
LS Mean Difference (SE)	-0.6 (0.24)	-0.5 (0.24)	-0.5 (0.23)
95% CI	(-1.03, -0.08)	(-1.02, -0.07)	(-1.01, -0.09)
Week 12			
LS Mean Difference (SE)	-0.4 (0.31)	-0.4 (0.31)	-0.3 (0.29)
95% CI	(-1.04, 0.18)	(-1.02, 0.19)	(-0.86, 0.29)
Week 24			
LS Mean Difference (SE)	-0.4 (0.29)	-0.4 (0.29)	-0.4 (0.23)
95% CI	(-0.97, 0.17)	(-0.98, 0.16)	(-0.88, 0.04)

Source: Tables 200-1.1 and 200-1.3; Module 5.3.5.1, 192024-093 Final CSR, Table 14.2-1.1

Table 22: Tipping point analysis result (95% CI) for IOP change from baseline using the simplified model with or without IOP data after rescue

		95% CI for Treatment Difference in IOP Change from Baseline (Bimatoprost SR – SLT)		
Shift value applied to Bimatoprost SR arm only	**Visit**	**Primary Efficacy (full model; excluded IOP data after receiving non-study treatment)**	**Simplified Model Excluding IOP Data After Rescue**	**Simplified Model Including all IOP Data Regardless of Rescue**
6 mmHg	Week 4	(-0.74, 0.37)	(-0.75, 0.36)	(-0.79, 0.29)
	Week 12	(-0.41, 1.10)	(-0.40, 1.10)	(-0.47, 0.84)
	Week 24	(-0.17, **1.51**)	(-0.17, **1.51**)	(-0.37, 0.79)
8 mmHg	Week 4	(-0.64, 0.53)	(-0.65, 0.53)	(-0.71, 0.41)
	Week 12	(-0.19, 1.43)	(-0.18, 1.44)	(-0.36, 1.02)
	Week 24	(0.17, **1.98**)	(0.17, **1.98**)	(-0.22, 1.02)
10 mmHg	Week 4	(-0.55, 0.70)	(-0.56, 0.70)	(-0.65, 0.54)
	Week 12	(0.02, **1.77**)	(0.03, **1.77**)	(-0.25, 1.20)
	Week 24	(0.50, **2.46**)	(0.49, **2.46**)	(-0.10, 1.25)

Source: Tables 200-1.2 and 200-1.4; Module 5.3.1, 192024-093 Final CSR, Table 14.2-5.3

To further evaluate the effect of a single BimSR implant, the applicant was asked to perform primary efficacy analysis at Week 16 before the second implant was administered.

Table 23: Primary efficacy analysis compared to analysis of 1 implant

Visit	Primary Efficacy Result	Primary Efficacy Result with 1 Implant
Week 4		
LS Mean Difference (SE)	-0.6 (0.24)	-0.6 (0.24)
95% CI	(-1.03, -0.08)	(-1.06, -0.11)
Week 12		
LS Mean Difference (SE)	-0.4 (0.31)	-0.4 (0.31)
95% CI	(-1.04, 0.18)	(-1.03, 0.17)
Week 15		
LS Mean Difference (SE)	N/A	0.2 (0.30)
95% CI	N/A	(-0.44, 0.75)
Week 24		
LS Mean Difference (SE)	-0.4 (0.29)	N/A
95% CI	(-0.97, 0.17)	N/A

LS Mean = difference between Bimatoprost SR versus SLT

N/A=not applicable. Week 15 is not a pre-specified time point in the primary efficacy analysis; Week 24 assessment is not applicable to the subgroup analysis before the second implant was administered.

Source: Module 5.3.5.1, 192024-093 Final CSR, Table 14.2-1.1; Table 200-3.1

Secondary and Other Efficacy Endpoints

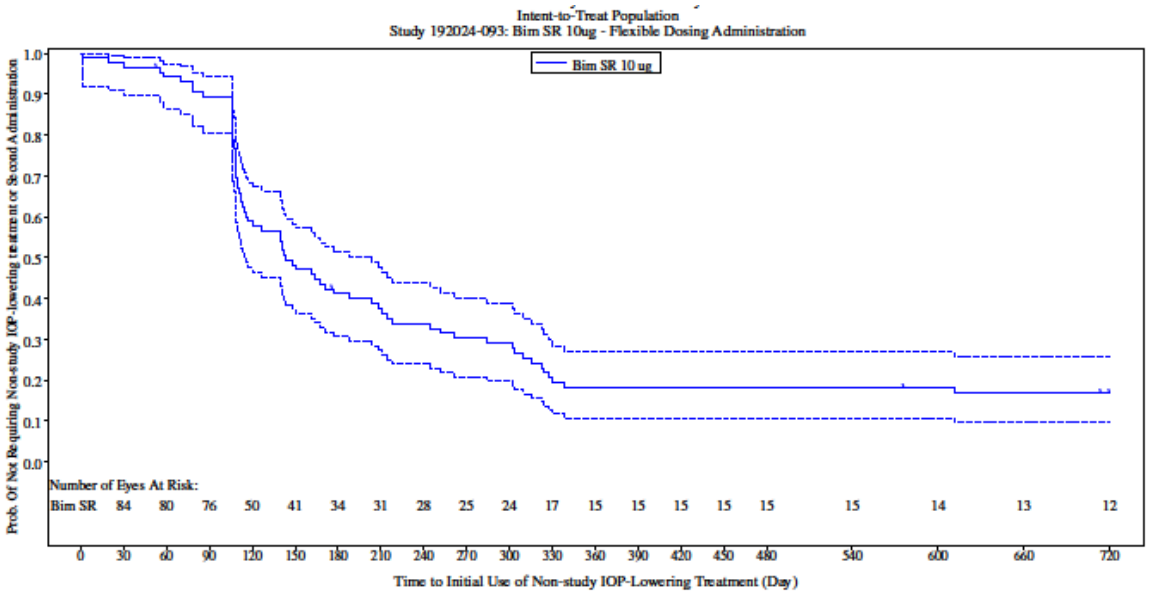
1. Superiority Test of bimatoprost SR 10 µg Versus SLT

Bimatoprost SR 10 µg had numerically larger mean IOP reductions from Baseline at all 3 visits compared with SLT; however, the upper limit of the 95% CI for the LS mean difference was below zero at only 1 out of 3 visits (Week 4) (Figure 2). Therefore, 2. superiority of bimatoprost SR 10 µg vs SLT was not achieved.

2. Time to Initial Use of Nonstudy IOP-Lowering Treatment

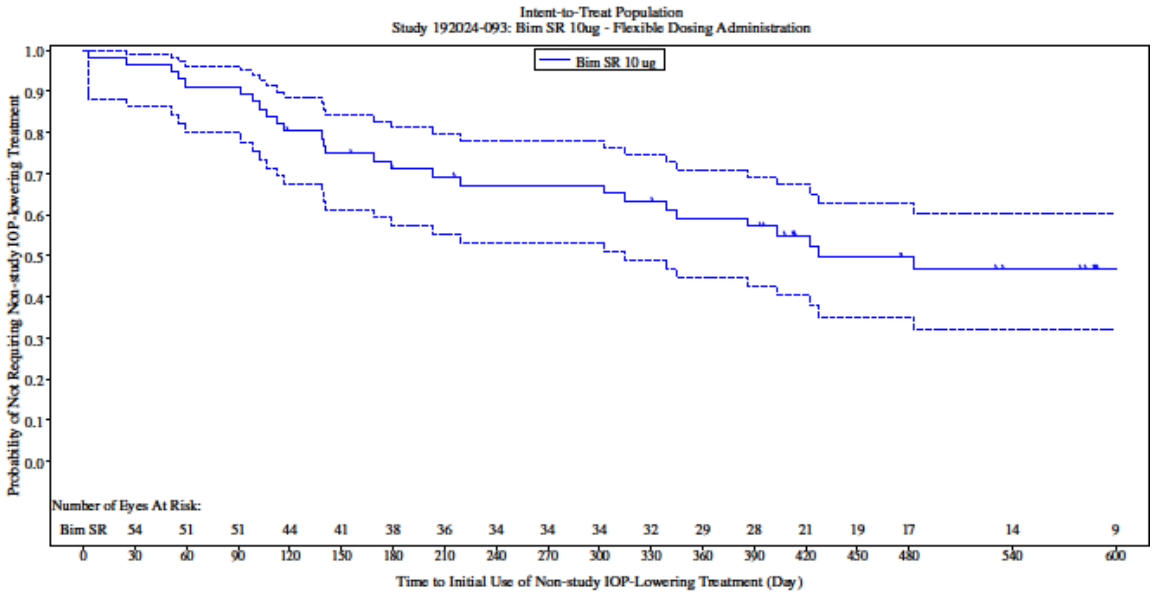
The applicant has presented data for "Time to initial use of rescue treatment from initial study treatments" and "Time to initial use of rescue treatment after the second bimatoprost SR treatment" for pooled BIM SR 10 µg fixed and flexible regimen.

The interpretation of the data regarding the "Time to initial use of rescue treatment from initial study treatments" is convoluted by the administration of second implant; especially since in the fixed regimen re-administration took place at Week 16, and in the flexible regimen could have taken place at any time point from Week 16 and prior to the Month 12 visit. Consequently, the applicant was asked to present Kaplan-Meier analyses for subjects in the flexible regimen, evaluating a) time to first rescue treatment or second administration after the first BimSR administration and b) time to rescue medication after second BimSR administration. They are presented below for the BIM SR 10 µg regimen, no comparative data for SLT have been presented:



Note: Probabilities are estimated using the Kaplan-Meier (KM) method. Time to initial use of non-study IOP-lowering treatment = (Date of earliest initial use of non-study IOP-lowering treatment or second administration -Date of initial study treatment) +1.
Backward slashes indicate censored observations. Censoring is at the study exit date or, if the study exit date is not available, last visit date for subjects who did not use any non-study IOP-lowering treatment or not receive the second administration.

Figure 8: Time to initial use of non-study IOP-lowering treatment (or second Bim SR administration) from initial study treatment event summary and survival analysis



Note: Probabilities are estimated using the Kaplan-Meier (KM) method. Time to initial use of non-study IOP-lowering treatment = (Date of earliest initial use of non-study IOP-lowerin treatment -Date of second study treatment) +1.
Backward slashes indicate censored observations. Censoring is at the study exit date or, if the study exit date is not available, last visit date for subjects who did not use any non-study IOP-lowering treatment.

Figure 9: Time to initial use of non-study IOP-lowering treatment after second administration event summary and survival analysis

3. Percentage of BIM SR and SLT eyes achieving ≥ 20% Reduction by Visit

A clinically meaningful reduction in IOP (≥ 20% from Baseline) was achieved for bimatoprost SR 10 µg treated eyes (71.2% to 75.3%) and for SLT-treated eyes (64.0% to 71.1%) through Week 12 in Cycle 1 (Week 4 through Week 12). In Cycle 2, 71.4% to 76.3% of bimatoprost SR 10 µg-treated eyes and

58.8% to 69.5% of SLT-treated eyes achieved a clinically meaningful reduction in IOP (≥ 20% from Baseline) (Week 4 through Week 12).

In addition, the number and percentage of bimatoprost SR 10 µg- and SLT-treated eyes that achieved a ≥ 20% reduction in IOP, regardless of cycle were presented. A clinically meaningful reduction in IOP (≥ 20% from Baseline) was achieved for bimatoprost SR 10 µg-treated eyes (75.2%, 66.4%, and 66.7%) and for SLT-treated eyes (73.2%, 78.4%, and 73.2%) at Weeks 24 and 52 and Month 24, respectively.

The applicant was asked to provide more details on all analyses comparing Bim SR 10 µg and SLT listed in the subsection other efficacy analyses. In particular, clarification was required how missing values or measured values after non-study IOP lowering medication use were considered. Moreover, two calculations, one with and one without values measured after initiation of non-study IOP lowering medication, and an impact assessment for inclusion/exclusion of such values were requested for the percentages of eyes achieving ≥ 15%, ≥ 20% and ≥ 30% reductions from baseline IOP by visit and IOP change from baseline and post-baseline IOP. The use of non-study IOP lowering medication was to be considered a competing event in the analysis of time to first achieving ≥ 20% IOP reduction. The requested data is presented below:

Table 24: Hour 0 IOP (mmHg): Proportions of eyes achieving 15%, 20% and 30% reduction at each visit regardless of analysis cycle

Intent-to-Treat Population – Including all IOP regardless of Nonstudy IOP-lowering Treatment Use
Study 192024-093: Bim SR 10ug

	SLT (N=183) n (%)	Bim SR 10 ug (N=183) n (%)
Bim SR Day 2		
N1	173	173
>= 15% IOP Reduction, n (%)	120 (69.4)	158 (91.3)
>= 20% IOP Reduction, n (%)	103 (59.5)	150 (86.7)
>= 30% IOP Reduction, n (%)	62 (35.8)	120 (69.4)
Week 4		
N1	173	173
>= 15% IOP Reduction, n (%)	137 (79.2)	145 (83.8)
>= 20% IOP Reduction, n (%)	119 (68.8)	125 (72.3)
>= 30% IOP Reduction, n (%)	71 (41.0)	82 (47.4)
Week 8		
N1	173	173
>= 15% IOP Reduction, n (%)	134 (77.5)	141 (81.5)
>= 20% IOP Reduction, n (%)	114 (65.9)	132 (76.3)
>= 30% IOP Reduction, n (%)	70 (40.5)	84 (48.6)
Week 12		
N1	168	168
>= 15% IOP Reduction, n (%)	137 (81.5)	137 (81.5)
>= 20% IOP Reduction, n (%)	123 (73.2)	121 (72.0)
>= 30% IOP Reduction, n (%)	69 (41.1)	86 (51.2)
Week 15		
N1	168	168
>= 15% IOP Reduction, n (%)	144 (85.7)	141 (83.9)
>= 20% IOP Reduction, n (%)	127 (75.6)	136 (81.0)
>= 30% IOP Reduction, n (%)	80 (47.6)	104 (61.9)

N1: Number of eyes with available data at both baseline and a given visit.
IOP data after non-study IOP-lowering medication were included in the analysis.

Table 200-2.1
Hour 0 IOP (mmHg): Proportions of Eyes Achieving 15%, 20% and 30% Reduction at Each Visit regardless of Analysis Cycle
Intent-to-Treat Population – Including all IOP regardless of Nonstudy IOP-lowering Treatment Use
Study 192024-093: Bim SR 10ug

	SLT (N=183) n (%)	Bim SR 10 ug (N=183) n (%)
Week 20		
N1	166	166
>= 15% IOP Reduction, n (%)	132 (79.5)	131 (78.9)
>= 20% IOP Reduction, n (%)	111 (66.9)	117 (70.5)
>= 30% IOP Reduction, n (%)	63 (38.0)	72 (43.4)
Week 24		
N1	165	165
>= 15% IOP Reduction, n (%)	140 (84.8)	140 (84.8)
>= 20% IOP Reduction, n (%)	124 (75.2)	125 (75.8)
>= 30% IOP Reduction, n (%)	71 (43.0)	84 (50.9)
Week 28		
N1	156	156
>= 15% IOP Reduction, n (%)	124 (79.5)	125 (80.1)
>= 20% IOP Reduction, n (%)	110 (70.5)	112 (71.8)
>= 30% IOP Reduction, n (%)	59 (37.8)	68 (43.6)
Week 31		
N1	158	158
>= 15% IOP Reduction, n (%)	130 (82.3)	119 (75.3)
>= 20% IOP Reduction, n (%)	115 (72.8)	103 (65.2)
>= 30% IOP Reduction, n (%)	60 (38.0)	62 (39.2)
Week 36		
N1	162	162
>= 15% IOP Reduction, n (%)	129 (79.6)	113 (69.8)
>= 20% IOP Reduction, n (%)	118 (72.8)	95 (58.6)
>= 30% IOP Reduction, n (%)	76 (46.9)	61 (37.7)

N1: Number of eyes with available data at both baseline and a given visit.
IOP data after non-study IOP-lowering medication were included in the analysis.

Table 25: Hour 0 IOP (mmHg): Proportions of eyes achieving 15%, 20% and 30% reduction at each visit regardless of analysis cycle

Intent-to-Treat Population - Excluding IOP data after Nonstudy IOP-lowering Treatment Use
Study 192024-093: Bim SR 10ug

	SLT (N=183) n (%)	Bim SR 10 ug (N=183) n (%)
Bim SR Day 2		
N1	171	172
>= 15% IOP Reduction, n (%)	118 (69.0)	157 (91.3)
>= 20% IOP Reduction, n (%)	101 (59.1)	149 (86.6)
>= 30% IOP Reduction, n (%)	61 (35.7)	119 (69.2)
Week 4		
N1	168	170
>= 15% IOP Reduction, n (%)	133 (79.2)	141 (82.9)
>= 20% IOP Reduction, n (%)	115 (68.5)	121 (71.2)
>= 30% IOP Reduction, n (%)	68 (40.5)	78 (45.9)
Week 8		
N1	164	166
>= 15% IOP Reduction, n (%)	125 (76.2)	134 (80.7)
>= 20% IOP Reduction, n (%)	105 (64.0)	125 (75.3)
>= 30% IOP Reduction, n (%)	65 (39.6)	80 (48.2)
Week 12		
N1	149	156
>= 15% IOP Reduction, n (%)	120 (80.5)	127 (81.4)
>= 20% IOP Reduction, n (%)	106 (71.1)	112 (71.8)
>= 30% IOP Reduction, n (%)	60 (40.3)	78 (50.0)
Week 15		
N1	147	152
>= 15% IOP Reduction, n (%)	117 (79.6)	105 (69.1)
>= 20% IOP Reduction, n (%)	96 (65.3)	93 (61.2)
>= 30% IOP Reduction, n (%)	53 (36.1)	61 (40.1)

N1: Number of eyes with available data at both baseline and a given visit.
IOP data after non-study IOP-lowering medication were excluded in the analysis.

Table 200-2.2
Hour 0 IOP (mmHg): Proportions of Eyes Achieving 15%, 20% and 30% Reduction at Each Visit regardless of Analysis Cycle
Intent-to-Treat Population - Excluding IOP data after Nonstudy IOP-lowering Treatment Use
Study 192024-093: Bim SR 10ug

	SLT (N=183) n (%)	Bim SR 10 ug (N=183) n (%)
Week 20		
N1	145	150
>= 15% IOP Reduction, n (%)	109 (75.2)	113 (75.3)
>= 20% IOP Reduction, n (%)	91 (62.8)	101 (67.3)
>= 30% IOP Reduction, n (%)	48 (33.1)	61 (40.7)
Week 24		
N1	138	145
>= 15% IOP Reduction, n (%)	116 (84.1)	120 (82.8)
>= 20% IOP Reduction, n (%)	101 (73.2)	109 (75.2)
>= 30% IOP Reduction, n (%)	52 (37.7)	69 (47.6)
Week 28		
N1	129	133
>= 15% IOP Reduction, n (%)	104 (80.6)	105 (78.9)
>= 20% IOP Reduction, n (%)	93 (72.1)	95 (71.4)
>= 30% IOP Reduction, n (%)	47 (36.4)	56 (42.1)
Week 31		
N1	126	132
>= 15% IOP Reduction, n (%)	100 (79.4)	97 (73.5)
>= 20% IOP Reduction, n (%)	85 (67.5)	82 (62.1)
>= 30% IOP Reduction, n (%)	41 (32.5)	48 (36.4)
Week 36		
N1	126	128
>= 15% IOP Reduction, n (%)	97 (77.0)	86 (67.2)
>= 20% IOP Reduction, n (%)	86 (68.3)	71 (55.5)
>= 30% IOP Reduction, n (%)	51 (40.5)	45 (35.2)

N1: Number of eyes with available data at both baseline and a given visit.
IOP data after non-study IOP-lowering medication were excluded in the analysis.

4. <u>IOP and IOP Change from Baseline at Weeks 8, 15, and 20</u>

Table 26: Hour 0 IOP (mmHg): Summary of baseline, postbaseline, and change from baseline at week 8, 15 (or 16), and 20 by analysis cycle – bimatoprost SR 10 µg/SLT (ITT Population)

Analysis Cycle	SLT (N=183)	Bim SR 10 ug (N=183)
Baseline		
Mean (SD)	25.1 (3.00)	25.2 (2.99)
Median	24.0	24.0
Q1, Q3	23.0, 26.0	23.0, 27.0
Min, Max	16.0, 34.0	15.0, 34.0
n	183	183
Cycle 1 Week 8		
Mean (SD)	18.8 (4.05)	18.2 (4.05)
Median	18.0	17.3
Q1, Q3	16.0, 21.0	15.5, 20.5
Min, Max	11.0, 35.0	11.0, 32.0
n	164	166
Change from baseline		
Mean (SD)	-6.1 (3.52)	-6.8 (3.96)
Median	-6.0	-7.0
Q1, Q3	-8.5, -4.0	-9.0, -5.0
Min, Max	-16.0, 4.0	-18.5, 7.0
n	164	166
Cycle 1 Week 15		
Mean (SD)	18.7 (3.83)	19.2 (4.51)
Median	18.0	19.0
Q1, Q3	16.0, 21.0	16.0, 22.0
Min, Max	10.5, 32.5	10.5, 34.0
n	147	152
Change from baseline		
Mean (SD)	-6.0 (3.48)	-5.7 (4.20)
Median	-6.0	-6.0
Q1, Q3	-8.5, -4.0	-9.0, -2.8
Min, Max	-16.0, 7.0	-17.5, 9.5
n	147	152
Cycle 1 Week 20		
Mean (SD)	18.3 (3.33)	18.7 (4.11)
Median	18.0	18.5
Q1, Q3	16.5, 19.5	16.0, 20.5
Min, Max	12.0, 31.0	12.0, 32.0
n	57	56
Change from baseline		
Mean (SD)	-6.3 (3.02)	-5.9 (4.37)
Median	-7.0	-6.0
Q1, Q3	-8.5, -5.0	-8.0, -3.0
Min, Max	-13.0, 2.5	-19.0, 8.0
n	57	56
Cycle 2 Week 8		
Mean (SD)	18.5 (3.96)	17.7 (4.36)
Median	18.0	17.0
Q1, Q3	16.0, 21.0	15.0, 20.0
Min, Max	11.0, 34.0	9.5, 41.0
n	106	118
Change from baseline		
Mean (SD)	-6.3 (3.63)	-7.2 (3.97)
Median	-6.0	-7.0
Q1, Q3	-8.5, -4.0	-9.0, -5.0
Min, Max	-18.5, 3.0	-18.0, 7.0
n	106	118
Cycle 2 Week 16		
Mean (SD)	18.1 (3.54)	19.5 (4.34)
Median	18.0	19.0
Q1, Q3	16.0, 20.0	17.0, 21.5
Min, Max	11.0, 29.0	11.0, 36.0
n	88	101
Change from baseline		
Mean (SD)	-6.8 (3.99)	-5.5 (4.25)
Median	-6.3	-5.5
Q1, Q3	-9.0, -4.0	-8.0, -3.0
Min, Max	-18.0, 4.5	-18.0, 7.0
n	88	101
Cycle 2 Week 20		
Mean (SD)	18.2 (3.43)	19.9 (4.46)
Median	18.0	19.8
Q1, Q3	16.0, 20.0	16.8, 22.5
Min, Max	11.5, 29.0	12.0, 32.0
n	87	96
Change from baseline		
Mean (SD)	-6.7 (3.61)	-5.3 (4.18)
Median	-6.0	-5.0
Q1, Q3	-9.0, -4.0	-7.5, -2.8
Min, Max	-17.0, 0.5	-14.0, 8.5
n	87	96

Each analysis cycle started from the respective Bim SR administration date.
Cross reference: Table 14.2-1.3

Ancillary analyses

Subgroup analyses

Ad Primary Efficacy Endpoint

IOP change from baseline (flexible re-administration regimen)

IOP change from baseline was evaluated in the subpopulation of subjects who were treated with Bimatoprost SR 10 µg on a flexible re-administration regimen, regardless of the actual number of implants received (1 or 2), for the ITT and PP populations using the same MMRM model as the primary analysis.

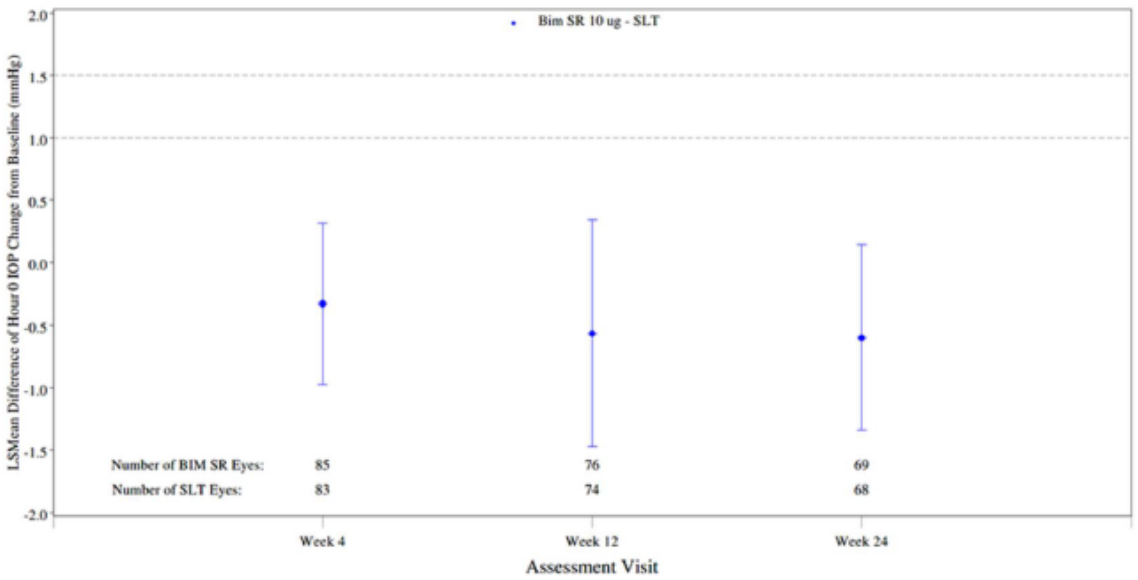
Table 27: Hour 0 IOP (mmHg): Summary of baseline, post-baseline, and analysis of change from baseline – MMRM flexible bimatoprost SR administration regimen – bimatoprost SR µg/SLT (ITT Population)

	SLT (N=88)	Bim SR 10 ug (N=88)
Baseline		
Mean (SD)	25.0 (2.88)	25.1 (2.95)
Median	24.0	24.0
Q1, Q3	23.0, 26.0	23.0, 27.0
Min, Max	22.0, 34.0	22.0, 34.0
n	88	88
Week 4		
Mean (SD)	18.7 (4.03)	18.5 (4.09)
Median	18.0	18.0
Q1, Q3	16.0, 21.0	15.0, 20.5
Min, Max	11.5, 30.0	11.5, 29.0
n	83	85
Change from baseline		
Mean (SD)	-6.1 (3.66)	-6.6 (3.84)
Median	-6.5	-7.0
Q1, Q3	-8.5, -4.0	-9.0, -4.0
Min, Max	-14.0, 5.0	-15.0, 5.0
n	83	85
Model [1]		
Least Square Mean (SE)	-6.1 (0.40)	-6.4 (0.40)
Difference vs. SLT (SE)		-0.3 (0.32)
95% CI		(-0.98, 0.31)
P-value		0.3084
Week 12		
Mean (SD)	18.1 (3.70)	17.6 (3.76)
Median	18.0	17.5
Q1, Q3	16.0, 19.5	15.0, 19.3
Min, Max	11.5, 30.0	9.0, 30.0
n	74	76
Change from baseline		
Mean (SD)	-6.4 (3.67)	-7.4 (3.94)
Median	-6.5	-8.0
Q1, Q3	-9.0, -4.0	-10.0, -4.8
Min, Max	-16.0, 7.0	-18.0, 4.0
n	74	76
Model [1]		
Least Square Mean (SE)	-6.4 (0.42)	-7.0 (0.41)
Difference vs. SLT (SE)		-0.6 (0.45)
95% CI		(-1.47, 0.34)
P-value		0.2165
Week 24		
Mean (SD)	17.9 (3.39)	17.2 (3.45)
Median	17.8	17.5
Q1, Q3	16.0, 19.8	15.0, 19.0
Min, Max	11.0, 29.0	7.0, 24.0
n	68	69
Change from baseline		
Mean (SD)	-6.6 (3.07)	-7.4 (4.08)
Median	-6.0	-7.0
Q1, Q3	-8.5, -4.0	-10.0, -5.0
Min, Max	-14.0, -1.0	-22.5, 0.5
n	68	69
Model [1]		
Least Square Mean (SE)	-6.7 (0.40)	-7.3 (0.40)
Difference vs. SLT (SE)		-0.6 (0.37)
95% CI		(-1.34, 0.14)
P-value		0.1097

Bim SR = Bimatoprost Sustained Release; CI = confidence interval; IOP = intraocular pressure; ITT = intent-to-treat; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; Q = quartile; SD = standard deviation; SE = standard error; SLT = selective laser trabeculoplasty

[1] A MMRM analysis was performed to compare IOP change from baseline between SLT and Bim SR 10 ug
In the model, IOP change from baseline is the response variable, baseline IOP is the covariate, and treatment, visit, eye, and treatment-by-visit, visit-by-baseline IOP, and visit-by-eye interactions are factors in the model. An unstructured covariance matrix for study visit and eyes were used for the analysis.

Cross reference: Study 192024-093 Month 12 CSR Table 14.5-1.1



Bim SR = Bimatoprost Sustained Release; CI = confidence interval; IOP = intraocular pressure; ITT = intent-to-treat; LS = least squares; MMRM = mixed model repeated measures; SLT = selective laser trabeculoplasty

An MMRM analysis was performed to compare IOP change from baseline between SLT and Bim SR 10 ug. In the model IOP change from baseline is the response variable, baseline IOP is the covariate, and treatment, visit, eye, and treatment-by-visit, visit-by-baseline IOP, and visit-by-eye interactions are factors in the model. An unstructured covariance matrix for study visit and eyes were used for the analysis.

Cross reference: Study 192024-093 Month 12 CSR Figure 14.5-1.1

Figure 10: LS mean and 95% CI for the difference between bimatoprost SR 10 µg and SLT in the change in hour 0 IOP from baseline at week 4, week 12, and week 24 – flexible administration subgroup – bimatoprost SR 10 µg/SLT (ITT population)

Ad Secondary Efficacy Endpoints

Time to second bimatoprost SR administration

Time to the second bimatoprost SR 10 µg administration from the initial bimatoprost SR 10 µg administration in the flexible re-administration subpopulation was evaluated using a Kaplan-Meier analysis.

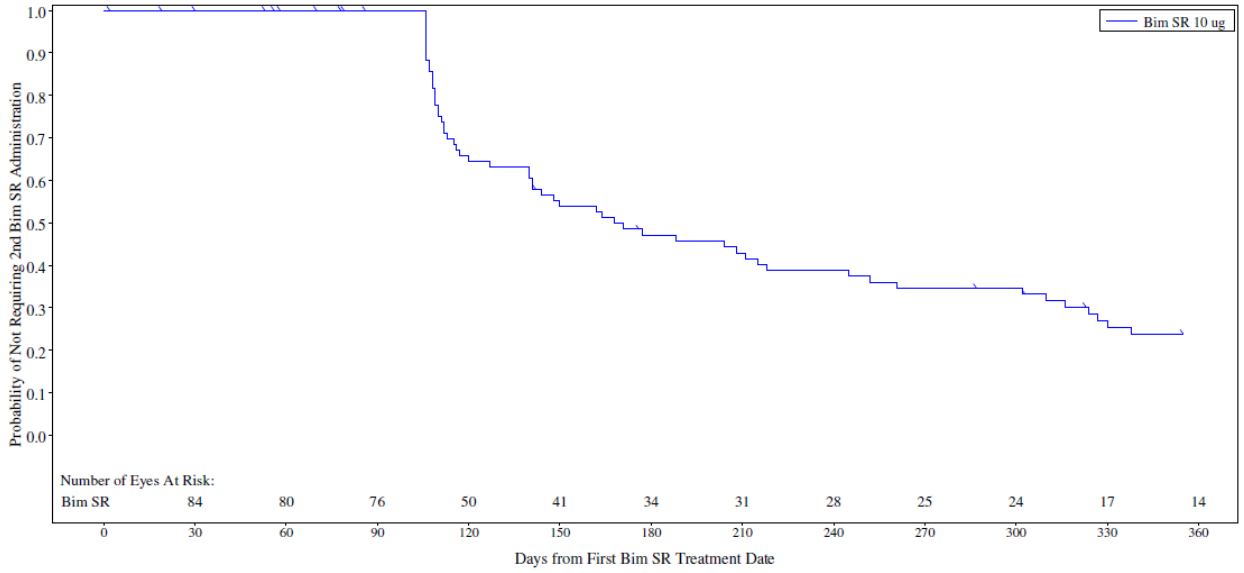
Table 28: Analysis of time to the second Bim SR administration from initial Bim SR administration

Event Summary and Survival Analysis
Flexible Bim SR Administration Regimen
Intent-to-Treat Population
Bim SR 10 ug

	Bim SR 10 ug
N1	86
Number of Events (Crude rate (%))	56 (65.1)
Time (Days) to Event [1]	
25 % percentile (95% CI)	111 (108.0, 120.0)
50 % percentile (95% CI)	168 (140.0, 218.0)
75 % percentile (95% CI)	338 (261.0, NA)
Number of Eyes at Risk	
120 Days	50
150 Days	41
180 Days	34
210 Days	31
240 Days	28
270 Days	25
300 Days	24
330 Days	17
360 Days	14
Probability of Not Receiving 2nd Bim SR Implant (95% CI) [2]	
120 Days	0.645 (0.526, 0.741)
150 Days	0.539 (0.420, 0.643)
180 Days	0.471 (0.355, 0.578)
210 Days	0.429 (0.316, 0.538)
240 Days	0.388 (0.278, 0.496)
270 Days	0.346 (0.241, 0.454)
300 Days	0.346 (0.241, 0.454)
330 Days	0.254 (0.160, 0.359)
360 Days	0.238 (0.146, 0.343)

Time to the Second Bim SR Administration = (Date of the second Bim SR treatment -Date of initial Bim SR treatment) +1.
The events are censored at the earliest event of second Bim SR treatment date, non-study IOP lowering treatment date, study exit date, or Month 12 visit date.
N1: Number of eyes with study treatments.
[1] 95% CI calculation is based on Brookmeyer and Crowley method.
[2] Probabilities of not having the second Bim SR implant are estimated using Kaplan-Meier (KM) method.

Figure 14.5-2.1
Time to the Second Bim SR Administration from Initial Bim SR Administration
Flexible Bim SR Administration Regimen
Intent-to-Treat Population
Bim SR 10ug



Probabilities are estimated using Kaplan-Meier (KM) method.
Time to the Second Bim SR treatment = (Date of the second Bim SR treatment - Date of initial Bim SR treatment) +1. The events are censored at the earliest event of non-study IOP lowering medication date, study exit date, or Month 12 visit date.

IOP analysis by disease diagnosis

IOP change from baseline was evaluated in the subpopulation of eyes by disease diagnosis of the primary eye as randomized in the intent-to-treat population, regardless of analysis cycle.

Open-angle glaucoma subgroup

Table 29: Hour 0 IOP (mmHg): Summary of baseline, post-baseline and change from baseline by visit regardless of analysis cycle

Intent-to-Treat Population
Bim SR 10ug/SLT: Open-Angle Glaucoma Subgroup

Visit	SLT (N=144)	Bim SR 10 ug (N=143)
Baseline		
Mean (SD)	25.0 (2.99)	25.2 (3.08)
Median	24.0	24.0
Q1, Q3	23.0, 26.0	23.0, 27.5
Min, Max	16.0, 34.0	15.0, 33.5
n	144	143
Bim SR Day 2		
Mean (SD)	19.3 (5.20)	15.8 (4.10)
Median	18.0	16.0
Q1, Q3	16.0, 21.5	13.0, 18.0
Min, Max	10.5, 40.0	7.5, 32.0
n	134	134
Change from baseline		
Mean (SD)	-5.7 (4.65)	-9.4 (4.39)
Median	-6.0	-9.0
Q1, Q3	-9.0, -3.5	-12.5, -7.0
Min, Max	-20.0, 11.5	-20.5, 8.0
n	134	134
Week 4		
Mean (SD)	18.4 (3.85)	18.2 (4.05)
Median	18.0	18.0
Q1, Q3	16.0, 21.0	15.0, 20.0
Min, Max	11.5, 32.0	11.5, 33.0
n	132	133
Change from baseline		
Mean (SD)	-6.5 (3.63)	-7.0 (3.78)
Median	-6.8	-7.5
Q1, Q3	-9.0, -4.5	-9.5, -4.5
Min, Max	-16.5, 3.0	-19.5, 3.0
n	132	133
Week 12		
Mean (SD)	17.7 (3.84)	17.7 (4.36)
Median	17.0	17.0
Q1, Q3	15.0, 19.5	15.0, 20.0
Min, Max	10.5, 30.0	9.0, 37.0
n	117	120
Change from baseline		
Mean (SD)	-6.9 (3.57)	-7.3 (4.24)
Median	-7.0	-8.0
Q1, Q3	-9.5, -5.0	-10.0, -4.5
Min, Max	-16.0, 7.0	-19.5, 7.0
n	117	120
Week 24		
Mean (SD)	17.4 (3.29)	17.1 (3.72)
Median	17.0	17.0
Q1, Q3	15.5, 19.0	14.5, 19.5
Min, Max	10.0, 29.0	7.0, 31.0
n	105	107
Change from baseline		
Mean (SD)	-6.9 (2.87)	-7.6 (3.82)
Median	-6.5	-7.5
Q1, Q3	-8.5, -5.0	-10.0, -5.5
Min, Max	-14.0, -0.5	-21.0, 1.0
n	105	107

Analysis visit is based on the protocol defined scheduled visit regardless of the number of Bim SR implants with which subjects were treated.

Ocular hypertension subgroup

Table 30: Hour 0 IOP (mmHg): Summary of baseline, post-baseline and change from baseline by visit regardless of analysis cycle

Intent-to-Treat Population
Bim SR 10ug/SLT: Ocular Hypertension Subgroup

Visit	SLT (N=39)	Bim SR 10 ug (N=40)
Baseline		
Mean (SD)	25.6 (3.03)	25.1 (2.68)
Median	24.5	24.0
Q1, Q3	23.0, 27.0	23.0, 26.8
Min, Max	22.0, 34.0	22.0, 34.0
n	39	40
Bim SR Day 2		
Mean (SD)	20.9 (3.86)	16.3 (3.55)
Median	20.5	16.0
Q1, Q3	18.0, 23.5	14.5, 19.0
Min, Max	14.5, 31.0	9.0, 25.0
n	37	38
Change from baseline		
Mean (SD)	-4.6 (3.96)	-8.8 (3.68)
Median	-5.0	-8.3
Q1, Q3	-7.5, -2.0	-11.0, -6.5
Min, Max	-16.0, 4.5	-18.0, -2.0
n	37	38
Week 4		
Mean (SD)	20.2 (4.56)	18.6 (4.09)
Median	19.3	18.5
Q1, Q3	16.8, 23.3	15.0, 21.0
Min, Max	13.5, 31.0	12.5, 29.0
n	36	37
Change from baseline		
Mean (SD)	-5.4 (3.80)	-6.5 (3.56)
Median	-5.8	-6.5
Q1, Q3	-8.0, -3.8	-9.5, -4.0
Min, Max	-12.0, 5.0	-12.0, 5.0
n	36	37
Week 12		
Mean (SD)	19.8 (3.44)	18.5 (4.03)
Median	19.0	18.3
Q1, Q3	17.5, 23.0	15.3, 20.0
Min, Max	14.0, 28.0	12.0, 30.0
n	32	36
Change from baseline		
Mean (SD)	-5.1 (2.95)	-6.4 (2.91)
Median	-5.5	-6.0
Q1, Q3	-6.5, -3.0	-8.5, -4.0
Min, Max	-13.0, 1.5	-12.0, -1.5
n	32	36
Week 24		
Mean (SD)	19.9 (3.07)	19.2 (3.42)
Median	19.5	18.8
Q1, Q3	18.0, 21.0	17.0, 22.0
Min, Max	15.0, 27.5	11.5, 28.0
n	33	38
Change from baseline		
Mean (SD)	-5.2 (3.15)	-5.9 (3.52)
Median	-5.0	-5.5
Q1, Q3	-7.0, -3.0	-7.0, -4.0
Min, Max	-13.0, 3.0	-22.5, -1.0
n	33	38

Analysis visit is based on the protocol defined scheduled visit regardless of the number of Bim SR implants with which subjects were treated.

Use of non-study IOP-lowering treatment (rescue treatment)

Table 31: Duration of permanent non-study IOP-lowering medications (Concomitant Use)

Intent-to-Treat Population
Study 192024-093: Bim SR 10ug

Treatment Period		SLT	Bim SR 10ug		
			Flex	Fixed	Total
		(N=183)	(N=88)	(N=95)	(N=183)
Overall	Duration of Rescue Med.(Days)				
	N1 [1]	180	88	92	180
	N2 [2]	66 (36.7)	43 (48.9)	36 (39.1)	79 (43.9)
	Mean (SD)	257 (214.3)	286 (227.6)	220 (173.5)	257 (206.9)
	Median	200	238	178	193
	Min, Max	1, 727	1, 713	1, 668	1, 713
Cycle 1	Duration of Rescue Med.(Days) in Cycle 1				
	N1 [1]	180	88	92	180
	N2 [2]	32 (17.8)	16 (18.2)	13 (14.1)	29 (16.1)
	Mean (SD)	249 (249.6)	318 (275.7)	254 (198.5)	288 (242.9)
	Median	148	313	236	241
	Min, Max	1, 727	1, 713	2, 668	1, 713
Cycle 2	Duration of Rescue Med.(Days) in Cycle 2				
	N1 [1]	126	56	70	126
	N2 [2]	40 (31.7)	27 (48.2)	23 (32.9)	50 (39.7)
	Mean (SD)	222 (171.5)	262 (180.9)	182 (147.3)	226 (170.3)
	Median	174	238	169	183
	Min, Max	1, 584	7, 562	1, 491	1, 562

[1] N1: Number of eyes in the treatment period and used for denominators of percentages.
[2] N2: Number of eyes received non-study IOP-lowering medication as concomitant use in the treatment period.

3.3.4.2.2. Study 1698-301-007: A Phase 3b Study to Evaluate the Duration of Effect of Bimatoprost SR in Participants with Open-Angle Glaucoma or Ocular Hypertension

Methods

Study 1698-301-007 is an ongoing multicentre, open-label, Phase 3b study to evaluate the duration of IOP-lowering effect and safety of up to 3 administrations of bimatoprost SR 10 µg in the study eye of subjects with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence). The purpose of this study is to obtain data on a PRN re-administration regimen of bimatoprost SR.

Under the original masked study design, subjects were randomized to receive either the 10-µg or 15-µg dose strength in a 1:1 randomisation ratio, and as such, some subjects received bimatoprost SR 15 µg. Upon implementation of Amendment 1, no new subjects were randomized to receive bimatoprost SR 15 µg, and eyes already treated with the 15 µg dose strength were no longer eligible to receive any additional bimatoprost SR administrations, thus changing the design to an open-label assessment. All subjects are being followed for at least 12 months after the last administration of bimatoprost SR (both dose strengths) in either eye.

Study Participants

Enrolment of up to approximately 490 participants in total is planned, with 62 already enrolled in the 15 µg group under the original protocol, and up to approximately 425 in total to be enrolled in the 10 µg group in approximately 130 global sites.

The eye that meets the entry criteria at study entry will be selected as the study eye. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 (9:00 AM ± 1 hour) will be

selected as the study eye. If both eyes have the same IOP, then the right eye will be designated as the study eye. The eye that is not selected as the study eye will be designated as the fellow eye.

In the fellow eye, subjects are to receive standard of care treatment for the duration of the study unless the fellow eye meets the treatment criteria for fellow eye administration. Of note, participants do not need to meet Fellow Eye Administration criteria to qualify for study entry. Fellow Eye Administration criteria are only for fellow eyes that are being considered for bimatoprost SR administration.

Key Inclusion Criteria for study eye

1. Male or female participants at least 18 years of age at the time of signing the informed consent

2. Written informed consent and authorisation for use and release of personal health information

3. A female participant is eligible to participate if she is not pregnant (i.e., has a negative urine pregnancy result at Baseline; see Appendix 7), not breastfeeding, and at least one of the following conditions applies: Not a WOCBP or a WOCBP who agrees to follow the contraceptive guidance in Appendix 7 during the study period

4. Participant is willing to withhold his/her IOP treatments according to the study requirements, and in the opinion of the investigator, can do so without significant risk

5. In the investigator's opinion, participant's IOP is not adequately managed with topical medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence)

6. Ocular Inclusion Criteria

- Diagnosis of either OAG (i.e., primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in the study eye, requiring IOP-lowering treatment
- In the investigator's opinion, the study eye can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analogue (eg, Lumigan, Xalatan, Travatan) eye drops as the sole therapy if medication was taken as directed
- The iridocorneal angle in the study eye must be, in the opinion of the investigator, able to safely receive at least 1 bimatoprost SR implant using the following criteria:

  a. Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle

  b. Peripheral anterior chamber depth by Van Herick examination ≥ ½ corneal thickness
- At the Baseline visit (9:00 AM ± 1 hour), IOP of ≥ 22 and ≤ 34 mm Hg in the study eye
- Central corneal endothelial cell density by specular microscopy deemed acceptable, in the opinion of the investigator (at Screening, a minimum endothelial cell density of 2000 cells/mm2 in the study eye by automated analysis)
- At the Baseline visit: BCVA (Snellen equivalent, by manifest refraction) of 20/50 or better in the study eye and 20/100 or better in the fellow eye

Key Exclusion Criteria for study eye

1. General Exclusion Criteria

- Previous use of commercially available bimatoprost SR in the study eye; concurrent enrolment in another Allergan bimatoprost SR study; or previous enrolment in which a bimatoprost SR implant was received in the study eye

Note: Participants with an eye that has not been previously treated with bimatoprost SR or participants previously enrolled in bimatoprost SR studies 192024-091/-092, and -041D who have an eye that was not treated with bimatoprost SR in that study may be enrolled, provided that the eye that did not receive bimatoprost SR meets entry criteria for this study.

- Known history of bleeding disorder or prolonged bleeding after surgery (in the opinion of the investigator)

Note: Participants receiving pharmacologic blood thinners (eg, aspirin, Coumadin) may be enrolled at the investigator's discretion

2. Ocular Exclusion Criteria

- History of previous laser trabeculoplasty in the study eye
- History or evidence of clinically relevant, substantial ocular trauma (eg, a traumatic cataract, traumatic angle recession, etc.) in the study eye
- The following surgical history in the study eye:

  a. History or evidence of complicated cataract/lens surgery: eg, surgery resulting in complicated lens placement (such as anterior chamber intraocular lens implant [IOL], sulcus IOL, aphakia, etc.) or intraoperative complications (such as a posterior capsular tear [with or without vitreous loss], substantial iris trauma, etc.)

  Note: history of uncomplicated cataract surgery is not an exclusion

  b. History of phakic IOL insertion for refractive error correction
- Intraocular surgery (including cataract surgery) in the study eye within the 6 months prior to treatment administration (Day 1 Cycle 1 Administration)
- Any history of corneal graft, including partial grafts (eg, Descemet's Stripping Endothelial Keratoplasty [DSEK], Descemet's Membrane Endothelial Keratoplasty [DMEK]); or incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions in the study eye
- Corneal or other ocular abnormalities that would preclude accurate readings with an applanation tonometer, specular microscope, and/or a contact pachymeter, or could confound study results in either eye, eg, moderate to severe corneal dystrophy, including Anterior Basement Membrane Disease (ABMD; i.e., Map-Dot-Fingerprint) and guttata. Mild ABMD or mild guttata are not exclusionary by clinical examination if, in the opinion of the investigator, the condition is stable and not likely to cause corneal changes during the course of the study
- Active or recurrent ocular disease in the study eye (eg, uveitis, ocular infection, chronic moderate to severe blepharitis or severe dry eye, ocular seasonal allergies) or sight threatening diseases (eg, neovascular age-related macular degeneration [AMD], diabetic macular oedema) that, in the opinion of the investigator, would put the participant at a significant risk or would interfere with the interpretation of the study data

Note: Participants with slowly progressive eye diseases (i.e., mild cataracts, non-neovascular AMD) can be enrolled at the discretion of the investigator. If a participant has a potentially exclusionary condition or disease in one eye that tends to be bilateral or is likely to affect both eyes, the investigator should consider excluding that participant

- Any history of external ocular or intraocular malignancy, and/or any history of benign ocular neoplasia in the study eye that in the investigator's opinion resulted in clinically significant ocular morbidity
- History of herpetic ocular diseases in the study eye (including herpes simplex virus and varicella zoster virus)
- Active ocular surface findings other than bulbar conjunctival hyperaemia, on either macroscopic or slit-lamp examination, > +1 (mild) at Baseline in the study eye
- Central corneal thickness of < 480 or > 620 micrometres in the study eye
- History of anatomically narrow angle resulting in evidence of angle changes or any history of closed angle glaucoma, in the study eye

Note: historically narrow angled participants whose angle has been opened by cataract surgery or peripheral iridotomy may be eligible for enrolment if they have no evidence of angle abnormalities

- History or evidence of a peripheral iridotomy/iridectomy in the inferior iris in the study eye
- Any history of trabeculectomy or other types of glaucoma surgery, including a glaucoma seton or aqueous bypass stents in the study eye
- Peripheral anterior synechiae (PAS) in the inferior iridocorneal angle on gonioscopic examination at Screening in the study eye
- Visual field loss in either eye that, in the opinion of the investigator, is functionally significant (eg, split fixation, field defect within the central 10 degrees that is visually significant or likely to cause central visual impairment upon progression) or shows evidence of progressive visual field loss within the year prior to Baseline

Note: The same test methodology should be used for all study-related examination for a given participant

- Evidence of macular oedema in either eye during screening or in participant's medical history

Permitted concomitant Interventions

Ophthalmic Treatments

The fellow eye will receive standard of care for IOP lowering, provided, in the investigator's opinion, there is no crossover effect to the study eye. If the fellow eye requires laser or surgical treatment, it must be performed not less than 3 days after any bimatoprost SR administration in the study eye.

From Week 16 through completion of the PRN treatment period, participants who meet treatment criteria for the fellow eye may receive a single administration of bimatoprost SR in the fellow eye. Upon the decision to administer bimatoprost SR in the fellow eye, standard of care medication will be stopped at least one day prior to Fellow Eye Administration. A second bimatoprost SR administration in the fellow eye will not be permitted.

As regards the use of artificial tear products, ocular decongestants or antihistamines and topical ocular antibiotics, ophthalmic corticosteroids and NSAIDs see Study -093.

Implant Removal: see study -093

Systemic Medications: see study -093

Rescue Treatment

In the event that the study eye IOP does not meet or does not maintain IOP-lowering expectations, and/or the participant does not meet bimatoprost SR administration criteria as determined by the investigator, *rescue IOP-lowering treatment* [medication(s) or procedure(s) or both] *can be initiated at the investigator's discretion*. Inadequate control of IOP should be confirmed at a subsequent visit (scheduled or unscheduled visit) not on the same day. Rescue treatment can be initiated at the investigator's discretion at any time during the study if it is in the best interest of the participant. From Week 16 through completion of the PRN treatment period, the participant should be considered for retreatment if he or she qualifies.

For participants who need additional IOP lowering treatment but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12-month period, topical IOP-lowering medication (intermittent rescue) may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator).

Treatments

In the study eye, subjects are to receive a bimatoprost SR 10 µg implant on Day 1 Cycle 1 Administration and, if re-administration criteria are met, up to 2 additional bimatoprost SR administrations (Cycle 2 Administration and Cycle 3 Administration) may be performed between 16 weeks after a previous bimatoprost SR administration through completion of the PRN re-administration period (up to and including the Month 36 visit from Day 1 Cycle 1 administration). No more than 2 administrations can be given in a 12-month period. A second administration can be given if the study eye has an investigator-determined clinically meaningful increase in IOP and there are no safety concerns or findings (re-administration criteria see below). For eyes that need additional IOP-lowering treatment but do not meet specific re-administration criteria, temporary use of topical IOP-lowering medication (intermittent rescue) is allowed until all re-administration criteria are met.

Table 32: Study treatment administered

Study Treatment Name	Bimatoprost SR
Dosage Formulation	Bimatoprost SR is an intraocular implant that contains preservative-free bimatoprost dispersed in a biodegradable polymer matrix (including PLA and/or PLGA). Implants are preloaded into an applicator to facilitate insertion of the implant into the AC of the eye.
Unit Dose Strength(s)/ Dosage Level(s)	A dose strength of either 10 µg (formula number 11047X) or 15 µg (formula number 11048X) bimatoprost will be administered.
Route of Administration	Intracameral
Administration Instructions	Bimatoprost SR is inserted directly into the AC of the eye using the prefilled applicator.
Packaging and Labeling	Study treatment will be provided in a sterile, laminated foil pouch in an individual carton. Each package will be labeled as required per country requirement. Study treatment of each dose strength will be supplied in identical-appearing packages to maintain masking of the investigator.
Manufacturer	Allergan

Table 33: Treatment scheduled by eye

Treatment Visits	Study Eye	Fellow Eye
Bimatoprost SR Day 1 Cycle 1 Administration	Bimatoprost SR 10 µg	Standard of Care or Bimatoprost SR 10 µg[a]
Bimatoprost SR Cycle 2 Administration: Week 16 up to and including Month 36	Bimatoprost SR 10 µg	
Bimatoprost SR Cycle 3 Administration: at least 16 weeks after Cycle 2 Administration up to and including Month 36	Bimatoprost SR 10 µg	

[a] The fellow eye may receive only one single administration of Bimatoprost SR from Week 16 through completion of the Month 36 visit (Fellow Eye Administration). Bimatoprost SR administration in the fellow eye must be separated by at least one week from administration in the study eye.

Intracameral administration technique: see study -093

Re-administration Criteria

Participants may receive up to two additional administrations of bimatoprost SR in the study eye through completion of the PRN treatment period, if they meet the following criteria:

- There is a clinically meaningful increase in IOP (eg, < 20% change from baseline IOP) in the study eye confirmed at a subsequent visit (scheduled or unscheduled) not on the same visit day; and/or, in the investigator's opinion, there are clinical signs or symptoms of disease worsening (eg, disc haemorrhage, worsened visual field).
- Each previously administered implant is < 25% of the original size
- Retreatments may not occur less than 16 weeks after a previous bimatoprost SR administration and no more than 2 administrations in the study eye may occur in a 12-month period
- The participant has not received any rescue treatment in the study eye
    - Note: For participants who need additional IOP lowering medication but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12-month period, topical intermittent rescue may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator). After all retreatment requirements have been met, if the decision to readminister bimatoprost SR in the study eye is made, topical IOP-lowering medications shall be stopped at least one day prior to bimatoprost SR administration
- There is no evidence of any of the following:
    - Significant corneal findings related to presence of the implant (including corneal oedema, peripherally adjacent to the implant location and/or central) at any visit
    - Endothelial cell density less than 2000 cells/mm2 by specular microscopy by automated analysis, confirmed at 2 consecutive visits on separate days
    - Persistent and progressive corneal endothelial cell density decrease ≥ 15% from baseline confirmed at 2 consecutive visits on separate days (scheduled or unscheduled)

- Remaining implant size or position from prior administration(s) that, based on the investigator's evaluation, precludes placement of another implant (eg, may cause chronic contact of the implants with the corneal endothelium)
- Clinically significant intraocular inflammatory findings (eg, PAS, uveitis, iridocyclitis, macular oedema, etc) at any visit. Note: mild intraocular inflammation related to the administration procedure itself that resolves rapidly (with or without NSAIDs or steroids) is not prohibitive

Objectives

The objectives of the study are to evaluate the duration of intraocular pressure (IOP)-lowering effect of bimatoprost SR and the safety of bimatoprost SR in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT) who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence).

Clinical Hypotheses

- Bimatoprost SR will be effective in lowering IOP for greater than 16 weeks after single and repeated PRN administration in participants with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).
- Bimatoprost SR will have an acceptable safety profile after single and repeated PRN administration in participants with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

No statistical hypotheses were defined. Regarding statistical methods, please refer to section Statistical methods in this report.

Outcomes/endpoints

Primary efficacy variable

The primary efficacy variable is the time from the first administration of bimatoprost SR in the study eye to the second administration of bimatoprost SR or to the first rescue treatment (permanent or intermittent), whichever occurred first (duration of effect of the first bimatoprost SR administration).

Additional efficacy variables

Additional time-to-event variables are as follows:

- The time to second administration of bimatoprost SR in the study eye regardless of intermittent rescue (duration of effect of the first bimatoprost SR administration regardless of intermittent rescue treatment);
- The time to third administration of bimatoprost SR in the study eye after second administration regardless of intermittent rescue (duration of effect of the second bimatoprost SR administration, regardless of rescue treatment);
- Time to the third administration of bimatoprost SR or first rescue treatment after second administration in the study eye (duration of effect of the second bimatoprost SR administration);
- Time to first rescue treatment after third administration in the study eye (duration of effect of the third bimatoprost SR administration).

In addition, IOP and IOP change from baseline are summarized descriptively and presented overall as well as for each treatment cycle.

Sample size

Based on the Phase 1/2 study (192024-041D), approximately 70% of participants among Generation 2 10µg implant did not require a second administration of Bim SR or rescue at 6 months, following a single administration of Bim SR. A more conservative assumption of 50% of participants having at least 6 months prior to meeting pre-specified criteria for a second administration was used for sample size calculation for this study. A sample size of 135 participants produces a two-sided 90% confidence interval, with a width no wider than 0.15 based on normal approximation with continuity correction. In the first version of the protocol, similar assumptions were used for the 15 µg group before this arm was stopped, and 62 participants were enrolled in the 15 µg group. Assuming 10% drop-out rate before Month 6 in the 10 µg group, a total 150 participants were to be enrolled under Amendment 1.

In Amendment 2, the sample size was increased to 425 participants receiving the treatment with the 10 µg implant to achieve a sufficient number of eyes receiving multiple administrations of 10µg Bim SR , in order to assess eyes undergoing multiple administrations of Bim SR.

Randomisation and blinding (masking)

Randomisation

For participants enrolled prior to Amendment 1, this was a dual arm study in which participants were randomized using a 1:1 ratio to either receive 10 µg or 15 µg bimatoprost SR in the study eye; central block randomisation was done by site and stratified by Baseline Hour 0 IOP (baseline study eye IOP ≤ 25 mm Hg or > 25 mm Hg). For participants enrolled after Amendment 1, all participants received 10 µg bimatoprost SR open label and no randomisation, masking, or stratification was performed.

Blinding (masking)

The participant, investigator, and the site staff were masked to the study treatment dose strength assignment prior to Amendment 1.

Statistical methods

Analysis sets

Full Analysis Set: All study eyes that had received study treatment and had at least one post-baseline IOP assessment contributed to the full analysis set (FAS), which was used for efficacy analyses.

Safety Analysis Set: All participants who had received at least 1 dose of study treatment in either eye contributed to the safety analysis set (SAS). All safety data collected from these participants were included in the SAS.

Analysis of baseline characteristics

Demographic parameters, weight and height were summarized descriptively by treatment group for the FAS population. Continuous variables were summarized by number of participants, mean, SD, median, 1st and 3rd quartiles, minimum, and maximum values. Categorical variables were summarized by number and percentage of participants. Baseline ocular and disease characteristics were summarized descriptively by treatment group for the study eye for the FAS population. A similar summary was provided for Bim SR -treated fellow eyes.

Non-ophthalmic medical and surgical history and non-ocular medications were summarized by treatment group, whereas ophthalmic medical and surgical history and ocular prior medications were summarized by treatment group for study eyes and fellow eyes in the SAS population.

Non-ocular concomitant medications were summarized by treatment group, whereas ocular concomitant medications were summarized by treatment group for study eyes, all fellow eyes, and Bim SR - treated fellow eyes (non-study ocular medications were administered on or after the data of the Bim SR administration in the fellow eye).

Analysis of the primary endpoint

The primary efficacy endpoint was duration of effect for Bim SR. Duration of effect was determined for the study eye as the time from the first administration of Bim SR to the second administration of Bim SR or to the first rescue treatment, whichever occurred first. Participants who did not receive the second administration or any rescue treatment (either intermittent or permanent) were censored at the time of study discontinuation or study exit visit, whichever occurred first.

The empirical survival function was estimated using the Kaplan-Meier (K-M) method. Corresponding K-M curves and survival probabilities with associated 95% CIs were presented.

Subgroup analyses

The primary efficacy analysis was performed for:

- Participants with a baseline disease diagnosis of OAG (primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma)
- Participants with a baseline disease diagnosis of OHT

Other efficacy analyses

There were four additional time-to event endpoints investigated by K-M curves:

1. *The time from first to second administration of Bim SR in the study eye regardless of intermittent rescue*

Duration of effect was determined for the study eye as the time from the first administration of Bim SR to the second administration of Bim SR or to the first permanent rescue treatment, whichever occurred first, regardless of intermittent rescue. Participants who did not receive the second administration or permanent rescue treatment were censored at the time of study discontinuation or study exit visit, whichever occurred first.

2. *The time to third administration of Bim SR in the study eye after second administration regardless of intermittent rescue*

The duration of effect of the second Bim SR administration regardless of intermittent rescue was evaluated in participants who received at least two administrations of Bim SR in the study eye. Participants who did not receive the third administration or permanent rescue treatment were censored at the time of study discontinuation or the study exit visit, whichever occurred first.

3. *Time to the third administration of Bim SR or first rescue treatment after second administration in the study eye*

The duration of effect of the second Bim SR administration was evaluated in participants who received at least two administrations of Bim SR in the study eye. Duration of effect was determined for the study eye as the time from the second administration of Bim SR to the third administration of Bim SR or to the first rescue treatment (intermittent or permanent) after the second Bim SR administration, whichever occurred first. Participants who did not receive the third administration or any rescue treatment (either intermittent or permanent) were censored at the time of study discontinuation or study exit visit, whichever occurred first.

4. Time to first rescue treatment after third administration in the study eye

The duration of effect of the third Bim SR administration was evaluated in participants who received three administrations of Bim SR in the study eye. Duration of effect will be determined for the study eye as the time from the third administration of Bim SR to the first rescue treatment after the third Bim SR administration. Participants who did not receive the rescue treatment were censored at the time of study discontinuation or the study exit visit, whichever occurred first.

IOP and IOP Change from Baseline

IOP and IOP change from baseline was summarized descriptively and presented overall as well as for each treatment cycle. The tabulations were presented by study eye treatment group and showed the data for the study eyes and fellow eyes of the subjects receiving the treatment. If the fellow eyes received Bim SR, data up to the last evaluation prior to Bim SR administration was included. Separate analyses were presented by treatment group (10 µg or 15 µg). for the fellow eyes treated with Bim SR. These analyses presented data at the scheduled visits after the Bim SR administration.

IOP values obtained after initiating the use of rescue treatment (medication or procedure) in an eye treated with Bim SR were excluded from the calculation of the summary statistics and the statistical analyses for that eye. These IOP values were presented in the listings. No imputation was performed for missing IOP data.

IOP and IOP Change from Baseline Regardless of Rescue Treatment

To evaluate the treatment effect regardless of use of non-study IOP-lowering treatment, IOP and IOP change from baseline was summarized descriptively and presented overall as well as for each treatment cycle for Bim SR 10ug – treated study eyes. IOP values obtained after initiating the use of rescue treatment (medication or procedure) were included in the calculation of the summary statistics.

Safety analysis

Ocular safety parameters included Ocular AEs, visual fields, BCVA, conjunctival hyperaemia, biomicroscopy, dilated ophthalmoscopy (including optic disc assessment), pachymetry, gonioscopy, and specular microscopy. Subject-level safety parameters included AEs, clinical laboratory assessments and vital signs.

Generally, tabulations were provided for overall (across treatment cycles) as well as for each treatment cycle. For study eyes and fellow eyes never treated with Bim SR or prior to fellow eye Bim SR administration, tabulations were presented by study eye treatment group. Separate analyses were presented by treatment group for fellow eyes treated with Bim SR.

Interim analysis

At least one interim database lock was planned to support regulatory and marketing submissions. Additional analyses should be performed with data from select US sites that evaluated the use of an alternate applicator in approximately 30 participants.

Interim analyses was performed based on participants with IOP data through at least Month 12 or who had an event prior to Month 12. Considered events were: received a second administration of Bim SR, received rescue treatment (either intermittent or permanent), or prematurely discontinued the study.

Results

Participant flow

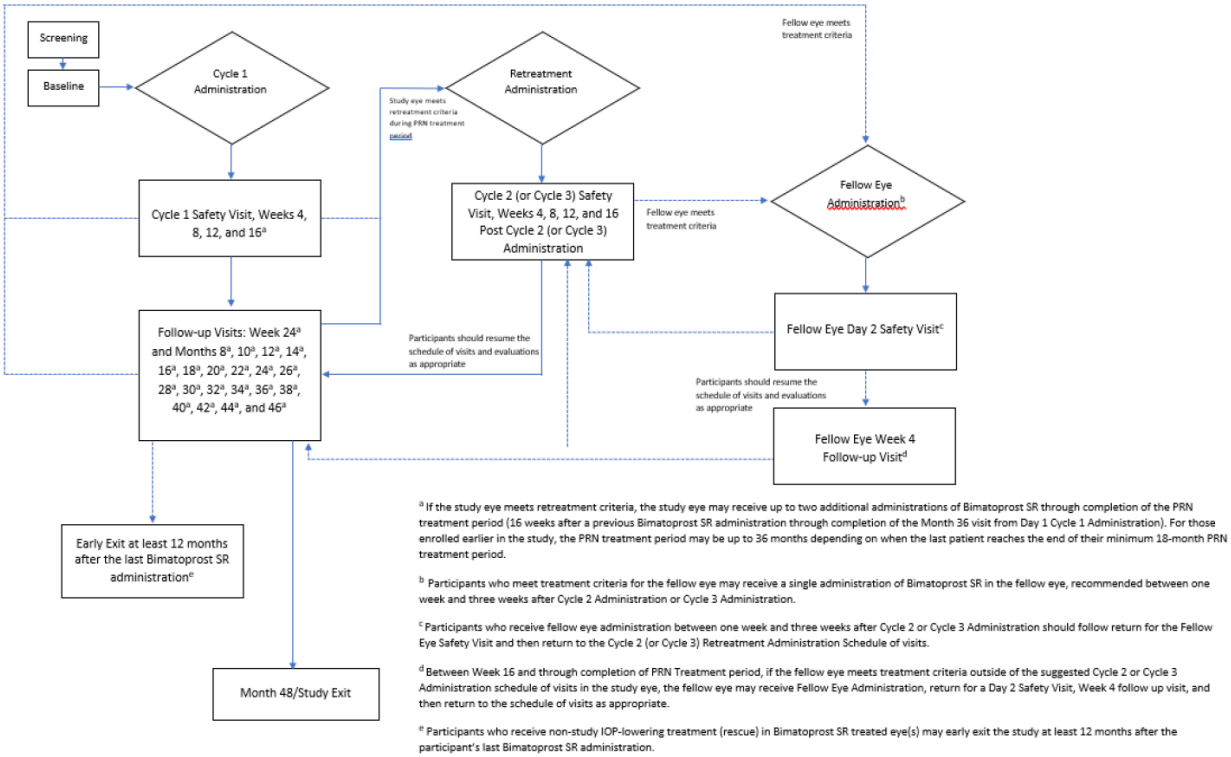


Figure 11: Study design

Subject Disposition

This is an ongoing study; therefore, not all subjects have completed all cycles and/or completed the Month 48/Study Exit visit.

As of the data cutoff date (29 July 2022), 319 subjects were randomized, or enrolled (after Amendment 1 of the protocol), to receive bimatoprost SR 10 µg at 62 sites in 10 countries.

Of the 319 subjects randomized or enrolled to receive bimatoprost SR 10 µg, 313 subjects (98.1%) were treated with bimatoprost SR 10 µg in the study eye, 12 subjects (3.8%) completed the study, 281 subjects (88.1%) are ongoing in the study, and 26 subjects (8.2%) discontinued from the study. The most frequently reported reasons for discontinuation were withdrawal by subject (7 subjects [2.2%]) and adverse events (7 subjects [2.2%]; 5 for nonocular adverse events and 2 for ocular adverse events). As of the data cutoff, 96 subjects have completed Cycle 1 and entered Cycle 2, and 22 subjects have completed Cycle 2 and entered Cycle 3.

Study visits impacted by the COVID-19 pandemic were limited and not considered significant to the conduct of the study.

Table 34: Disposition of subjects (Randomized or Enrolled Subjects)

	Bim SR 10ug n (%)
Number of Subjects Randomized or Enrolled	319 (100.0)
Number of Subjects Treated [1]	313 (98.1)
Number of Subjects Enrolled but Not Treated [2]	6 (1.9)
Number of Subjects Completed study	12 (3.8)
Number of Subjects Ongoing in the Study [3]	281 (88.1)
Number of Subjects Discontinued from study	26 (8.2)
Reasons for Discontinuation	
Adverse Event	7 (2.2)
Ocular AE	2 (0.6)
Non-ocular AE	5 (1.6)
Lack of efficacy	1 (0.3)
Withdrawal by Subject	7 (2.2)
Lost to Follow-Up	6 (1.9)
Pregnancy	0
Death	0
Progressive Disease	0
Protocol Deviation	0
Study Terminated by the Sponsor	0
Site Terminated by the Sponsor	0
Disease Relapse	0
Technical Problems	0
Other	5 (1.6)
Entered Cycle 1	313 (98.1)
Number of Subjects Discontinued During Cycle 1	20 (6.3)
Reasons for Discontinuation from Cycle 1	
Adverse Event	6 (1.9)
Ocular AE	2 (0.6)
Non-ocular AE	4 (1.3)
Lack of efficacy	1 (0.3)
Withdrawal by Subject	5 (1.6)
Lost to Follow-Up	6 (1.9)
Pregnancy	0
Death	0
Progressive Disease	0
Protocol Deviation	0
Study Terminated by the Sponsor	0
Site Terminated by the Sponsor	0
Disease Relapse	0
Technical Problems	0
Other	2 (0.6)
Entered Cycle 2	96 (30.1)
Number of Subjects Discontinued During Cycle 2	1 (0.3)
Reasons for Discontinuation from Cycle 2	
Adverse Event	0
Ocular AE	0
Non-ocular AE	0
Lack of efficacy	0
Withdrawal by Subject	0
Lost to Follow-Up	0
Pregnancy	0
Death	0
Progressive Disease	0
Protocol Deviation	0
Study Terminated by the Sponsor	0
Site Terminated by the Sponsor	0
Disease Relapse	0
Technical Problems	0
Other	1 (0.3)
Entered Cycle 3	22 (6.9)
Number of Subjects Discontinued During Cycle 3	0

[1] Subjects are counted as treated if either eye received study treatment.

[2] Subjects who were enrolled and discontinued without receiving study treatment and subjects who were enrolled prior to or on the data cutoff date but who did not receive study treatment by the cutoff date.

[3] Subjects who have received treatment and are ongoing at the time of the data cutoff and subjects who, at the time of data cutoff, have not received treatment and have not been discontinued from the study.

Note: Table presents data from the Bimatoprost SR 10 µg group only.

Protocol Deviations

Protocol deviations were defined in accordance with the ICH guidelines and included, but were not limited to, the following: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. Deviations were assessed for their impact on analyses and data integrity or subject safety.

A total of 21 of 319 randomized or enrolled subjects (6.6%) in the bimatoprost SR 10 µg group had significant protocol deviations.

Table 35: Protocol deviations: Number (%) of subjects with significant deviations (Randomized Subjects)

Protocol Deviation Category	Protocol Deviation Code	Bim SR 10 ug (N=319) n (%)
Overall		21 (6.6)
Compromised study intervention given		1 (0.3)
	SI-01	1 (0.3)
Incorrect dose (ICH)		2 (0.6)
	SI-04	2 (0.6)
Prohibited concomitant medication taken (ICH)		3 (0.9)
	CM-01	3 (0.9)
Retreatment criteria not met		16 (5.0)
	RTR-100	16 (5.0)

Notes: Patients were counted only once under each protocol deviation category.
Protocol deviations designated as significant (Code+SD, Code Sequence = 01) in the system report were summarized in the table. Protocol deviation categories with 0 counts were not presented.
RTR-100 is defined as study eye retreated in Cycle 2 despite not meeting retreatment criteria. All protocol deviation codes are provided in Listing 16.2.2-1.1.
Table presents data from the Bimatoprost SR 10 µg group only.

Recruitment

This is an ongoing study. As of the data cutoff date (29 July 2022), 319 subjects were randomized, or enrolled (after Amendment 1 of the protocol), to receive bimatoprost SR 10 µg at 62 sites in 10 countries (the United States, the United Kingdom, the Czech Republic, Poland, Germany, South Africa, Denmark, Ireland, Bulgaria, and Italy).

First patient, First Visit: 28 February 2019

Last patient, Last Visit at data cutoff: 29 July 2022

Conduct of the study

Protocol Compliance

The original protocol (November 2018, 135 subjects) had 2 amendments. The amendments and number of subjects enrolled under each amendment were as follows:

- Amendment 1 (March 2020, 119 subjects)
- Amendment 2 (March 2021, 127 subjects)

Under the original protocol, 62 subjects received bimatoprost SR 15 µg. With the implementation of Amendment 1, the 15 µg dose strength was discontinued, and these subjects were no longer eligible to receive additional bimatoprost SR administrations. Subjects who received bimatoprost SR 15 µg are being followed for at least 12 months after the last administration of bimatoprost SR in either eye. With Amendment 2, retreatment with bimatoprost SR was changed to be administered from Week 16 up to and including Month 36 (extension of the PRN treatment period).

GCP Inspections

No GCP inspection have been requested nor taken place.

Baseline data

The focus is on baseline characteristics of subjects who received bimatoprost SR 10 µg because the bimatoprost SR 15 µg dose strength was discontinued with the implementation of Amendment 1 of the protocol.

Demographics

Overall, the median age of subjects was 64.0 years in the bimatoprost SR 10 µg group (range 29 to 88 years), with 44.1% of subjects over 65 years of age.

Approximately half of the subjects (54.3%) were female, and the majority of subjects were white (80.2%) and were not Hispanic or Latino (95.2%).

Ocular baseline characteristics

Most subjects (81.5% [255/313]) had a diagnosis of OAG in the study eye. The baseline Hour 0 IOP was ≤ 25 mmHg for 52.4% of study eyes (164/313) in the bimatoprost SR 10 µg group. The baseline Shaffer Grade was 3 for 47.9% (150/313) of study eyes and 4 for 52.1% (163/313) of study eyes, and the majority of study eyes (76.4% [239/313]) were phakic. The median CECD (based on autocount data) was 2622.3 cells/mm2 and median corneal thickness was 553.3 µm. The mean (SD) IOP at baseline was 25.6 mmHg (2.91).

For bimatoprost SR 10 µg-treated fellow eyes, baseline Hour 0 IOP was ≤ 25 mmHg for almost all (97.8% [90/92]; Table 14.1-4.4). Baseline Shaffer Grade was 3 for 39.1% of fellow eyes (36/92) and 4 for 60.9% of fellow eyes (56/92) that received bimatoprost SR, and most (75.0% [69/92]) were phakic. The median CECD (by autocount) was 2652.5 cells/mm2 and median corneal thickness was 558.5 µm. The mean (SD) IOP at baseline (last non-missing assessment, at a scheduled visit, prior to being treated with bimatoprost SR) was 17.5 (4.14) mmHg.

The most common reasons for IOP to not be adequately managed with topical medications for bimatoprost 10 µg study eyes were memory loss (49.2% [154/313]) and intolerant/side effects of drop therapies (24.9% [78/313]). Other reasons were physical inability to administer medication, memory loss and physical inability to administer medication, and other. Reasons in fellow eyes were similar to those in the study eyes. Within the "other" category, the most common reasons were cost of medication and nonadherence/inconsistency with use of topical medications.

Prior, Concomitant, Standard of Care, and Rescue Medications and Procedures

In the safety analysis set, the majority of subjects in the bimatoprost SR 10 µg group reported use of prior (83.7% [262/313]) and concomitant (85.6% [268/313]) nonocular medications.

Among subjects in the bimatoprost SR 10 µg group, prior ocular medications were reported for 95.8% of study eyes (300/313) and for 94.2% of fellow eyes (295/313). Concomitant ocular medications were reported for 99.0% of study eyes (310/313) and 83.7% of fellow eyes receiving standard of care (262/313). The most frequently reported concomitant medications (by drug class) for study eyes (≥ 30%) were local anaesthetics (98.7%), other anti-infectives (97.1%), fluoroquinolones (94.9%), and other surgical aids (80.8%). The majority of subjects in the bimatoprost SR 10 µg group reported topical IOP-lowering medications at screening (93.0% of study eyes and 88.8% of all fellow eyes).

The standard of care reported during the study for the fellow eye prior to being treated with bimatoprost SR 10 µg consisted of (in order of frequency) prostaglandin analogues, beta blocking agents, carbonic anhydrase inhibitors, and sympathomimetics in glaucoma therapy. One fellow eye in the bimatoprost SR 10 µg group received selective laser trabeculoplasty as standard of care. As of the data cutoff date, this fellow eye has not received bimatoprost SR administration.

During the study, 22.7% of study eyes (71/313) in the bimatoprost SR 10 µg group received rescue treatment; 12.8% received permanent rescue treatment and 12.1% received intermittent rescue treatment (see table below). Rescue medications in the study eye consisted of antiglaucoma preparations and miotics, beta blocking agents, carbonic anhydrase inhibitors, parasympathomimetics (permanent rescue only), prostaglandin analogues, and sympathomimetics in glaucoma therapy.

The mean (SD) duration of intermittent rescue for study eyes was 121.6 (127.86) days during Cycle 1 and 205.3 (107.50) days during Cycle 2.

Table 36: Number (%) of subjects who received rescue treatment in the study eye during each cycle

Safety Analysis Set

	Bim SR 10ug SE (N=313) n (%)
Any Rescue Treatment	
During the Study	71 (22.7)
Cycle 1	42 (13.4)
Cycle 2	26 (8.3)
Cycle 3	9 (2.9)
Permanent Rescue Treatment	
During the Study	40 (12.8)
Cycle 1	23 (7.3)
Cycle 2	8 (2.6)
Cycle 3	9 (2.9)
Intermittent Rescue Medications	
During the Study	38 (12.1)
Cycle 1	21 (6.7)
Cycle 2	19 (6.1)
Cycle 3	0

Some study eyes received rescue treatment in more than one cycle.
Some study eyes received both intermittent and permanent rescue treatment.

Treatment compliance

Not applicable; bimatoprost SR was administered by the investigator.

Numbers analysed

The following data sets were analysed:

- FAS: All study eyes that have received study treatment and have at least one postbaseline IOP assessment will contribute to the FAS, which will be used for efficacy analyses.
- SAS: All subjects who have received at least 1 dose of study treatment in either eye will contribute to the SAS. All safety data collected from these subjects will be included in the SAS.

A total of 313 subjects in the bimatoprost SR 10 µg group were included in both the FAS and the SAS.

Outcomes and estimation

Primary Efficacy Endpoint

Time to Second Administration of bimatoprost SR or First Rescue Treatment After the First Administration in the Study Eye

The duration of effect of bimatoprost SR 10 µg was evaluated by the time to second administration of bimatoprost SR 10 µg or first rescue treatment (i.e., initiation of intermittent [use of rescue IOP-lowering medication until the subject became eligible for and received an additional bimatoprost SR administration] or permanent rescue treatment), whichever occurred first, after the first administration in the study eye. Of the 313 study eyes that received a first administration of bimatoprost SR 10 µg, 131 study eyes (41.9%) had received a second administration or initiated rescue treatment by the data cutoff date (see table below). At the time of data cutoff, the median time from initial administration of bimatoprost SR 10 µg to requiring a second administration or rescue treatment in the study eye on a PRN re-administration regimen was 377 days (> 1 year) with 95% confidence interval of 330.0 to 512.0 days, based on data from all subjects regardless of follow-up time (see table below). The cumulative probability of not requiring a second administration of bimatoprost SR 10 µg or rescue treatment at 360 days (approximately 12 months) was 55.1% (see figure below).

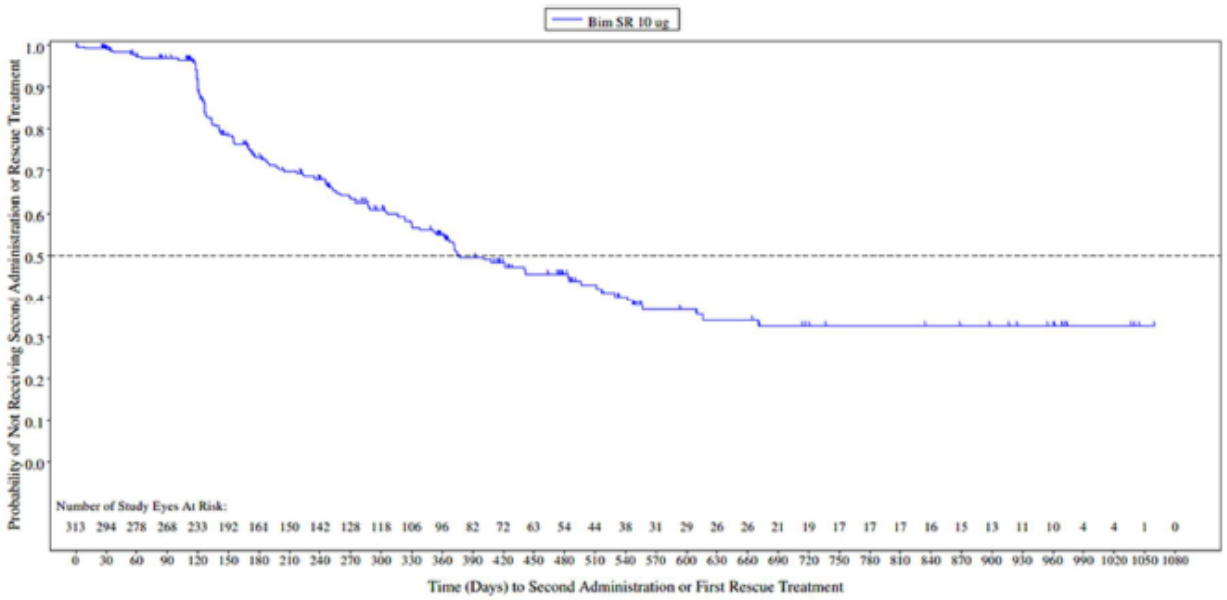
Table 37: Time to second administration of bimatoprost SR or first rescue treatment after first administration in the study eye – event summary and survival analysis (Full Analysis Set)

	Bim SR 10ug SE (N=313)
N1	313
Number of Events (Crude rate (%))	131 (41.9)
Time (Day) to Event [1]	
25 % percentile (95% CI)	170 (140.0, 217.0)
50 % percentile (95% CI)	377 (330.0, 512.0)
75 % percentile (95% CI)	NA (670.0, NA)
Number of Eyes at Risk [2]	
180 Days	161
360 Days	96
540 Days	38
Probability of Not Receiving Second Administration or Rescue (95% CI)	
180 Days	0.731 (0.672, 0.782)
360 Days	0.551 (0.482, 0.614)
540 Days	0.400 (0.325, 0.473)

[1] Percentiles (95% CI) are based on Kaplan-Meier estimates

[2] Number of study eyes that have neither had the event nor been censored by the tabulated timepoint

Notes: N1 = number of study eyes that received at least 1 Bim SR administration.
Time (days) to first event is calculated as the date of second administration or first rescue, whichever comes first, minus the date of the first administration + 1.
Eyes that did not have an event are censored at the time of study completion or discontinuation.
Table presents data from the Bimatoprost SR 10 µg group only.



Bim SR = Bimatoprost Sustained Release; KM = Kaplan-Meier

Probabilities are estimated using the KM method.

Time (days) to first event is calculated as the date of the second administration or first rescue, whichever comes first, minus the date of first administration + 1. Eyes that did not have an event are censored at the time of study completion or discontinuation.

Figure 12: Time to second administration of bimatoprost SR or first rescue treatment after the first administration in the study (Full Analysis Set)

Sensitivity Analysis

Time to Second Administration of Bimatoprost SR or First Rescue in Subjects With at Least 12 Months Exposure

As this is an ongoing study, with study eyes having different durations of exposure to bimatoprost SR at the data cutoff date, a sensitivity analysis was performed for the primary variable (time from the

first treatment administration to the second administration of bimatoprost SR 10 µg or initiation of rescue treatment) in a subgroup of study eyes to evaluate the efficacy profile in eyes with longer-term exposure to bimatoprost SR. This subgroup included 215 study eyes that either had at least 12 months of exposure to bimatoprost SR 10 µg at data cutoff or had an event (bimatoprost SR re-administration, rescue treatment, or study discontinuation) prior to Month 12. Of these, 131 study eyes (60.9%) had received a second administration or initiated rescue treatment by the data cutoff date.

At the time of data cutoff, the median time from initial administration of bimatoprost SR 10 µg in the study eye to requiring a second administration or initiating rescue treatment on a PRN re-administration regimen was 362 days (approximately 12 months) (see table below). The cumulative probability of not receiving a second administration of bimatoprost SR 10 µg or rescue treatment in the study eye regardless of intermittent rescue at 360 days (approximately 12 months) was 50.2% (see figure below).

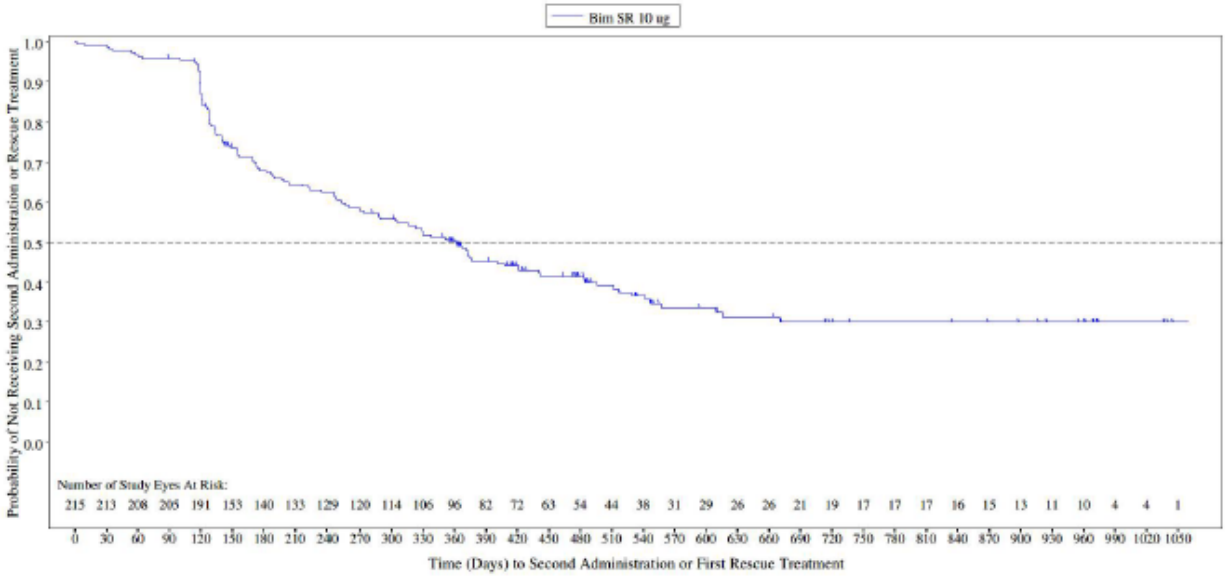
Table 38: Time to second administration of bimatoprost SR or first rescue treatment after first administration in the study eye – subgroup: subjects with at least 12 months exposure at interim data cutoff (Full Analysis Set)

	Bim SR 10ug SE (N=215)
N1	215
Number of Events (Crude rate (%))	131 (60.9)
Time (Day) to Event [1]	
25 % percentile (95% CI)	141 (127.0, 173.0)
50 % percentile (95% CI)	362 (287.0, 421.0)
75 % percentile (95% CI)	NA (616.0, NA)
Number of Subjects at Risk [2]	
180 Days	140
360 Days	96
540 Days	38
Probability of Not Receiving Second Administration or Rescue (95% CI)	
180 Days	0.679 (0.611, 0.737)
360 Days	0.502 (0.433, 0.568)
540 Days	0.365 (0.293, 0.436)

[1] Percentiles (95% CI) are based on Kaplan-Meier estimates.

[2] Number of study eyes that have neither had the event nor been censored by the tabulated timepoint.

Notes: Subgroup includes all subjects who had at least 12 months of follow-up after the first Bim SR administration, or had an event prior to 12 months.
N1= Number of study eyes that received at least 1 Bim SR administration.
Time (days) to first event is calculated as the date of the second administration or first rescue, whichever comes first, minus the date of the first administration + 1.
Eyes that did not have an event were censored at the time of study completion or discontinuation.
Table presents data from the Bimatoprost SR 10 µg group only.



Bim SR = Bimatoprost Sustained Release; KM = Kaplan-Meier

Subgroup includes all subjects who had at least 12 months of follow-up after the first Bimatoprost SR administration or had an event prior to 12 months.

Probabilities are estimated using KM method.

Time (days) to first event is calculated as the date of second administration or first rescue, whichever comes first, minus the date of first administration + 1. Eyes that did not have an event are censored at the time of completion or discontinuation.

Figure 13: Time to second administration of bimatoprost SR or first rescue treatment after first administration

Secondary (other) Efficacy Endpoints

Time to Second Administration of bimatoprost SR in the Study Eye Regardless of Intermittent Rescue

The duration of effect of bimatoprost SR 10 µg regardless of intermittent rescue, was evaluated by assessing the time to second administration of bimatoprost SR or permanent rescue treatment, whichever occurred first, after the first administration in the study eye. Intermittent rescue (use of rescue IOP-lowering medication until the subject became eligible for and received an additional bimatoprost SR administration) is not considered in this analysis.

Of the 313 eyes that had received a first bimatoprost SR 10 µg administration by the data cutoff date, 119 eyes had received a second administration or initiated permanent rescue treatment. At the time of data cutoff, the median time from initial administration of bimatoprost SR 10 µg to requiring a second administration or permanent rescue was 462 days. The cumulative probability of not receiving a second administration of bimatoprost SR 10 µg in the study eye or permanent rescue at 360 days (approximately 12 months) was 58.6%.

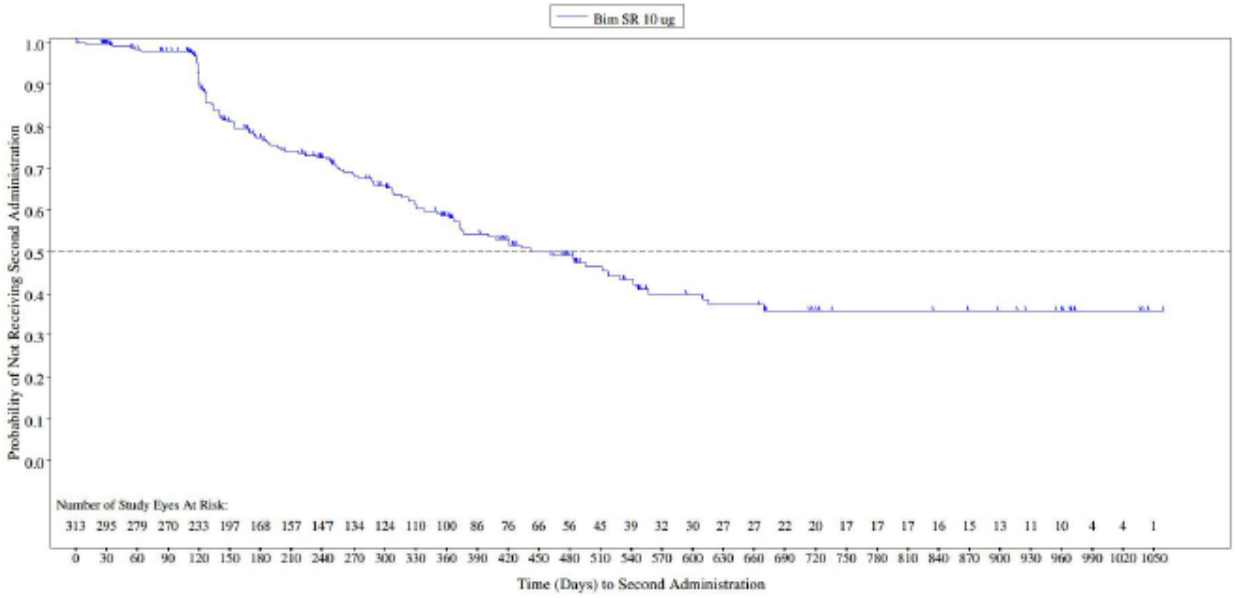
Table 39: Time to second administration of bimatoprost SR in the study eye regardless of intermittent rescue – event summary and survival analysis (Full Analysis Set)

	Bim SR 10ug SE (N=313)
N1	313
Number of Events (Crude rate (%))	119 (38.0)
Time (Day) to Event [1]	
25 % percentile (95% CI)	197 (155.0, 256.0)
50 % percentile (95% CI)	462 (372.0, 542.0)
75 % percentile (95% CI)	NA (NA, NA)
Number of Subjects at Risk [2]	
180 Days	168
360 Days	100
540 Days	39
Probability of Not Receiving Second Administration Regardless of Intermittent Rescue (95% CI)	
180 Days	0.772 (0.715, 0.820)
360 Days	0.586 (0.517, 0.649)
540 Days	0.433 (0.355, 0.509)

[1] Percentiles (95% CI) are based on Kaplan-Meier estimates

[2] Number of study eyes that have neither had the event nor been censored by the tabulated timepoint

Notes: N1 = number of study eyes that received at least 1 Bim SR administration.
Time (days) to first event is calculated as the date of second administration or permanent rescue, whichever comes first, minus the date of the first administration + 1.
Eyes that did not have an event are censored at the time of study completion or discontinuation.
Table presents data from the Bimatoprost SR 10 µg group only.



Bim SR = Bimatoprost Sustained Release; KM = Kaplan-Meier

Probabilities are estimated using the KM method.

Time (days) to first event is calculated as the date of the second administration or first permanent rescue, whichever comes first, minus the date of the first administration + 1. Eyes that did not have an event are censored at the time of study completion or discontinuation.

Figure 14: Time to second administration of bimatoprost SR in the study eye regardless of intermittent rescue (Full Analysis Set)

Time to Third Administration of Bimatoprost SR or First Rescue Treatment in the Study Eye After the Second Administration

The duration of effect of the second bimatoprost SR 10 µg administration was also evaluated by analysing the time to third administration of bimatoprost SR or first rescue treatment (i.e., initiation of intermittent [use of rescue IOP-lowering medication until the subject became eligible for and received

an additional bimatoprost SR administration] or permanent rescue treatment), whichever came first, after the second administration in the study eye. Of the 96 eyes that had received a second bimatoprost SR 10 µg administration by the data cutoff date, 39 eyes had received a third administration or initiated rescue treatment.

At the time of database lock, the median time to requiring a third administration or initiating rescue treatment after the second administration of bimatoprost SR 10 µg in the study eye, under a PRN re-administration regimen was 297 days (approximately 10 months). The cumulative probability of not receiving a third administration of bimatoprost SR 10 µg or rescue treatment after the second administration in the study eye at 360 days (approximately 12 months) was 35.1% in this limited cohort.

Table 40: Time to third administration of bimatoprost SR or first rescue treatment after second administration in the study eye

Event Summary and Survival Analysis
Full Analysis Set

	Bim SR 10ug SE (N=313)
N1	96
Number of Events (Crude rate (%))	39 (40.6)
Time (Day) to Event [1]	
25 % percentile (95% CI)	180 (127.0, 248.0)
50 % percentile (95% CI)	297 (258.0, 357.0)
75 % percentile (95% CI)	500 (356.0, NA)

Time to Third Administration of bimatoprost SR in the Study Eye Regardless of Intermittent Rescue

The duration of effect of the second bimatoprost SR 10 µg administration was evaluated by analysing the time to third administration of bimatoprost SR 10 µg or permanent rescue treatment, whichever occurred first, after the second administration in the study eye regardless of intermittent rescue. Of the 96 study eyes that received a second bimatoprost SR 10 µg administration by the data cutoff date, 30 study eyes had received a third administration or initiated permanent rescue.

At the time of database lock, the median time to requiring a third administration of bimatoprost SR 10 µg or initiation of permanent rescue treatment in the study eye, regardless of intermittent rescue, was 358 days (approximately 12 months). The cumulative probability of not receiving a third administration of bimatoprost SR 10 µg or initiation of permanent rescue treatment in the study eye regardless of intermittent rescue at 360 days (approximately 12 months) was 50.0% in this limited cohort.

Table 41: Time to third administration of bimatoprost SR in the study eye after second administration regardless of intermittent rescue

Event Summary and Survival Analysis
Full Analysis Set

	Bim SR 10ug SE (N=313)
N1	96
Number of Events (Crude rate (%))	30 (31.3)
Time (Day) to Event [1]	
25 % percentile (95% CI)	296 (248.0, 316.0)
50 % percentile (95% CI)	358 (314.0, NA)
75 % percentile (95% CI)	NA (427.0, NA)

Time to First Rescue Treatment After Third Administration of Bimatoprost SR in the Study Eye

Of the 22 eyes that had received a third administration by the data cutoff (29 July 2022), 9 eyes had initiated rescue treatment.

Table 42: Time to first rescue treatment after third administration in the study eye

Event Summary and Survival Analysis
Full Analysis Set

	Bim SR 10ug SE (N=313)
N1	22
Number of Events (Crude rate (%))	9 (40.9)
Time (Day) to Event [1]	
25 % percentile (95% CI)	58 (31.0, 112.0)
50 % percentile (95% CI)	132 (57.0, NA)
75 % percentile (95% CI)	NA (112.0, NA)

IOP and IOP Change from Baseline

Analyses of IOP and IOP change from baseline excluded eyes that received rescue (permanent or intermittent) treatment (medication or procedure) from all visits after the initiation of rescue treatment. IOP measurements at baseline, each postbaseline visit, and change from baseline were summarized for all subjects. IOP measurements at baseline, each postbaseline visit, and change from baseline were also summarized for each treatment cycle (see Table below, results are shown for week 4, 12 and 24 for both treatment cycles).

Table 43: IOP: Summary of baseline, postbaseline, and change from baseline by cycle

Full Analysis Set

Cycle 1

	Bim SR 10ug SE [1] (N=313)
Cycle 1 Week 4	
Mean (SD)	17.8 (3.84)
Median	17.5
Q1, Q3	15.5, 20.0
Min, Max	8.5, 34.0
n	299
Change from baseline	
Mean (SD)	-7.9 (3.56)
Median	-8.0
Q1, Q3	-10.0, -6.0
Min, Max	-21.5, 7.5
n	299
Cycle 1 Week 12	
Mean (SD)	17.5 (3.65)
Median	17.0
Q1, Q3	15.0, 19.8
Min, Max	9.0, 30.0
n	260
Change from baseline	
Mean (SD)	-8.0 (3.63)
Median	-8.0
Q1, Q3	-10.0, -6.0
Min, Max	-21.0, 1.5
n	260
Cycle 1 Week 24	
Mean (SD)	18.1 (4.03)
Median	17.5
Q1, Q3	15.8, 20.0
Min, Max	10.0, 32.5
n	180
Change from baseline	
Mean (SD)	-7.1 (3.86)
Median	-7.0
Q1, Q3	-10.0, -5.0
Min, Max	-18.0, 6.0
n	180
Cycle 2	

	Bim SR 10ug SE [1] (N=96)

Cycle 2 Week 4	
Mean (SD)	17.9 (3.15)
Median	17.5
Q1, Q3	16.0, 19.5
Min, Max	12.0, 26.0
n	83
Change from baseline	
Mean (SD)	-8.2 (4.06)
Median	-8.0
Q1, Q3	-10.5, -6.0
Min, Max	-19.5, 2.0
n	83
Cycle 2 Week 12	
Mean (SD)	18.6 (4.11)
Median	18.0
Q1, Q3	16.0, 21.0
Min, Max	12.0, 33.5
n	66
Change from baseline	
Mean (SD)	-7.4 (4.03)
Median	-7.8
Q1, Q3	-10.0, -5.0
Min, Max	-16.0, 3.5
n	66
Cycle 2 Week 24	
Mean (SD)	20.1 (4.47)
Median	20.0
Q1, Q3	17.5, 21.5
Min, Max	10.0, 30.0
n	43
Change from baseline	
Mean (SD)	-5.8 (4.97)
Median	-5.5
Q1, Q3	-9.0, -2.5
Min, Max	-17.5, 5.0
n	43

[1] Eyes that received rescue (permanent or intermittent) treatment (medication or procedure) are excluded from all visits after the initiation of rescue treatment.
[2] Includes data for assessments occurring prior to fellow eye being treated with Bimatoprost SR or fellow eye never treated with Bimatoprost SR.

Ancillary analyses

Subgroup Analyses

Time to Second Administration of Bimatoprost SR or First Rescue Treatment After the First Administration in the Study Eye by Disease Diagnosis

OAG subgroup

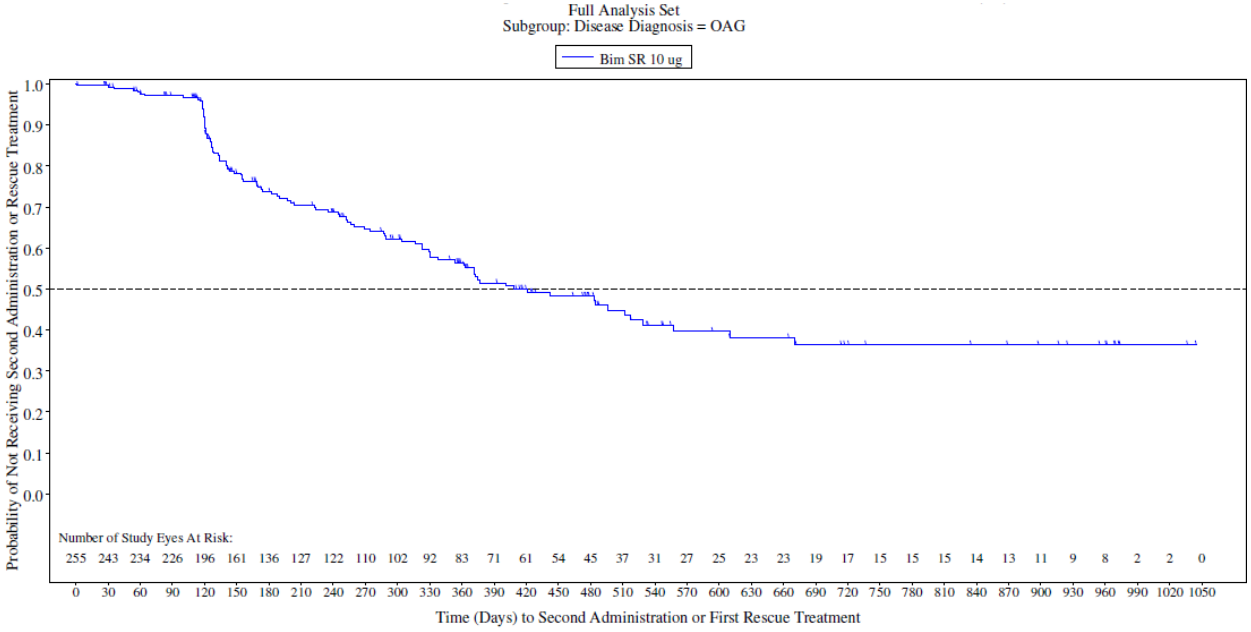
At the time of data cutoff in the OAG subgroup, the median time from initial administration of bimatoprost SR 10 µg to requiring a second administration on a PRN re-administration regimen or to initiation of rescue treatment in the study eye was 408 days (> 1 year) with 95% confidence interval of 338 to 529 days, based on data from all subjects regardless of follow-up time. The probability of OAG subjects not receiving a second administration or initiation of rescue treatment in the study eye was 56.4% at 360 days (approximately 12 months).

Table 44: Time to second administration of bimatoprost SR or first rescue treatment after first administration in the study eye

Full Analysis Set
Subgroup: Disease Diagnosis = OAG

	Bim SR 10ug SE (N=255)
N1	255
Number of Events (Crude rate (%))	105 (41.2)
Time (Day) to Event [1]	
25 % percentile (95% CI)	170 (140.0, 235.0)
50 % percentile (95% CI)	408 (338.0, 529.0)
75 % percentile (95% CI)	NA (NA, NA)

N1= Number of study eyes that received at least one Bim SR administration.
Time (days) to first event is calculated as the date of the second administration or first permanent rescue, whichever comes first, minus the date of the first administration + 1.
Eyes that did not have an event are censored at the time of study completion or discontinuation.
[1] Percentiles (95% CI) are based on Kaplan-Meier estimates.



Probabilities are estimated using the Kaplan-Meier (KM) method.
Time (days) to first event is calculated as the date of the second administration or first rescue, whichever comes first, minus the date of administration + 1.
Eyes that did not have an event are censored at the time of study completion or discontinuation

Figure 15: Time to second administration of bimatoprost SR or first rescue treatment after first administration in the study eye

OHT subgroup

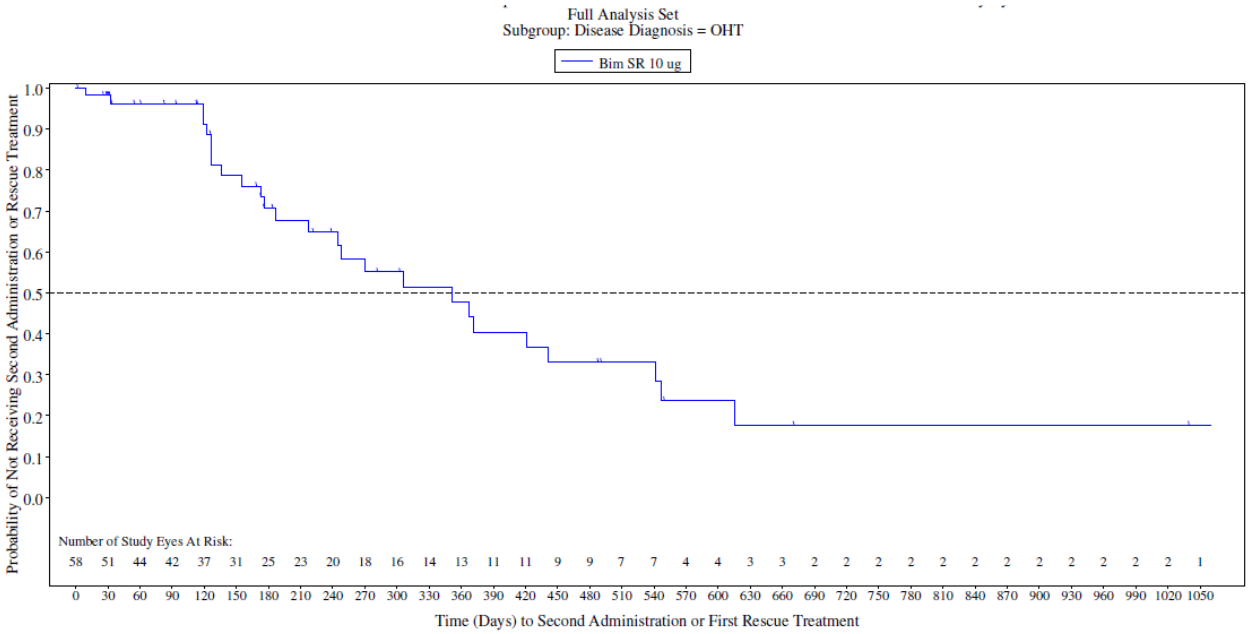
At the time of data cutoff in the OHT subgroup, the median time from initial administration of bimatoprost SR 10 µg to requiring a second administration or initiation of rescue treatment in the study eye on a PRN re-administration regimen was 351 days (approximately 1 year) with 95% confidence interval of 217 to 441 days, based on data from all subjects regardless of follow-up time. The probability of OHT study eyes not receiving a second administration or initiation of rescue treatment was 47.8% at 360 days (approximately 12 months).

Table 45: Time to second administration of bimatoprost SR or first rescue treatment after first administration in the study eye

Full Analysis Set
Subgroup: Disease Diagnosis = OHT

	Bim SR 10ug SE (N=58)
N1	58
Number of Events (Crude rate (%))	26 (44.8)
Time (Day) to Event [1]	
25 % percentile (95% CI)	173 (122.0, 248.0)
50 % percentile (95% CI)	351 (217.0, 441.0)
75 % percentile (95% CI)	547 (372.0, NA)

N1= Number of study eyes that received at least one Bim SR administration.
Time (days) to first event is calculated as the date of the second administration or first permanent rescue, whichever comes first, minus the date of the first administration + 1.
Eyes that did not have an event are censored at the time of study completion or discontinuation.
[1] Percentiles (95% CI) are based on Kaplan-Meier estimates.



Probabilities are estimated using the Kaplan-Meier (KM) method.
Time (days) to first event is calculated as the date of the second administration or first rescue, whichever comes first, minus the date of first administration + 1.
Eyes that did not have an event are censored at the time of study completion or discontinuation.

Figure 16: Time to second administration of bimatoprost SR or first rescue treatment after first administration in the study eye

3.3.4.2.3. Studies 192024-091 and 192024-092

Methods

<u>192024-091 and 192024-092</u>

These studies were phase 3, multicentre, randomized, parallel-group, patient- and efficacy evaluator-masked, 20-month evaluation (52-week active treatment period with 8 months extended follow-up) of the safety and efficacy of bimatoprost SR (10 µg and 15 µg) compared to timolol 0.5% (hereafter referred to as timolol) in patients at least 18 years of age who have been diagnosed with open-angle glaucoma (OAG) or ocular hypertension (OHT).

The length of each study was approximately 22 months for each patient, consisting of screening of up to 28 days before washout, washout period of up to 42 days before initial administration of study medication, 52-week treatment period, plus 8 months extended follow-up.

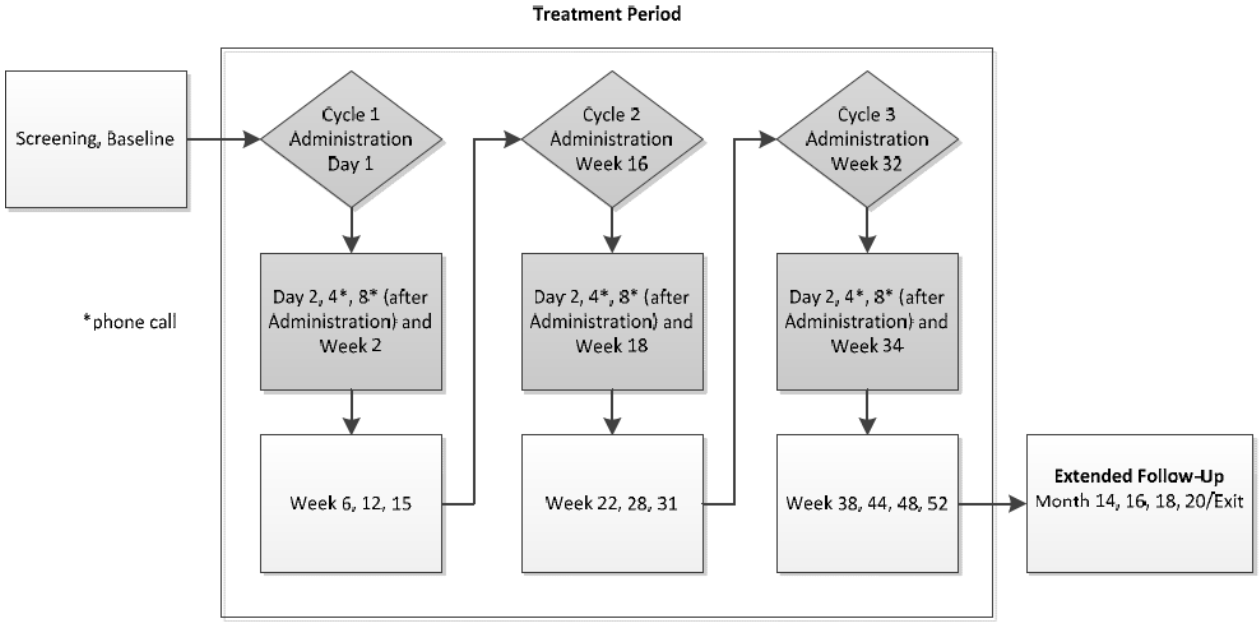


Figure 17: Study schema 192024-091 and 192024-092

Both studies were of the same design. The last bimatoprost SR administration was at Week 32. Thereafter patients were followed until Month 20, which corresponds to approximately 12 months of follow-up. While the dosing regimen investigated in these studies is not fully in line with that proposed in the label (1 to 2 administrations, as needed) and studies were conducted in an arguably different population, they provide important evidence for the efficacy and safety of 1 and 2 administrations of bimatoprost SR 10 µg, when the second implant is injected 4 months after the first implant which is also the minimum interval as proposed by the applicant; and are therefore discussed in more detail. The question of long term efficacy and safety of 1 or 2 administrations cannot be addressed by this study.

Study Participants

192024-091 and **192024-092**

Eligibility criteria were the same in both studies and included male or female subjects ≥ 18 years of age with a diagnosis of either OAG (i.e., primary, pseudoexfoliation, or pigmentary glaucoma) or OHT in each eye and both eyes require IOP-lowering treatment (diagnosis did not have to be the same in both eyes). In the investigator's opinion, either eye could have been treated adequately with 1) topical ophthalmic beta-blocker (eg, timolol) eye drops; and 2) with topical prostamide, prostaglandin, or PGA (eg, Lumigan, Xalatan, Travatan) eye drops as the sole therapy. The iridocorneal angle in the study eye must have been independently confirmed as being qualified by 2 ophthalmologists using the following criteria: i) Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle; ii) Peripheral AC depth by Van Herick examination ≥ 1/2 corneal thickness. At Screening, patients were required to have a minimum central endothelial cell density of 1800 cells/mm2 in at least 1 eye by automated analysis. Endothelial cell density qualification for study entry will be determined by the Reading Centre based on specular microscopy assessment.

At the Baseline visit, the patient was appropriately washed out of all IOP-lowering medications. At the Baseline visit the following criteria had to be met: i) Hour 0 IOP in the study eye of ≥22 mm Hg and ≤32 mm Hg, and in the fellow eye of ≤32 mm Hg; Hour 2 IOP in the study eye of ≥19 mm Hg and ≤32 mm Hg, and in the fellow eye of ≤32 mm Hg; ii) BCVA (Snellen equivalent, by manifest refraction) of 20/50 or better in the study eye and 20/100 or better in the fellow eye; iii) final central

endothelial cell density in both eyes was confirmed as being qualified by reading centre assessment, with at least 1 eye qualified for inclusion as the study eye.

Exclusion criteria included (but were not limited to): non-responsiveness to topical ophthalmic beta-blockers and/or topical prostamides, prostaglandins, or prostaglandin analogues; substantial ocular trauma in the study eye; history of complicated cataract surgery or phakic IOL insertion for refractive error correction in the study eye; intraocular surgery (including cataract surgery) and/or any ocular laser surgery within the 6 months prior to treatment in the study eye; incisional refractive surgery; active or recurrent ocular disease in either eye; central corneal thickness of <480 µm or >620 µm in the study eye; history of closed angle glaucoma in either eye; history of trabeculectomy or other types of glaucoma surgery; history of laser trabeculoplasty within 6 months prior to Screening in the study eye; visual field loss in either eye that, in the opinion of the investigator, was functionally significant (eg, split fixation, field defect within the central 10 degrees that was visually significant or likely to cause central visual impairment upon progression) or showed evidence of progressive visual field loss within the year prior to baseline (2 visual fields were required for qualification, 1 performed within the 10 months prior to or at screening, and 1 performed at Baseline or during the washout period using the protocol-required testing method); evidence of macular oedema on screening OCT evaluation or in medical history in either eye. Non-ocular criteria for exclusion included among other contraindications to beta-blocker therapy, history of a bleeding disorder or prolonged bleeding after surgery.

Treatments

192024-091 and **192024-092**

Patients were randomized in a 1:1:1 ratio one of 3 treatment groups as follows:

- Bimatoprost 10 µg SR treatment at fixed intervals of 16 weeks (Day 1, Week 16, and Week 32)
- Bimatoprost 15 µg SR treatment at fixed intervals of 16 weeks (Day 1, Week 16, and Week 32)
- Timolol maleate 0.5% twice daily [BID] eye drops

The eye that met the entry criteria was selected as the study eye. If both eyes met the entry criteria, the eye with the higher IOP at Baseline Hour 0 was selected as the study eye. If both eyes had the same IOP, then the right eye was designated as the study eye. In order to mask the treatment, patients receiving bimatoprost SR as intracameral injection also received vehicle eye drops twice daily (in the morning and evening), while patients receiving timolol eye drops also received sham needleless procedure on Day 1, Week 16 and Week 32.

Treatment	Study Eye Treatment	Fellow Eye Treatment
Bimatoprost SR 10 µg	Dose strength: 10 µg Eye drops: Vehicle BID	Sham administration procedure Eye drops: Timolol BID
Bimatoprost SR 15 µg	Dose strength: 15 µg Eye drops: Vehicle BID	Sham administration procedure Eye drops: Timolol BID
Control	Sham administration procedure Eye drops: Timolol BID	Sham administration procedure Eye drops: Timolol BID

BID = twice daily

Given that bimatoprost eye drops are already authorised for use in 'reduction of elevated pressure in chronic open-angle glaucoma and ocular hypertension' (Lumigan 0.1 mg/ml eye drops, solution) the applicant was advised during several national scientific advice procedures to use bimatoprost eye drops as a comparator in at least 1 of these two studies, in order to fully inform on the risks/benefits of a different route of administration. Although this advice was not followed, this is not seen critically for the purpose of establishing efficacy of BIM SR implant, since timolol eye drops have an established

efficacy compared to placebo for the treatment of elevated IOP in patients with OAG and OHT and, while being replaced by prostaglandin analogues as the agent of choice for single-drug therapy, are still used in clinical practice. Timolol eye drops were administered in line with approved posology. Therefore, timolol eye drops can be considered an acceptable comparator for the purpose of establishing efficacy of BIM SR implant, although Lumigan would have been preferred. This of course pre-supposes that patients are eligible for the treatment with eye drops in general.

Nonstudy IOP-lowering Medications (rescue medications):

Use of any topical ophthalmic medication containing an ocular antihypertensive, other than use of study medication (timolol) in Control group or fellow eyes, was prohibited as concurrent therapy in either eye, unless necessary for the safety of the patient due to inadequate control of IOP as determined by the investigator. Inadequate control of IOP had to be confirmed at a subsequent visit (scheduled or unscheduled visit). Prior to Week 52, the investigator was expected to attest to the need for additional non-study IOP- lowering medication for safety reasons. After the Week 52 visit, nonstudy topical IOP-lowering medications were permitted if in the investigator's clinical judgment, the IOP is not adequately controlled at two consecutive visits.

BIM SR Re-administration

Patients who have not received rescue medication (prohibited prior to Week 52) in both eyes were to receive a repeat administration of bimatoprost SR (or Sham administration in Control group study eyes and all fellow eyes) at the Week 16 and Week 32 visits as indicated. Patients who have received non-study IOP-lowering medication in both eyes were to be followed for at least 12 months following the last administration of bimatoprost SR or Sham, at which time they were allowed to exit early at the investigator's discretion.

Objectives

192024-091 and **192024-092**

Primary efficacy analysis

The primary efficacy variable is the study eye **time-matched IOP change from baseline** at each hour evaluated (Hours 0 and 2). Mean IOP change from baseline was compared between each bimatoprost SR dose strength and the timolol group for each evaluation hour using the **ITT population**. The comparison at **Week 12** was considered the primary analysis.

Secondary efficacy analyses

The secondary efficacy analyses were to test the superiority of each BIM SR dose strength versus timolol for time-matched IOP change from baseline. Superiority was defined as the upper limit of the 95% CI being < 0 mm Hg for each of the 6 primary timepoints (Hour 0 and 2 at Weeks 2, 6, and 12 of Cycle 1). BIM SR 15 µg (or 10 µg) was considered superior to timolol if it demonstrated a significant difference in favour of BIM SR 15 µg (or 10 µg) at each of the 6 timepoints within the 12-week period (H0 and H2 at Weeks 2, 6, and 12).

Similarly, the superiority test of study eye IOP at each hour of a visit was to be performed. BIM SR 15µg (or 10µg) was considered superior to timolol if it demonstrated a significant difference in favour of BIM SR 15µg (or 10µg) at each of the 6 timepoints within the 12-week period (H0 and H2 at Weeks 2, 6, and 12).

Outcomes/endpoints

192024-091 and **192024-092**

The primary efficacy variable was the study eye time-matched IOP change from baseline. Mean IOP change was compared between each BIM SR dose strength and the timolol group for each hour (Hours 0 and 2) using the ITT population. Hour 0 (08:00) and Hour 2 (10:00) correspond to the trough and peak IOP of timolol eye drops when administered in the morning and in the evening. The comparisons at Week 12 was considered the primary analysis. The applicant also provided results of the comparison of the mean IOP change from baseline at Weeks 2 and 6, which were taken into consideration during assessment, in order to assess consistency of results.

IOP was measured using a Goldmann applanation tonometer. Examiners masked to the treatment assignment were to perform all efficacy IOP measurements at approximately the same time of day for a given patient throughout the study whenever possible. A 2-person reading method was to be used for all efficacy IOP measurements, wherein 1 person adjusts the dial in a masked fashion and a second person reads and records the value. Two consecutive measurements were taken of each eye. If the first 2 measurements differ by >1 mm Hg, a third measurement was to be taken. If the first 2 measurements differ by 1 mm Hg or less, the IOP for the given eye was the average of the 2 readings. If the difference between the first 2 measurements is >1 mm Hg, the IOP for the given eye was the median of the 3 readings.

Other efficacy analyses included IOP and time-matched IOP change from baseline at various time points for each treatment cycle (see table below).

Table 46: Study weeks by treatment cycle

Weeks within each Cycle	Week 2	Week 6	Week 12	Week 15	Week 16	Week 20
Cycle 1 (Treatment at Day 1)	Week 2	Week 6	Week 12	Week 15	NA	NA
Cycle 2 (Retreatment 1 at Week 16)	Week 18	Week 22	Week 28	Week 31	NA	NA
Cycle 3 (Retreatment 2 at Week 32)	Week 34	Week 38	Week 44	NA	Week 48	Week 52

Time to Non-study IOP lowering Medication or Procedure

The cumulative number and percentage of patients in the ITT population who used a nonstudy IOP-lowering medication or procedure in the study eye were summarized by treatment group and visit. 'Time to non-study IOP lowering medication or procedure *from the third injection* for patients who had 3 injections' and 'Time to non-study IOP lowering medication or procedure *from the last injection* for patients who had at least 1 injection' were also analysed.

Sample size

The sample size calculation was based on the primary efficacy analysis of the time-matched IOP for US FDA review because the sample size based on the primary efficacy analysis for other regions was expected to be smaller.

The sample size was estimated based on a 2-sided t-test with $\alpha = 0.05$ at each timepoint and the assumption that the mean IOP difference between bimatoprost SR 10 µg and timolol is -0.25 mm Hg (i.e., bimatoprost SR 10 µg is 0.25 mm Hg better in IOP-lowering than timolol) at Weeks 2 and 6 and 0 mm Hg at Week 12, with a common SD of 4.0 mm Hg and a common within-subject correlation of 0.6.

It was also assumed that the efficacy (IOP-lowering effect) of bimatoprost SR 15 µg is better than that of bimatoprost SR 10 µg by 0.25 mm Hg at each timepoint (Hours 0 and 2). These assumptions were based on the data obtained from the ongoing clinical study 192024-041D. Based on simulations, a sample size of 540 patients (180 per group) should provide approximately 95% and 81% power to show noninferiority of bimatoprost SR 15 µg and bimatoprost SR 10 µg, respectively, to timolol at all 6 scheduled timepoints based on a noninferiority margin of 1.5 mm Hg and at 3 or more timepoints based on an noninferiority margin of 1.0 mm Hg. Assuming a premature discontinuation rate of 10% within 12 weeks (before primary database lock), approximately 600 patients (200 per group) were to be enrolled into this study.

The sample size was reduced for Study 192024-092. As part of ongoing centralized data monitoring of masked study data, some of the initial assumptions used for sample size calculation have been revisited. The rate of discontinued or rescued patients in the first 12 weeks is approximately 5%, which was less than the rate of 10% assumed at the study design phase. Furthermore, the masked common IOP variability (pooled standard deviation across treatments and timepoints) was approximately 3.8 mm Hg, which was also less than the assumed 4.0 mm Hg at the study design phase. With the updated assumption on the common IOP standard deviation of 3.8 mm Hg, a sample size of 486 patients (162 per group) should provide approximately 95.1% and 83.5% power to show NI of bimatoprost SR 15 µg and bimatoprost SR 10 µg, respectively, to timolol at all 6 scheduled timepoints based on an NI margin of 1.5 mm Hg; and at 3 or more timepoints based on an NI margin of 1.0 mm Hg. With the updated premature discontinuation or rescue rate of 5% within 12 weeks, approximately 510 patients (170 per group) were to be enrolled into this study.

Randomisation and blinding (masking)

Eligible patients were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio to receive study bimatoprost SR 10 µg, bimatoprost SR 15 µg, or timolol. Randomisation was stratified by Baseline Hour 0 IOP (baseline study eye IOP ≤ 25 mm Hg or > 25 mm Hg).

An automated Interactive Voice/Web Response System (IV/WRS) was used to manage the randomisation and treatment assignment based on a randomisation scheme prepared by Allergan Biostatistics.

Patients in the Control group received timolol eye drops BID plus Sham administration in both eyes. Vehicle eye drops were be used BID to mask the treatment of patients receiving bimatoprost SR in the study eye. Treatment for fellow eyes of patients assigned to 1 of the 2 bimatoprost SR dose groups was a Sham administration procedure and timolol eye drops BID.

The site coordinator and designated staff were not masked to whether the patient received 1 of the 2 dose strengths of bimatoprost SR or the Sham administration procedure, but were masked to the specific implant dose strength. The patient and the remaining staff were masked to the patient's treatment assignment. Efficacy IOP measurements were masked by using a 2-person reading method.

The site staff who perform IOP readings were masked regarding the study eye (which eye received bimatoprost SR or the Sham administration procedure), bimatoprost SR dose strength, and the study treatments that are delivered in bottles. Site personnel and patients were instructed and reminded throughout the study not to discuss study medication assignments to ensure maintenance of the masking.

Statistical methods

Analysis sets

Intention-to-treat population: The intent-to-treat (ITT) population consisted of all randomized patients.

Per-protocol population: The per-protocol (PP) population consisted of the subset of patients in the ITT population who had the primary efficacy variable measured. In particular, a patient was considered in the PP population if the patient received the randomized treatment in the study eye and had at least 1 IOP measurement from the 6 timepoints (Hour 0 and Hour 2 at Week 2, Week 6 or Week 12 analysis visits). Patients with baseline hour 0 IOP less than 20 mm Hg were not to be included in the PP population. IOP measures deemed being influenced by other medications would be excluded from PP analysis. The PP population was to be used to confirm the primary efficacy analyses. A separate document included further criteria and details of data to be excluded from the PP analyses and was to be finalized prior to the Week 12 database lock.

Safety population: The safety population consisted of all patients who received at least 1 dose of study treatment.

Analysis of the primary endpoint

The primary efficacy variable was the study eye time-matched IOP change from baseline at each hour evaluated (Hours 0 and 2). Mean IOP change from baseline were compared between each bimatoprost SR dose strength and the timolol group for each evaluation hour using the ITT population. The comparisons at Week 12 at Hour 0 and 2 were considered the primary analysis.

The null and alternative hypotheses for the comparison between a given bimatoprost SR dose strength and timolol at each evaluation hour of Week 12 were:

- Null hypothesis: the difference in mean IOP change from baseline between the given bimatoprost SR dose strength and timolol (bimatoprost SR minus timolol) is > 1.5 mm Hg.
- Alternative hypothesis: the difference (bimatoprost SR minus timolol) in mean IOP change from baseline between the given bimatoprost SR dose strength and timolol is ≤ 1.5 mm Hg.

Intraocular pressure change from baseline was analysed using a mixed-effects model with repeated measures (MMRM). The model included IOP time-matched change from baseline as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint-by-baseline time matched IOP interaction. An unstructured covariance matrix was used for repeated measures on the same patient; if the model with unstructured covariance matrix failed to converge, multiple imputation (MI) was implemented before MMRM.

Mis-stratified subjects, if any, were analysed based on the stratum to which the subjects should have been randomized.

Within the framework of this model, the mean difference between each bimatoprost SR dose strength and timolol (bimatoprost SR minus timolol) and the corresponding 2-sided 95% confidence interval were provided for each hour (Hours 0 and 2) at each visit. The formal noninferiority test was performed at each evaluation hour of Week 12 for each bimatoprost SR dose strength versus timolol using a noninferiority margin of 1.5 mmHg.

A gatekeeping procedure was used to control the overall type I error rate at the 0.05 level for each hour at Week 12, testing bimatoprost SR 15 µg against timolol first and followed by the comparison between bimatoprost SR 10 µg and timolol. The test of bimatoprost SR 10 µg versus timolol was valid only if the noninferiority of bimatoprost SR 15 µg to timolol was demonstrated. Bimatoprost SR 15 µg (or 10 µg) were declared noninferior to timolol if the upper limit of the 95% confidence interval was ≤ 1.5 mm Hg for both Hours 0 and 2 at Week 12.

For the analysis, IOP values obtained after initiating the use of non-study IOP-lowering medication or procedure in an eye were excluded from the calculation of the summary statistics and the statistical analyses for that eye but raw values will be presented in the listings.

Sensitivity analyses

PP population analysis

The analysis outlined for primary efficacy analysis was repeated on the PP population.

Time-matched last observation carried forward (LOCF) analysis

Missing values were imputed by time-matched LOCF method. At each visit/hour, treatment difference and its 95% confidence interval were based on least square means by using an Analysis of Covariance (ANCOVA) model with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate.

Multiple imputation implementation before performing ANCOVA analysis

Step 1: Intermittent missing values at each hour of Week 2, 6, and 12 were first imputed by treatment group using Markov chain Monte Carlo (MCMC) method (defined as the MCMC step) with seed=79214203 resulting in data with a monotone pattern.

Step 2: Multiple imputation by treatment group using linear regression with factors of demographics and baseline characteristics including but not limited to race group, sex, and lens status; and age, baseline IOP values at both Hour 0 and Hour 2 as covariates (defined as the regression step) was applied to the data obtained from the MCMC step. The seed for the second multiple imputation step=63128917.

Step 2 immediately followed step 1 and the entire procedure was repeated 25 times to provide reliable statistical inference.

Analysis of secondary efficacy endpoints

The 2-sided 95% confidence interval for the mean difference in study eye time-matched IOP change from baseline between each bimatoprost SR dose strength and timolol (bimatoprost SR minus timolol) derived in the primary analysis was used for secondary analysis of superiority comparison. If the upper 95% confidence limit was less than zero, the difference was considered significant and in favour of the given bimatoprost SR dose strength for the given timepoint. Bimatoprost SR 15 µg (or 10 µg) was to be considered superior to timolol if it demonstrates significant difference in favour of bimatoprost SR 15 µg (or 10 µg) at each of the 6 timepoints within the 12-week period (Hours 0 and 2 at Weeks 2, 6, and 12).

Similarly, the superiority test of study eye IOP at each hour of a visit was performed using the same MMRM model as described above with the response variable of study eye IOP.

Analysis of other efficacy endpoints

Intraocular pressure and IOP change from study baseline at other evaluation visits including Cycle 1 Day 2 visit and visits after Week 12 was analysed by timepoint.

Efficacy Analyses Planned for Treatment Cycle 2 and Cycle 3

Administration of bimatoprost SR or Sham occurred at fixed intervals of 16 weeks, up to a total of 3 administrations. Treatment cycle was defined based on the study treatment administration:

- Cycle 1: Day 1 (the first study treatment administration) to retreatment 1 date (the second study treatment administration at Week 16) -1, or Month 20/study exit (if only 1 study treatment administration), whichever is earlier.
- Cycle 2: Retreatment 1 date to retreatment 2 date (the third study treatment administration date at Week 32) - 1, or Month 20/study exit (if only 2 study treatment administrations), whichever is earlier.
- Cycle 3: Retreatment 2 date to Week 52, or Month 20/study exit, whichever is earlier. Visits and the corresponding weeks within each cycle for analysis are presented below. Weeks within each Cycle Week 2 Week 6 Week 12 Week 15 Week 16 Week 20

For patients who had received study retreatment(s) in the study eye, IOP and IOP change from study baseline was analysed by visits within each cycle (i.e., Cycle 2 Week 2, 6, and 12). Study baseline was used for change from baseline calculation for any cycle. At each evaluation hour at visits of Weeks 2, 6, and 12 within each cycle, treatment difference and its 95% confidence interval were provided based on least square means by using the MMRM model with fixed factors of treatment, timepoint (Hours 0 and 2 at Weeks 2, 6, and 12 within a cycle) and baseline IOP stratification; the treatment-by-timepoint and timepoint-by-baseline time-matched IOP interactions; as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate. Unstructured covariance matrix was assumed, if the model with unstructured covariance matrix fails to converge, multiple imputation was to be implemented before MMRM.

Observed IOP and IOP change from baseline at other visits of each cycle (including Day 2, Weeks 15 in cycles 1 and 2 or 16 in cycle 3, and Week 20 for cycle 3) and at visits in follow-up extension from Month 14 through Month 20 for patients who received 3 injections only, was summarized by visit and hour.

Time to non-study IOP lowering medication or procedure

The cumulative number and percentage of patients in the ITT population who had used non-study IOP lowering medication or procedure in the study eye were summarized by treatment group and visit. The distribution, including the 25th percentile and median, of the time to non-study IOP lowering medication or procedure was estimated using Kaplan-Meier method by treatment group. The analyses were conducted to the following group of patients:

• Time to non-study IOP lowering medication or procedure from the 3rd injection for patients who had 3 injections;

• Time to non-study IOP lowering medication or procedure from the last injection for patients who had at least 1 injection.

The time to non-study IOP lowering medication or procedure after the 3rd injection was defined as the days from the 3rd injection date to the start day of the 1st time use of nonstudy IOP lowering medication or procedure in the study eye. If a patient did not use any non-study IOP lowering medication or procedure in the study eye during the study, the patient's study exit date (or the last visit date if the exit date is not available) was used as the censoring date.

Similarly, the time to non-study IOP lowering medication or procedure after the last injection was defined as the days from the last injection date to the start day of the 1st time use of non-study IOP lowering medication or procedure.

Results

The applicant applied only for the dose strength 10 µg, and not for the 15 µg due to above mentioned safety findings. This is acceptable as both treatment arms met the primary endpoint for non-inferiority according to the predefined testing sequence. Consequently, results for 15 µg are not discussed in detail.

Participant flow

Results for studies -091 and -092 were presented individually for each study and pooled together in an integrated safety analysis (see section 3.3.4.6 Analysis performed across trials). In the interest of space results regarding patients' disposition and demographics are presented pooled, while outcomes and estimates are presented for each study separately. Of note, the results from the integrated efficacy analysis are in line with results from individual studies.

A total of 1122 patients were randomized in both studies (374 in each arm); and 1111 (99.0%) patients were treated. Of patients who entered Cycle 1, 96% completed Cycle 1; 96.4% of patients who entered Cycle 2 completed Cycle 2 and 95.0% % of patients who entered Cycle 3 completed Cycle 3. The completion rates were overall comparable between pooled timolol and pooled BIM SR 10 µg across all cycles. The overall proportion of subjects who completed the study was slightly higher in pooled BIM SR 10 µg arms (90.65) compared to pooled timolol arms (87.4%). The lowest completion rate was in the pooled BIM SR 15 µg arms (84.0%), where more patients discontinued the study compared to other two treatments, mostly due to adverse events. Generally, the differences between BIM SR 10 µg and timolol arm, whether in pooled or in individual studies in terms of patient disposition were rather small and do not give rise to concerns.

Recruitment

Both studies were conducted at multiple sites, including sites in Europe. Both studies are completed. For study -091, the first patient was enrolled ion 15 Dec 2014; the last patient' last visit occurred on 19 Jul 2019. For study -092, the first patient was enrolled on 15 Dec 2014; the last patient' last visit occurred on 22 Jul 2020.

Conduct of the study

Protocol amendments

<u>Study 192024-091</u>

The protocol was amended 2 times (Protocol Amendment 1, and Protocol Amendment 2. With Amendment 1 (dated 11 Aug 2015) some sections were clarified and to modify the inclusion/exclusion were modified. With Amendment 2 (dated 16 Mar 2017) screening requirement for angle eligibility confirmation in the study eye was amended, statistical analyses were clarified, inclusion/exclusion criteria were modified/clarified, statistical analyses were clarified and additional procedures for patients with sickle cell disease were changed from required to optional. Changes to the study protocol can be accepted and are not considered to affect the validity of the study results.

<u>Study 192024-092</u>

The original protocol was approved on 17 Sep 2014. The protocol was amended 3 times. With Amendment 1 (dated 19 Aug 2015) and Amendment 2 (dated 16 Mar 2017) same changes were introduces as for the study -091 discussed above. An additional amendment was implemented for study -092 (Amendment 3, dated 05 Jun 2018) which was not implemented in study -091. With the last amendment the sample size was reduced. This is further discussed in the statistical part.

Baseline data

In the pooled analysis (see section 3.3.4.6 Analysis performed across trials), the mean age of the study population was 64 (range: 19 to 92 years), with 7% (79/1122) of patients in the <45 years of age group; 49.9% (560/1122) in the ≥45 to ≤65 years of age group and 43.0% (483/1122) in the >65 years of age group. The majority of patients (63.3% [710/1122]) were white. Approximately half of the patients were female (49.6% [557/1122]). A total of 22.5% (252/1122) subjects had a diagnosis of OHT, and 74.7% (838/1122) had a diagnosis of primary OAG. The number of patients with Pseudoexfoliation and pigmentary OAG was very low [(8/1122 (0.7%)] and 24/1122 (2.1%), respectively].

Numbers analysed

Study 192024-091

A total of 594 patients (198 patients in each treatment group) were enrolled; all were included in the ITT population. The PP population consisted of the subset of patients in the ITT population who had received the randomized treatment in the study eye, with study eye baseline hour 0 IOP ≥ 20 mm Hg and at least 1 IOP measurement from the 6 primary efficacy timepoints.

In the PP population, there were 192 patients in the bimatoprost SR 15 µg group, 197 patients in the bimatoprost SR 10 µg group, and 196 patients in the timolol group; a total of 9 patients were excluded from the PP population. The safety population consisted of all patients who received at least 1 dose of study treatment and included 193 patients in the bimatoprost SR 15 µg group, 197 patients in the bimatoprost SR 10 µg group, and 197 patients in the timolol group.

Table 47: Analysis populations (All Randomized or Treated Patients)

Parameter	BimSR 15 ug (N=198)	BimSR 10 ug (N=198)	Tim BID (N=198)
Intent-to-Treat Population, N	198	198	198
Per-Protocol Population, N	192	197	196
Safety Population, N	193	197	197

Study 192024-092

A total of 528 patients (176 patients in each treatment group) were randomized; all were included in the ITT population. The PP population consisted of the subset of patients in the ITT population who had received the randomized treatment in the study eye, with study eye baseline Hour 0 IOP ≥ 20 mm Hg and at least 1 IOP measurement from the 6 primary efficacy timepoints. In the PP population, there were 174 patients in the bimatoprost SR 15 µg group, 173 patients in the bimatoprost SR 10 µg group, and 171 patients in the timolol group; a total of 10 patients were excluded from the PP population. The safety population consisted of all patients who received at least 1 administration of study treatment and included 176 patients in the bimatoprost SR 15 µg group, 175 patients in the bimatoprost SR 10 µg group, and 173 patients in the timolol group.

Table 48: Analysis populations (All Randomized or Treated Patients)

Parameter	BimSR 15 ug (N=176)	BimSR 10 ug (N=176)	Tim BID (N=176)
Intent-to-Treat Population, N	176	176	176
Per-Protocol Population, N	174	173	171
Safety Population, N	176	175	173

Outcomes and estimation

Primary Efficacy Analysis (time-matched IOP change from baseline)

For countries/regions outside the US, the primary efficacy variable was time-matched IOP (mm Hg) change from baseline at each hour evaluated (Hours 0 and 2) of Cycle 1 Week 12 for the ITT population. Mean IOP change from baseline was compared between each bimatoprost SR dose strength and timolol for each evaluation hour. If a nonstudy IOP-lowering medication or procedure was used for an eye, IOP values obtained after initiation of nonstudy IOP-lowering medication or procedure were excluded from analyses.

Table 49: IOP (mm Hg) baseline and change from baseline in the study eye at cycle 1, weeks 2, 6, and 12 (ITT Population)

			192024-091			**192024-092**		
Visit	Hour		BIM 15	BIM 10	TIM	BIM 15	BIM 10	TIM
			N=198	N=198	N=198	N=176	N=176	N=176
Baseline	0	Mean (SD)	24.76 (2.84)	24.64 (2.67)	24.63 (2.63)	24.39 (2.46)	24.28 (2.43)	24.46 (2.53)
		n	198	198	198	176	176	175
	2	Mean (SD)	23.56 (3.13)	23.29 (3.09)	23.19 (2.93)	23.41 (2.81)	23.24 (2.76)	23.43 (3.06)
		n	198	198	198	176	175	175
Week 2	0	Mean (SD)	-7.94 (3.51)	-7.63 (3.56)	-6.84 (3.71)	-7.88 (3.60)	-7.64 (3.71)	-7.17 (3.61)
		n	191	196	196	170	172	171
		LS mean (SE)	-7.17 (0.25)	-6.97 (0.25)	-6.17 (0.25)	-7.12 (0.27)	-6.94 (0.27)	-6.36 (0.27)
		Difference vs. TIM (SE)	-1.01 (0.34)	-0.80 (0.34)		-0.76 (0.36)	-0.58 (0.36)	
		95% CI	(-1.68, -0.34)	(-1.47, -0.13)		(-1.48, -0.04)	(-1.29, 0.14)	
	2	Mean (SD)	-7.35 (3.51)	-7.20 (3.70)	-6.24 (3.51)	-7.72 (3.26)	-7.25 (3.68)	-6.65 (3.82)
		n	191	196	196	170	171	171
		LS mean (SE)	-7.52 (0.22)	-7.57 (0.22)	-6.67 (0.22)	-7.77 (0.25)	-7.38 (0.25)	-6.67 (0.25)
		Difference vs. TIM (SE)	-0.85 (0.31)	-0.90 (0.30)		-1.10 (0.34)	-0.71 (0.34)	
		95% CI	(-1.45, -0.25)	(-1.50, -0.31)		(-1.76, -0.43)	(-1.38, -0.05)	
Week 6	0	Mean (SD)	-7.67 (3.56)	-7.76 (3.22)	-6.99 (3.44)	-7.56 (3.74)	-7.63 (3.63)	-7.26 (3.83)
		n	188	197	194	172	171	167

		LS mean (SE)	-6.91 (0.24)	-7.11 (0.23)	-6.29 (0.24)	-6.81 (0.28)	-6.93 (0.28)	-6.35 (0.29)
		Difference vs. TIM (SE)	-0.63 (0.32)	-0.82 (0.32)		-0.46 (0.38)	-0.59 (0.38)	
		95% CI	(-1.26, 0.01)	(-1.46, -0.19)		(-1.22, 0.29)	(-1.34, 0.17)	
	2	Mean (SD)	-7.25 (3.89)	-7.12 (3.42)	-6.40 (3.43)	-7.67 (3.59)	-7.15 (3.89)	-6.72 (3.93)
		n	187	197	193	172	170	167
		LS mean (SE)	-7.37 (0.23)	-7.48 (0.22)	-6.83 (0.23)	-7.74 (0.26)	-7.33 (0.26)	-6.69 (0.27)
		Difference vs. TIM (SE)	-0.54 (0.32)	-0.66 (0.31)		-1.05 (0.36)	-0.65 (0.36)	
		95% CI	(-1.16, 0.08)	(-1.27, -0.04)		(-1.76, -0.34)	(-1.36, 0.06)	
Week 12	0	Mean (SD)	-7.19 (3.84)	-7.01 (3.63)	-6.69 (3.98)	-7.21 (4.07)	-6.93 (3.99)	-6.99 (3.87)
		n	185	192	191	168	169	165
		LS mean (SE)	-6.46 (0.29	-6.38 (0.28)	-6.05 (0.28)	-6.47 (0.30)	-6.18 (0.30)	-6.11 (0.30)
		Difference vs. TIM (SE)	-0.41 (0.39)	-0.33 (0.39)		-0.36 (0.41)	-0.08 (0.41)	
		95% CI	(-1.17, 0.36)	(-1.09, 0.43)		(-1.17, 0.44)	(-0.88, 0.73)	
	2	Mean (SD)	-7.11 (3.70)	-6.33 (3.92)	-6.05 (4.00)	-7.10 (3.82)	-6.59 (4.00)	-6.39 (4.17)
		n	183	192	191	168	168	165
		LS mean (SE)	-7.18 (0.26)	-6.69 (0.25)	-6.48 (0.25)	-7.16 (0.28)	-6.72 (0.28)	-6.36 (0.29)
		Difference vs. TIM (SE)	-0.70 (0.35)	-0.21 (0.35)		-0.80 (0.39)	-0.36 (0.39)	
		95% CI	(-1.40, -0.01)	(-0.90, 0.47)		(-1.57, -0.04)	(-1.12, 0.41)	

SE = Standard Error. Baseline refers to the study baseline.
Each cycle starts after patients receive the corresponding injections. Cycle visits are relative to re-treatment dates.
[1] Based on a mixed-effects model with repeated measures (MMRM) including IOP time-matched change from baseline as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used in the MMRM model.

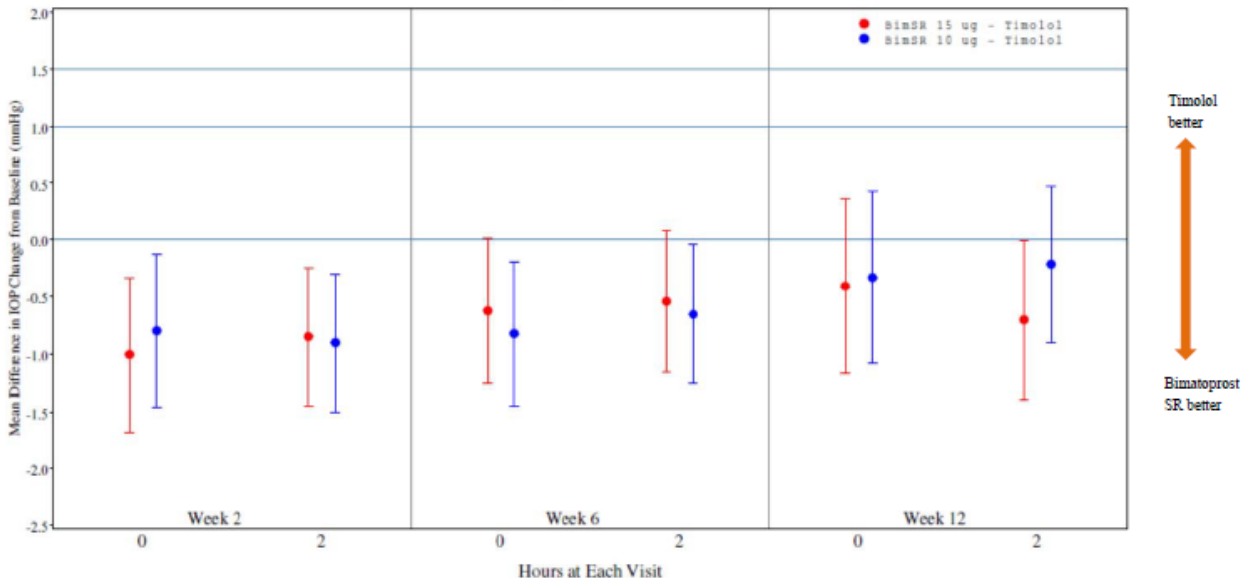


Figure 18: Mean difference in IOP change from baseline at weeks 2, 6, and 12 of cycle 1 (ITT Population) (192024-091)

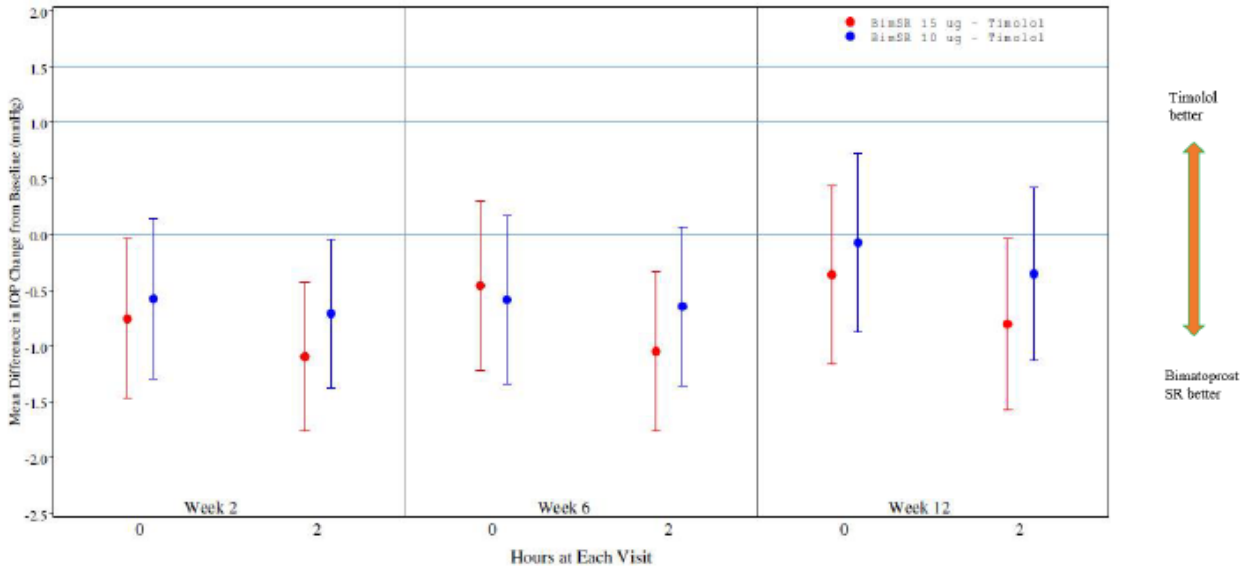


Figure 19: Mean difference in IOP change from baseline at cycle 1, weeks 2, 6, and 12 (ITT Population) (192024-092)

Baseline mean IOP of all treatment groups for both trials were similar. Both dose strengths of bimatoprost SR met the pre-specified criteria for non-inferiority (upper limit of the 95% CI ≤ 1.5 mm Hg at Week 12 of Cycle 1 (both Hour 0 and 2) in the ITT population in both trials. In addition, the change from baseline in mean IOP at Week 2, 6 were similar for BIM SR and timolol in both trials. In both studies, the change from baseline in mean IOP (point estimates) was numerically greater for bimatoprost SR (15 µg and 10 µg) compared to timolol at each hour evaluated (Hours 0 and 2) at Weeks 2, 6, and 12 of Cycle 1, although the corresponding 95% CIs included unity at several time points.

Mean IOP change from baseline findings for the PP population (the subset of patients in the ITT population who had the primary efficacy variable measured) also confirmed noninferiority. Results from the sensitivity analysis on IOP change from baseline at each hour evaluated (Hours 0 and 2) at Weeks

2, 6, and 12 of Cycle 1 using ANCOVA model with LOCF imputation as well as the sensitivity analysis using ANCOVA model with multiple imputation were similar to the primary analysis. However, further analyses based on MNAR assumption and another estimand, complying with the ITT principle, were requested (see section on statistical methods).

Superiority to timolol

Since bimatoprost SR 15 µg did not meet superiority criteria, no test was performed for bimatoprost SR 10 µg per gatekeeping multiplicity control. This applies to both studies.

IOP in Cycle 2 and Cycle 3 *(graphs below were created by the assessor)*

Study -091

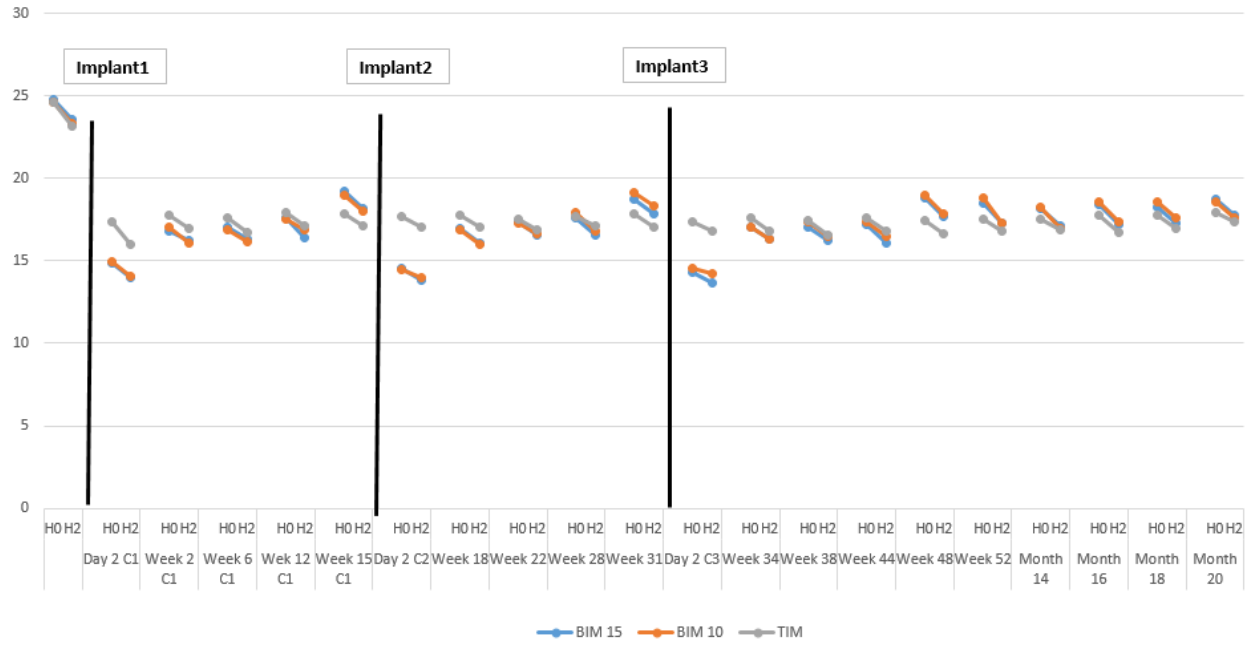


Figure 20: Mean IOP through month 20

Study -092

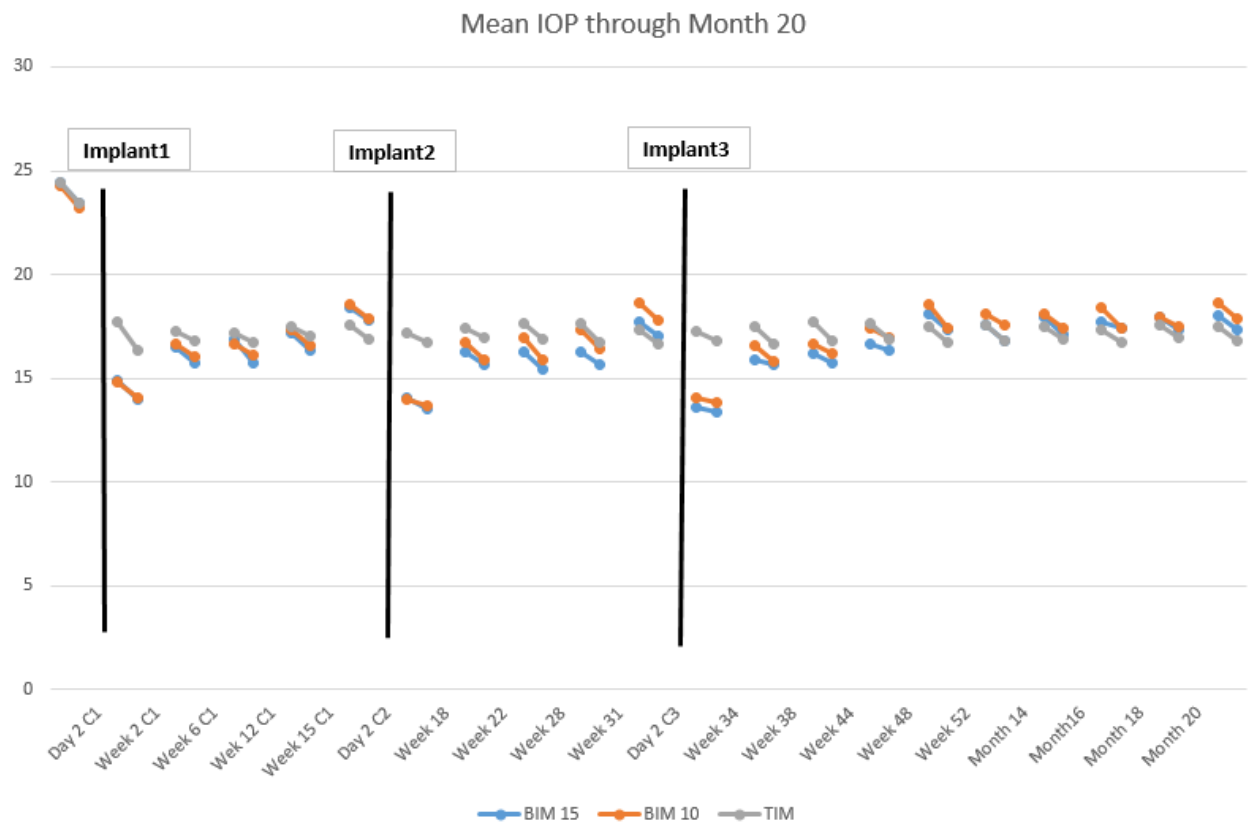


Figure 21: Mean IOP through month 20

In BIM SR 10 µg group (both studies combined) the mean IOP dropped at the beginning of each new cycle (Day 2 of Cycle 1, Cycle 2 and Cycle 3) (mean IOP from 13.7 to <15 mmHg in both BIM SR groups); stabilized between Week 2 and Week 6 (mean IOP from 15.8 to 17.4 mmHg); started increasing around Week 12 (mean IOP from 16.4 to 18 mmHg); and further increased around Week 15 (mean IOP from 17.4 to 19.2 mmHg). The last IOP measurements were carried out at Month 20 i.e. approximately 12 months after the injection of the third implant. At Month 20 mean IOP values were 18.6 mmHg and 17.5 mmHg at Hour 0 and 17.9 mmHg and 16.8 mmHg at Hour 2 in BIM 10 µg and timolol group, respectively. This demonstrates that after 3 administrations of BIM SR implant, with a fixed time interval of 4 months between two injections, the IOP-lowering effect of BIM SR exists over the timespan of 12 months since the last administered dose, however, the effect starts diminishing at Week 12 post-injection. While the IOP values at Month 20 were still markedly lower compared to the baseline IOP values (around 23-25 mm Hg), around 20% of patients had to resort to rescue medication. IOP reduction after the injection of first implant and after re-administration were similar, suggesting there is no cumulative IOP-lowering effect of previous implants, although the remains of them were still detected in the eye. The lack of a cumulative effect suggests that the active substance is used up before the next implant is injected, which justifies re-administration. However, the degradation of implant itself appears to take longer than that of the active substance, which poses concerns.

Use of rescue medication

- Number of Patients Using Non-study IOP-lowering Medications or Procedures

Study -091

Table 50: Cumulative number (%) of patients with IOP exclusion due to Use of nonstudy IOP lowering medications or procedures in study eye

Intent-to-Treat Population

Cycle	Up to Visit	BimSR 15 ug (N=198)	BimSR 10 ug (N=198)	Tim BID (N=198)
1	n	193	197	197
	up to Week 2/Cycle 1 Week 2	2/193 (1.0)	0/197	1/197 (0.5)
	up to Week 6/Cycle 1 Week 6	3/193 (1.6)	0/197	2/197 (1.0)
	up to Week 12/Cycle 1 Week 12	4/193 (2.1)	2/197 (1.0)	2/197 (1.0)
	up to Week 15/Cycle 1 Week 15	6/193 (3.1)	5/197 (2.5)	5/197 (2.5)
	patients with nonstudy IOP lowering	18/193 (9.3)	7/197 (3.6)	6/197 (3.0)
2	n	170	188	184
	up to Week 18/Cycle 2 Week 2	2/170 (1.2)	2/188 (1.1)	0/184
	up to Week 22/Cycle 2 Week 6	4/170 (2.4)	3/188 (1.6)	1/184 (0.5)
	up to Week 28/Cycle 2 Week 12	6/170 (3.5)	6/188 (3.2)	4/184 (2.2)
	up to Week 31/Cycle 2 Week 15	10/170 (5.9)	6/188 (3.2)	4/184 (2.2)
	patients with nonstudy IOP lowering	15/170 (8.8)	9/188 (4.8)	7/184 (3.8)
3	n	151	176	173
	up to Week 34/Cycle 3 Week 2	0/151	1/176 (0.6)	0/173
	up to Week 38/Cycle 3 Week 6	0/151	3/176 (1.7)	1/173 (0.6)
	up to Week 44/Cycle 3 Week 12	1/151 (0.7)	6/176 (3.4)	1/173 (0.6)
	up to Week 48/Cycle 3 Week 16	3/151 (2.0)	6/176 (3.4)	1/173 (0.6)
	up to Week 52/Cycle 3 Week 20	7/151 (4.6)	12/176 (6.8)	1/173 (0.6)
	patients with nonstudy IOP lowering	10/151 (6.6)	21/176 (11.9)	3/173 (1.7)
Extended Safety Follow-Up	n	137	150	163
	up to Month 14	2/137 (1.5)	1/150 (0.7)	1/163 (0.6)
	up to Month 16	3/137 (2.2)	6/150 (4.0)	3/163 (1.8)
	up to Month 18	6/137 (4.4)	10/150 (6.7)	4/163 (2.5)
	up to Month 20	11/137 (8.0)	13/150 (8.7)	6/163 (3.7)
	patients with nonstudy IOP lowering	11/137 (8.0)	15/150 (10.0)	8/163 (4.9)

For each patient, only the first use of a non-study IOP lowering medications or procedures in study eye will be counted.
A patient is counted in a cycle based on the number of administration(s) prior to receiving the non-study IOP lowering medications or procedures.
A patient's IOP will be treated as missing in efficacy analysis after initiation of nonstudy IOP lowering medications or procedure.

Study -092

Table 51: Cumulative number (%) of patients with IOP exclusion due to use of nonstudy IOP lowering medications or procedures in study eye

Intent-to-Treat Population

Cycle	Up to Visit	BimSR 15 ug (N=176)	BimSR 10 ug (N=176)	Tim BID (N=176)
1	n	176	175	173
	up to Week 2/Cycle 1 Week 2	2/176 (1.1)	0/175	1/173 (0.6)
	up to Week 6/Cycle 1 Week 6	2/176 (1.1)	0/175	1/173 (0.6)
	up to Week 12/Cycle 1 Week 12	2/176 (1.1)	1/175 (0.6)	1/173 (0.6)
	up to Week 15/Cycle 1 Week 15	3/176 (1.7)	3/175 (1.7)	2/173 (1.2)
	patients with nonstudy IOP lowering	10/176 (5.7)	4/175 (2.3)	2/173 (1.2)
2	n	163	165	163
	up to Week 18/Cycle 2 Week 2	3/163 (1.8)	0/165	0/163
	up to Week 22/Cycle 2 Week 6	6/163 (3.7)	0/165	1/163 (0.6)
	up to Week 28/Cycle 2 Week 12	6/163 (3.7)	0/165	3/163 (1.8)
	up to Week 31/Cycle 2 Week 15	6/163 (3.7)	1/165 (0.6)	5/163 (3.1)
	patients with nonstudy IOP lowering	12/163 (7.4)	6/165 (3.6)	5/163 (3.1)
3	n	142	153	154
	up to Week 34/Cycle 3 Week 2	0/142	3/153 (2.0)	1/154 (0.6)
	up to Week 38/Cycle 3 Week 6	0/142	4/153 (2.6)	3/154 (1.9)
	up to Week 44/Cycle 3 Week 12	2/142 (1.4)	4/153 (2.6)	3/154 (1.9)
	up to Week 48/Cycle 3 Week 16	7/142 (4.9)	8/153 (5.2)	3/154 (1.9)
	up to Week 52/Cycle 3 Week 20	12/142 (8.5)	13/153 (8.5)	5/154 (3.2)
	patients with nonstudy IOP lowering	15/142 (10.6)	17/153 (11.1)	9/154 (5.8)
Extended Safety Follow-Up	n	125	134	142
	up to Month 14	4/125 (3.2)	2/134 (1.5)	1/142 (0.7)
	up to Month 16	7/125 (5.6)	8/134 (6.0)	2/142 (1.4)
	up to Month 18	9/125 (7.2)	14/134 (10.4)	2/142 (1.4)
	up to Month 20	14/125 (11.2)	16/134 (11.9)	2/142 (1.4)
	patients with nonstudy IOP lowering	19/125 (15.2)	22/134 (16.4)	5/142 (3.5)

For each patient, only the first use of a non-study IOP lowering medications or procedures in study eye will be counted.
A patient is counted in a cycle based on the number of administration(s) prior to receiving the non-study IOP lowering medications or procedures.
A patient's IOP will be treated as missing in efficacy analysis after initiation of nonstudy IOP lowering medications or procedure.

The use of rescue treatment was higher in BIM SR 10 µg compared to timolol group in each cycle; this imbalance is particularly pronounced in Cycle 3 (after the injection of the third implant). During Cycle 3, the percentage of patients who received rescue treatment was 11.9% (21/176) vs. 1.7% (3/173) in study -091; and 11.1% (17/153) vs. 5.8% (9/154) in study -092 in BIM SR 10 µg and timolol group, respectively. In both studies the utilisation of rescue medication in BIM SR 10 µg group increased with each following cycle. Since in each cycle only participants who had not used rescue medication remain, the increase in use of rescue medication might be observed based on the phenomenon of regression-to-the-mean and its possible impact should be discussed by the applicant.

Most patients did not require rescue treatment within 360 days following their last administration of BIM SR (which could have been first, second or third). The proportion of patients who did not require a rescue treatment within this time frame was highest in the timolol group (88.9%) and lowest in the BIM SR 15 µg group (73.0%). Most patients in all groups did not require rescue treatment within 360 days following the third administration of BIM SR, however it should be highlighted that only patients who were not rescued in the study eye before the 3rd administration were included in the analysis, which might impose bias and should be discussed by the applicant. The proportion of patients who did not require a rescue treatment within this time frame was highest in the timolol group (95.2%) and lowest in the BIM SR 10 µg group (82.1%). In the extended safety follow-up (up to Month 20), the percentage of patients who received rescue treatment was also markedly higher in BIM SR 10 µg group compared to timolol group [10.0% (15/150) vs 4.9% (8/163) in study -091; and 16.4% (22/134) vs. 3.5% (5/142) in study -092]. This data shows an increase in need for rescue medication after the third administration.

3.3.4.3. Summary of main efficacy results

Summary of Main Efficacy Results.doc

3.3.4.4. Clinical studies in special populations

No studies were conducted with specific focus on special populations.

The applicant provided the requested table depicting the IOP-lowering effect of BimSR 10 ug in different age groups (65-74 years, 75-84 years and >= 85 years) at Week 12 for studies 091/092, 093 and 301-007. However, to better contextualize these results, the applicant is asked to update this table to also include data on the respective active comparator for studies 091 and 092 (combined results) and study 093.

3.3.4.5. In vitro biomarker test for patient selection for efficacy

N/A

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

The integrated efficacy analysis combines the two studies of bimatoprost SR vs. timolol (192024-091 and 192024-092) into a single group. Studies 192024-041D, 192024-093, and 192024-095 are not included in the ISE. Study 192024-041D has a different study design and limited number of patients with repeat administration of bimatoprost SR 10 or 15 µg, and studies 192024-093 and 192024-095 are still ongoing masked studies with no data available for the ISE analyses. Unless otherwise specified, the analyses for all variables in the ISE were performed in the similar manner as in the individual studies (study 192024-091 and 192024-092) on the pooled data from the two studies.

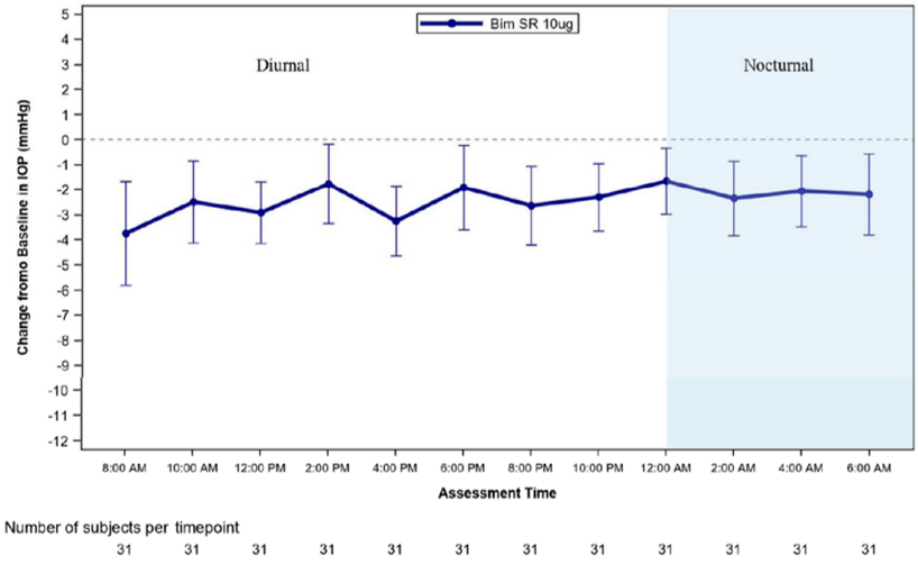
The IOP-lowering effect of BIM SR 10 and 15 µg was greater compared to timolol eyedrops at Week 2 and 6 of each cycle. At Week 12 of each cycle difference between BIM SR 10 and timolol decreased and was not significant. These results are in line with results from individual studies. The difference between BIM SR 15 and timolol at Week 12 remained similar as at earlier time points. Further details are provided in the Clinical Assessment Report.

3.3.4.7. Supportive study(ies)

Study 1698-304-007 was a multicentre, open-label, Phase 3b study in subjects with Open-Angle Glaucoma (OAG) or Ocular Hypertension (OHT). The purpose of this study was to obtain data on the 24-hour IOP-lowering effect at Week 8 of bimatoprost SR 10 µg treatment, with safety assessed until Month 12.

Subjects in the bimatoprost SR cohort received a 10µg implant in the study eye on Day 1. At 1 site, an additional cohort of subjects was enrolled to receive topical bimatoprost (Lumigan 0.1 mg/ml eye drops) in the study eye (once daily, at 20:00 ± 1 hour, starting with the evening dose on Day 1). Subjects were assigned to the bimatoprost SR cohort or Lumigan 0.1 mg/ml cohort by the investigator. The subjects and investigators were not masked to the study treatment assignment for the duration of the study. The primary efficacy endpoint was the time-matched IOP change from the Baseline Sleep Lab visit at the Week 8 Sleep Lab Visit in bimatoprost SR-treated eyes. The secondary endpoint was the change from baseline in the range of IOP in eyes treated with bimatoprost SR at the Week 8 Sleep Lab Visit. The IOP fluctuation was defined as the range of IOP over 24 hours (maximum minus minimum). The primary efficacy measures of IOP collected over 24 hours at the Baseline Sleep Lab

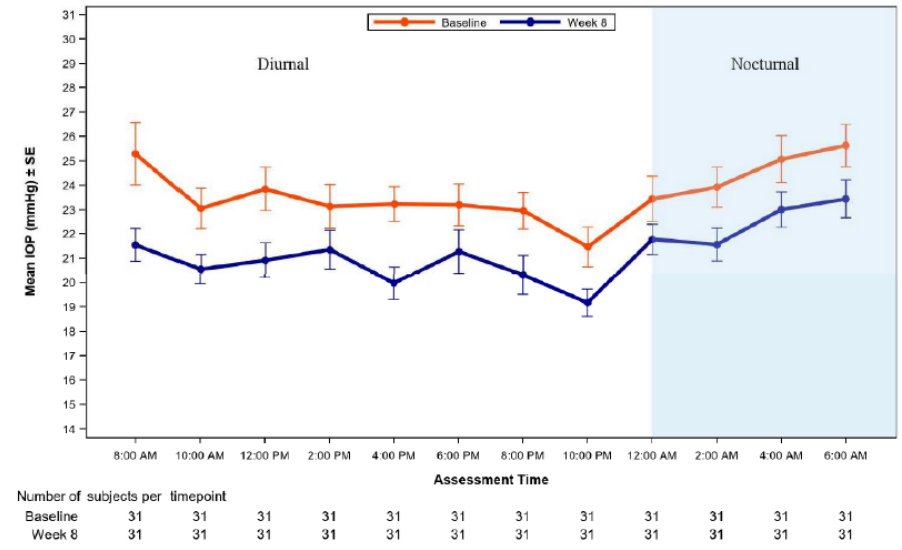
Visit and Week 8 Sleep Lab Visit were measured using a Reichert Model 30 pneumatonometer. Goldmann applanation tonometry (GAT) was used for all IOP measurements at office visits. A total of 31 subjects were treated with bimatoprost SR 10 µg and 6 subjects were treated with Lumigan 0.01% in the study eye.



IOP = intraocular pressure. Habitual IOP is the diurnal IOP in a sitting position and the nocturnal IOP in a supine position.

Source: Figure 14.2-1.1.1

Figure 22: 95% CI for bimatoprost SR 10 µg study eye in the mean change in 24-hour time-matched habitual IOP from baseline at week 8 (Full Analysis Set)



IOP = intraocular pressure. Habitual IOP is the diurnal IOP in a sitting position and the nocturnal IOP in a supine position. IOP was measured by pneumatonometer at sleep lab visits.

Source: Figure 14.2-1.1.2

Figure 23: Mean 24-hour habitual IOP curve for bimatoprost SR 10 µg study eye at baseline and week 8 (Full Analysis Set)

The lack of randomisation and the small size of the reference cohort (N=6)) pose limitations to the interpretation of study results. In addition, there were imbalances between the BIM SR and Lumigan in important baseline characteristics, such as diagnosis and baseline IOP. The observed mean time-

matched 24-hour habitual IOP change from baseline measured using the pneumatonometer ranged from -3.7 to -1.7 mmHg in the bimatoprost SR treated eyes (diurnal IOP ranged from -3.7 to -1.8 mmHg and nocturnal IOP ranged from -2.4 to -1.7 mmHg) at the Week 8 Sleep Lab visit. The IOP was reduced from baseline (post-washout) at each individual time point.

On-treatment IOP was highest at 8:00 in the morning during diurnal measurements, and highest at 6:00 in the morning during nocturnal measurements. Nocturnal IOP (measured between 00:00 and 6:00) values were generally higher than diurnal values. (NOTE: In Fig 3 above, the IOP was measured by pneumatonometer. IOP values obtained with pneumatonometer tend to overestimate IOP relative to GAT). The mean range of IOP measured by pneumatonometer over a 24-hour period was 9.9 mmHg at Baseline and 8.3 mmHg at the Week 8 Sleep Lab Visit for eyes treated with bimatoprost SR, with a mean change from baseline of IOP range over the 24-hour period at Week 8 of -1.6 mmHg. This reduction in IOP fluctuation on BIM SR treatment is considered very modest considering the washout period patients had to go through before baseline and that at baseline patients could be considered untreated.

Study 192024-095 was a randomized, participant- and efficacy evaluator-masked, paired-eye comparison evaluating the safety and IOP-lowering effects of repeated administrations of 15 µg BIM SR in participants with OAG or OHT who are not adequately managed with topical medication (eg, due to intolerance or nonadherence). The study was conducted in 2 stages:

- Stage 1: subjects were randomized to receive either SLT (1 administration at the beginning of the study, Day 1) or 3 fixed administrations (every 16 weeks i.e. Day 4, W16 and W32) of BIM SR 15µg in the primary eye, with the alternate treatment in the other eye (and vice versa); subjects in Stage 1 were those who reached the W32 visit prior to implementation of protocol Amendment 2 and were eligible for the third cycle of administration. With protocol Amendment the number of administration cycles was reduced from 3 to 2.

- Stage 2: subjects received either SLT or 2 fixed administration cycles of BIM SR 15 µg (administered at Day 1 and W16) in either eye; this included all subjects enrolled who had not yet reached W32 prior to implementation of Amendment 2 at the site, plus all new subjects enrolled under protocol Amendment 2.

With implementation of Amendment 3, administration of the 15µg dose strength was discontinued. No new subjects could be enrolled into the study and study treatment/retreatment of enrolled subjects was not permitted. All subjects were followed for safety for the duration of the study through the Week 52/Exit visit.

The primary efficacy endpoint was the change from baseline in IOP at Weeks 4, 12, and 24.

BIM SR 15 µg met the pre-specified criteria for statistical and clinical noninferiority to SLT in the mITT and ITT population. A numerically greater reduction from baseline in mean IOP and a lower mean IOP was observed for bimatoprost SR 15 µg compared with SLT Hour 0 at Weeks 4, 12 and 24. A number of concerns/uncertainties have been identified, similar to those described for study -093, however they are not raised for study -095, as only the 15 µg dose strength (which was discontinued based on safety findings) was investigated in this study.

Study 1698-302-007 is an ongoing multicentre, Phase 3 extension study in subjects with OAG or OHT who completed 1 of the 4 lead-in Phase 3 bimatoprost SR studies (192024-091, 192024-092, 192024-093, or 192024-095) and received BIM SR, or who received commercial Durysta (BIM SR 10 µg) in the open-label Phase 4 Study MED-MA-EYE-0648 and completed (or exited early from) that study with no ongoing safety concerns. The objectives of this study are to evaluate the safety and the duration of the IOP-lowering effect of BIM SR in subjects with OAG or OHT. Approximately 600 subjects who participated in the lead-in studies are planned for enrolment.

The duration of the extension study is a minimum of 24 months, with a 12-month PRN re-administration period, for protocol-specified patients who are eligible. Additional administrations (up to 4 administrations in total) are planned for subjects who received 1 or 2 administrations in lead-in studies. No data on efficacy have been presented. The applicant has not made any additional labelling claims based on these studies, therefore the efficacy data from these studies is not requested for now.

Study MED-MA-EYE-0648 (ARGOS) is an ongoing Phase 4, observational, open-label, multicentre, prospective study in subjects with OAG or OHT who are scheduled for administration of Durysta by their ophthalmologist. The purpose of this study is to prospectively collect effectiveness and safety data after administration of Durysta in clinical practice. Approximately 230 subjects are planned for enrolment; both eyes from the same subject may be treated if eligibility criteria are met. No data on efficacy have been presented. The applicant has not made any additional labelling claims based on these studies, therefore the efficacy data from these studies is not requested for now.

3.3.5. Discussion on clinical efficacy

The applicant submitted the initial marketing authorisation application (MAA) for bimatoprost sustained release (BIM SR) 10 µg intracameral implant developed for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medications for reasons other than medication efficacy (e.g., due to intolerance or nonadherence).

Bimatoprost is the active ingredient in Lumigan, a topical IOP-lowering therapy approved since 2002 in the EU. The clinical development programme comprises two randomized controlled Phase III studies comparing BIM SR to timolol (192024-091 and 192024-092), two randomized controlled Phase III studies comparing BIM SR to Selective Laser Trabeculoplasty (192024-093 and 192024-095, the latter investigating 15 µg only), one open label Phase IIIb study (1698-301-007) and one Phase I/II study (192024-041D).

BIM SR 10µg is intended for up to 2 as-needed administrations per eye. The main clinical evidence supporting this posology in the target population is based on the randomised, active-controlled Phase III study 192024-093 (093) and the ongoing single-arm, open label Phase IIIb study 1698-301-007 (007). In general, the efficacy of a new treatment in OAG/OHT should be demonstrated in two double-blind, randomized, controlled clinical trials. In this case only one randomized, controlled study has been submitted. However, taking into account that bimatoprost is a well-known medicinal product for the treatment of the intended condition and that two further replicated double-blind, randomized, controlled clinical trials are submitted (192024-091, 192024-092) this is considered sufficient to substantiate the efficacy of bimatoprost SR.

As stated above, data from completed Phase III studies 192024-091, 192024-092, and 192024-095, as well as Phase I/II study 192024-041D and Phase IIIb study 1698-304-007 are considered supportive. Studies 192024-091 and 192024-092 evaluated the IOP-lowering efficacy and safety of 3 administrations of BIM SR (10 µg and 15 µg) implant with a fixed 4-month interval between two administrations in patients with OAG or OHT. While the dosing regimen investigated in these studies is not fully in line with that proposed in the label (1 to 2 administrations, as needed) and studies were conducted in an arguably different population, these studies provide important evidence for the efficacy and safety of 1 and 2 administrations of BIM SR 10 µg, when the second implant is injected 4 months after the first implant which is also the minimum interval as proposed by the applicant; and are therefore discussed in more detail.

The population investigated in studies -091 and -092 (patients with OAG and OHT) differs from the population investigated in studies -093 and -301-007 (patients with OAG and OHT whose disease in

not adequately controlled with eye drops due to intolerance/non-adherence) in having *different prognosis*. However, there is no evidence that non-compliance with eye drops can be predictive of success or failure with BIM SR implant. The proposed target population describes a population that exists but cannot easily be defined, as neither non-compliance nor intolerance are straightforward to determine. Making 'compliance' or 'intolerance' a part of the condition/disease is not the usual way how the target populations are defined.

In case non-compliance with eye drops is the reason for inadequate reduction of IOP, this leaves room to believe that the BIM SR implant could be of benefit to the patient. However, it is unclear how nonadherence is determined for subjects to render implanting BIM SR meaningful, i.e. if nonadherence is based on experience or other information. The definition of "unsuitable for topical IOP-lowering medications" and how such patients can be identified should be clarified in the SmPC.

Moreover, given that the intended treatment means a long-term exposure to bimatoprost, it would seem reasonable to assure that patients have an adequate response to bimatoprost or at least to prostaglandin analogues prior to administration of BIM implant. The applicant has included this requirement in the Section 4.2 of the SmPC. However, considering the invasive nature of the bimatoprost SR treatment and the duration of the effect, the responsiveness of the patient to receive a sustained release implant is relevant. According to published studies up to 66.9% of patients treated with bimatoprost eye drops achieved at least a 20% reduction of IOP at month 1; 60.2% at month 3 and 57.9% at month 6. Therefore, there is still a percentage of non-responder patients. In this regard the proposed recommendation in Section 4.2 does not seem to be sufficient. Only the patients who show a response to prostaglandins/prostamides should be treated with bimatoprost SR, therefore this should be indicated in section 4.1.

Design and conduct of clinical studies

Study 192024-093

Study 192024-093 was a randomized, subject and efficacy evaluator-masked RCT with a single Selective laser trabeculoplasty (SLT) therapy as active comparator. The study was designed as non-inferiority study.

Patient population

The included patient population as defined by inclusion and exclusion criteria is considered to reflect the intended target population and appears adequate. Only subjects who are, in the investigator's opinion, not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence) were recruited.

Intervention

The study protocol allowed up to 2 administrations of BIM SR and a single performance of SLT. The initial study protocol allowed up to 3 BIM SR administrations (cycles) in a fixed (Q16W) regimen. With subsequent protocol amendments, the number of cycles was reduced from 3 to 2 (Amend. 3) and the dosing regimen was changed from fixed to flexible (retreatment possible between week 16 and month 12 visit, Amend. 6). Retreatment was allowed, if retreatment criteria, mainly based on patient's safety and IOP control, were met. The use of 17 mmHg as the IOP retreatment threshold was questioned during EMA Scientific Advice procedure (January 2021). The limit of 17 mm Hg or less was considered arbitrary since ideally, an individualised "treat to target IOP" approach should be aimed for. The applicant's justification for the use of 17 mm Hg as threshold IOP is mainly based on the Advanced Glaucoma Intervention Study where an IOP of > 17.5 mm Hg was defined as high IOP. While the 17 mm Hg threshold can be considered acceptable for a structured clinical study setting, this is not

reflective for administration in clinical practice as treatment of glaucoma patients is complex and individualized and is based on 'treat to target IOP'.

Of note, the retreatment criteria used in study -093 differ from those in study -301-007 (see below), which renders comparison of study results (i.e., time to second dose/duration of effect) difficult. Similarly, due to different retreatment criteria across studies, no single, standardized re-treatment criteria to be specified in the SmPC can be determined. Nonetheless, since clinical practice typically aims to treat patients to their target IOP, this is considered acceptable, and a reference to clinical practice guidelines would be considered sufficient.

Control

A single Selective Laser Trabeculoplasty (SLT) was selected as active comparator, which was already accepted during preceding Scientific Advice procedures. In principle patients treated with SLT can be retreated with additional procedures if needed (European Glaucoma Society. Terminology and guidelines for glaucoma. 5th ed, 2020). This is not the case of patients randomized to SLT in the Study -093, where only a SLT procedure was performed. Given that this restriction may potentially overestimate the effect of BIM SR. Especially, considering that flexible regimen is allowed for BIM SR and some secondary endpoints assess time to rescue therapy initiation, the repeated use of SLT could be of relevance. The applicant has explained that at the time of conducting the study the efficacy of retreatment with SLT was not well established and the expected durability of SLT was between 1 and 5 years. Therefore, repeated use of SLT was not considered in the study, which is acknowledged.

Sham procedures were planned for bimatoprost SR administration and for SLT in order to keep patients masked to the treatment assignment for each eye. Also, site staff (including those who performed the IOP readings) was to be masked to treatment assignment except for the site coordinator and designated staff. The blinding strategy is acceptable.

Non-inferiority margin

No systematic review or (quantitative) meta-analysis on SLT or placebo performance was provided to justify the non-inferiority margin of 1.5 mm Hg. Literature on initial SLT treatment confirms a range of IOP lowering of -6 to -9 mmHg, but it is unclear at which time-points, and the same NI margin for all three time points (Weeks 4, 12, and 24) assumes consistent performance of SLT across these time points. Studies 192024-093 and 192024-095 showed an average IOP reduction at the 3 prespecified efficacy time points from approximately -6.3 to -6.5 mmHg. Furthermore, published data (Sharpe et al. 2014 being a meta-analysis of the placebo effect in prior early-phase glaucoma clinical studies and Kawamura et al. 2016 being a retrospective cohort study from two RCTs) report a placebo effect of approximately 1.5 mmHg in Hour 0 IOP reduction from baseline, indicating a treatment difference of approximately 5 mmHg between SLT and placebo. Based on data from Study 192024-093 and a placebo effect of -1.5 mmHg in IOP change from baseline and the same variance as observed in SLT eyes for the placebo effect, a noninferiority margin of 1.5 mmHg would preserve approximately 63% of the SLT effect and a margin of 1.0 mmHg would preserve approximately 75% of the SLT effect. However, the treatment effect of SLT is uncertain due to the necessity of indirect comparison to untreated patients and the lack of justification of chosen literature reports. Ideas such as choosing delta to be a percentage of the expected difference between active and placebo have been advocated, but this is not considered an acceptable justification for the choice. Such ideas ensure that the reference product was superior to the placebo but do not justify the clinical irrelevance of the difference. For a claim of non-inferiority to SLT, a clinical justification that a difference of 1mmHg is clinically irrelevant would be needed. However, for Study 192024-093 the upper bound of the 95% confidence interval for the differences in IOP change from baseline was around 0 at the 3 time points, and the upper bound for Week 4 fell below 0, which ensures that BIM SR was superior to a (putative) placebo.

The primary endpoint

The primary efficacy variable was the IOP change from baseline assessed at weeks 4, 12, and 24, compared between BIM SR 10 µg and the SLT group (ITT population). Of note, the week 24 timepoint includes data of up to two bimatoprost administrations in a fixed and flexible dosing regimen. Timepoints for primary endpoint evaluation were discussed during Scientific Advice procedures and pre-submission interactions. In principle, the timespan for primary endpoint assessment was agreed. It was advised to have the primary efficacy endpoint at week 12 (when both treatments will have reached a steady effect level), week 16 (lowest effect of BIM SR) or at week 20. Alternatively, a comparison of efficacy at timepoints across the 4-month efficacy period as a primary endpoint was suggested. Moreover, the applicant justified that the choice of a 24-week primary efficacy analysis period is supported by literature, which suggests that the effect of SLT on IOP is stabilized by approximately 8 weeks post treatment, with the effect lasting to at least 6 months in most patients. Given that, timepoints for primary efficacy analysis are in general acceptable, however further analysis was requested at week 16 to better understand the treatment effect after a single bimatoprost administration (see results). Secondary efficacy analyses included time to initial use of rescue medication, percentage of eyes achieving ≥ 20% reduction in IOP from baseline at each postbaseline visit and the IOP CFB at Week 8, 15 and 20. Owing to the generally slowly progressing visual field loss in glaucoma, a reduction in IOP has been the established efficacy measure in this therapeutic area for decades. There is epidemiologic evidence demonstrating that a reduction of the IOP reduces the risk for a future visual field loss (Wickström K, Moseley J. 2017). Overall, primary and secondary endpoints are considered acceptable for the purpose of evaluating efficacy of BIM SR.

Statistical methods

From the methodological view, the statistical methods chosen for descriptive as well as inferential analyses are considered suitable. The use of MMRM for the primary efficacy evaluation of data on IOP change from baseline assumes missing data to occur at random (MAR) and might reveal too optimistic results. However, the applicant also conducted a sensitivity analysis, where MNAR was assumed to prove robustness of the results obtained in the primary analysis. Basically, the primary analysis corresponds to a hypothetical strategy of addressing intercurrent events and the analysis concerning the Treatment Effect Regardless of Non-Study IOP Treatment Use corresponds to a treatment policy strategy, the latter reflecting the ITT principle. These two estimands are considered most important for showing non-inferiority. In addition, other sensitivity analyses (Tipping point, Impact of flexible administration scheme) support the final conclusion to rule out a relevant impact of missing values or deviations from assumptions made in the analysis are deemed appropriate. The use of LOCF for missing values is not considered adequate since bimatoprost does not appear to show a constant effect and thus carrying forward favourable values for patients discontinuing treatment in a sensitivity analysis might be biased towards non-inferiority of bimatoprost.

Moreover, the MMRM-model for the primary analysis and most sensitivity analyses might be over-specified since many terms (eye, visit-by-baseline and visit-by-eye) were included without justification for their inclusion. Therefore, applicant was asked to provide a simplified model for the primary and selected sensitivity analyses (see results).

Rescue treatment

Rescue was initiated at investigators' discretion and no IOP criteria triggering rescue have been specified in the study protocol. This is acceptable, assuming that allocation concealment was maintained at all times.

In the event a subject was rescued per investigator discretion, the subject was no longer eligible for additional implants. Following rescue, IOP values for that subject were excluded from all efficacy

analyses to ensure results would not be confounded by the rescue medication. However, it is repeatedly claimed that only IOP measurements obtained after initiating the rescue were treated as missing. The decision on rescue treatment was taken for each eye individually and IOP values after rescue were excluded from all efficacy analyses. The applicant should clarify if rescue treatment was considered for a subject or each eye individually and which data was excluded.

Study 1698-301-007

Study 1698-301-007 is an ongoing, open-label, Phase IIIb study to evaluate the duration of IOP-lowering effect and safety of up to 3 administrations of Bim SR 10 µg. The purpose of this study is to obtain data on a PRN (pro re nata, as needed or flexible) re-administration regimen of Bim SR.

The study was originally designed to evaluate the duration of IOP-lowering effect of the 10µg and 15µg BimSR dose, however, with implementation of Amendment 1, administration of bimatoprost SR 15 µg was discontinued, thus changing the design to an open-label single-arm study. Since no statistical hypothesis was generated, results are considered rather descriptive than confirmative. Overall, the MAH has conducted two amendments to the original protocol without statistical implications. There are no changes to the analyses specified in the protocol. However, there is a version 2 of SAP, which was finalized prior to the date of this report (29 July 2022), clarifying issues as how handled in K-M analysis for the events considered for the primary endpoints. The overall plan is supported.

The eligibility criteria are largely in line with the eligibility criteria for the randomized Phase III study 093 and appear adequate for the intended population. The eye that meets the entry criteria at study entry is selected as the study eye. In the fellow eye, subjects are to receive standard of care treatment for the duration of the study unless the fellow eye meets the treatment criteria for fellow eye administration, allowing for a single BimSR 10µg implant.

Subjects receive a BimSR 10 µg implant on Day 1 (Cycle 1) in the study eye and if re-administration criteria are met, up to 2 additional BimSR administrations (Cycle 2, Cycle 3) may be performed. Re-administration criteria are largely in line with re-administration criteria in the Phase III study 093. Some changes were applied, notably, the criterion regarding the IOP was changed from a threshold IOP of > 17 mm Hg to a clinically meaningful increase in IOP (eg, < 20% change from baseline IOP). For eyes that need additional IOP-lowering treatment but do not meet specific re-administration criteria, temporary use of topical IOP-lowering medication (intermittent rescue) is allowed until all re-administration criteria are met. Rescue treatment in study 1698-301-007, either permanent or intermittent, in the primary analysis (time to second administration or rescue) was always considered as an event. The same applied for the time from the second administration to the third administration or rescue. Therefore, the durability of effect after the initial or second administration was not influenced by the use of intermittent rescue and reflected only the period without any use of non-study IOP-lowering treatments. Intermittent rescue could only be used if a subject required subsequent treatment but did not qualify because the previous implant had not degraded to < 25% of its original size or because of the limitation of 2 implant administrations in a 12-month period.

Long term efficacy data for subjects that received rescue and those that did not receive rescue showed that overall, IOP was similar between the 2 subgroups regardless of rescue. Demographics of the subgroup of subjects that received rescue and those that did not, showed that higher percentage of subjects that received rescue had a baseline IOP > 25 mmHg. A similar trend was found when comparing the subgroups of receiving first rescue in Cycle 1 versus receiving first rescue in Cycle 2. The mean (SD) duration of intermittent rescue use for study eyes was 172.7 (184.55) days during Cycle 1 and 227.3 (217.99) days during Cycle 2. In this regard, a warning about the need of close monitoring in patients with high baseline IOP (i.e. > 25 mmHg) and the potential requirement of concomitant topical IOP-lowering medication should be implemented in the SmPC.

One of the criteria for implant re-administration is that the previously administered implant is less than 25% of its original size, and with the recommendation of re-administration 16 weeks apart from the previous administration. Most implants decrease to non-visible/completely degraded or < 25% of their original size by Month 12. The median time of from initial administration to a second administration or rescue under the study re-administration regimen was 392 days and the cumulative probability of not requiring a second bimatoprost SR administration or rescue treatment by Day 360 was 57.5%. If the biodegradation profile of bimatoprost SR in Study 1698-301-007 shows that the majority of implants were ≤ 75% of their original size by Month 8 (~Week 31) more precise recommendations should be provided to the prescriber on retreatment criteria after 4 months due to implant size requirements, particularly if no/minimal reduction of their original size of the implant is observed (**SmPC OC**).This of course presupposes that the B/R for the re-administration is considered positive, which is currently not the case.

This is an open-label, uncontrolled study (no placebo control or active comparator was applied).

The primary efficacy endpoint is the duration of effect of the first Bim SR administration defined as 'the time from the first administration of Bim SR in the study eye to the second administration of Bim SR or to the first rescue treatment (permanent or intermittent), whichever occurred first'. Additional (secondary) efficacy time-to-event variables included the time to second administration of BimSR (regardless of intermittent rescue), time to third administration of Bim SR (regardless of intermittent rescue), time to the third administration of Bim SR or first rescue treatment after second administration in the study eye and time to first rescue treatment after third administration in the study eye. Overall, primary and secondary endpoints are considered acceptable for the purpose of informing on the durability of IOP-lowering effect when administering up to three as-needed Bim SR 10µg implants. Evaluation of the durability of the IOP-lowering effect appears crucial for a temporary treatment in a chronic disease. The pre-planned analyses of efficacy endpoints have nevertheless to be interpreted with caution due potential inherent biases that follow the study design. Analyses for patients who received two or three administrations might be biased due to the phenomenon of regression to the mean since only participants without (permanent) rescue medication receiving a second or third administration were considered. Thus, it appears likely that the second cycle is/will be enriched with subjects that had a positive experience with the treatment during the first cycle (and probably are more susceptible to the effects of Durysta), therewith introducing bias for following observations. The descriptive summaries of IOP and IOP Change from Baseline at different time points have limited interpretational value due to its study design. Two types of descriptive summaries were provided, one excluding values following rescue treatment, and one including these values in the calculation, labelled as "regardless of rescue treatment". The first type regards only a subgroup of participants wo are still without rescue medication, and the latter includes values, which might bias the estimate since rescue medication lowers the IOP. However, data provided from interim analyses (data cutoff date: 15 September 2023) do imply that the exclusion of eyes that received rescue treatment does not appear to crucially impact reported results on IOP at least during cycle 1 and for the first 12 month of cycle 2.

The conducted interim analysis revealing the presented results was not adequately planned, which bears the potential for bias and hence, overestimation of time to second Bim SR administration. Upon request the applicant clarified that the time point for the interim analysis was aligned with the submission for MAA, in order to achieve a maximum amount of available data, rather than a specific treatment aim.

The study is ongoing. Only 2 subjects have currently completed cycle 3, but 65 and 195 patients have completed cycles 2 and 1 from in total 441 patients that entered cycle 1, respectively (table 300-2.1). Of note, a third administration of Durysta is not subject of this MAA and cycle 3 cannot be evaluated at the current status as too little patients have completed it.

Studies 192024-091 and 192024-092

Studies 192024-091 and 192024-092 were phase 3, randomized, patient- and efficacy evaluator-masked, parallel-group studies that evaluated the IOP-lowering efficacy and safety of 3 administrations of bimatoprost SR (10 µg and 15 µg) compared to timolol eyedrops in adult patients with OAG or OHT.

The study population comprised patients with OAG and OHT. The criteria for the baseline (post-washout) IOP were following: i) Hour 0 IOP in the study eye of ≥22 mm Hg and ≤32 mm Hg, and in the fellow eye of ≤32 mm Hg; and ii) Hour 2 IOP in the study eye of ≥19 mm Hg and ≤32 mm Hg, and in the fellow eye of ≤32 mm Hg. Both studies were of practically the same design. Patients were randomized (1:1:1) to receive either bimatoprost 15 µg SR, bimatoprost 10 µg SR treatment or timolol eye drops. Bimatoprost SR was administered in the same dose strength on Day 1, Week 16 and Week 32 (fixed schedule), while timolol eye drops were administered twice daily (BID). While the dosing regimen investigated in these studies is not fully in line with that proposed in the label (single re-administration, if needed i.e. max 2 administrations in total), and studies were conducted in an arguably different population, they are considered to provide important evidence for the efficacy and safety of 1 and 2 administrations of bimatoprost SR 10 µg, when the second implant is injected 4 months after the first implant which is also the minimum interval as proposed by the applicant. The question of long-term efficacy and safety of 1 or 2 administrations cannot be addressed by this study. As mentioned earlier, the dose strength 15 µg was not applied for, and the results are not discussed herein.

The objective of these studies was to evaluate the intraocular pressure (IOP)-lowering efficacy and safety of bimatoprost SR in patients with OAG or OHT after initial and repeated administrations. The primary efficacy variable was the study eye time-matched IOP change from baseline at each hour evaluated (Hours 0 and 2, which correspond to the trough and peak IOP of timolol eye drops when administered in the morning and in the evening) at Week 12 of Cycle 1. Mean IOP change from baseline was compared between each bimatoprost SR dose strength and the timolol group for each evaluation hour using the ITT population. The choice of Week 12 for a single time point for the primary analysis was not justified; however, the applicant also provided respective results for Weeks 2 and 6, which were taken into consideration during assessment, in order to assess consistency of results. Other efficacy analyses included IOP and time-matched IOP change from baseline at various time points for each treatment cycle as well as the use of rescue medication or procedure.

Studies 192024-091 and 192024-092 were non-inferiority studies; the selection of the NI margin of 1.5 mm Hg has not been justified neither from a clinical nor from a statistical perspective. Based on the results, the difference between treatments was <1.0 mmHg and is therefore considered a clinically not relevant difference. Based on literature reports for the IOP reduction from baseline of timolol and for placebo, the applicant justified the performance of timolol. The applicant reports a placebo effect of ~ 1.5 mmHg from two literature studies (Sharpe et al. 2014 being a meta-analysis of the placebo effect in prior early-phase glaucoma clinical studies and Kawamura et al. 2016 being a retrospective cohort study from two RCTs). Using data from Studies 091 and 092, the lowest value of the average IOP reduction at the 3 prespecified efficacy time points (Weeks 2, 6 and 12) was approximately -6.1. Subtracting 1.5 from 6.1 the applicant arrived at an estimated treatment difference of at least 4.6 mmHg between timolol and placebo. However, the treatment effect of timolol is uncertain due to the necessity of indirect comparison to untreated patients and the lack of justification of chosen literature reports. A 95% confidence interval for the estimated treatment difference is also lacking to judge statistical superiority to (a putative) placebo. In addition, no rationale for selection of presented studies was provided as outlined in the relevant EMA guidance (EMEA/CPMP/EWP/2158/99). Nevertheless, and the above considered, there is evidence that the performance of timolol was according to expectations in studies 091 and 092, although uncertainties pertaining to the literature search exist. The observed confidence intervals for the difference between timolol and BimSR in

studies 091 and 092 showed that the upper bound of the confidence interval of the treatment difference was mostly < 0 (at Week 2 and Week 6) or < 0.5 (at Week 12) in study 091 and in the range of -0.05 (Week 2) and 0.73 (Week 12). Based on these results and the reported placebo effect in glaucoma trials, it seems plausible that BimSR can be considered superior to a putative placebo.

Prior to Week 52, the use of rescue treatment medication was prohibited as concurrent therapy in either eye, unless necessary for the safety of the patient due to inadequate control of IOP as determined by the investigator. Inadequate control of IOP had to be confirmed at a subsequent visit (scheduled or unscheduled visit). After the Week 52 visit, non-study topical IOP-lowering medications were permitted if in the investigator's clinical judgment, the IOP is not adequately controlled at two consecutive visits. This pertained to any use of rescue, including short course of eye drops. There were no objective rescue criteria pre-specified, but the decision to administer rescue treatment was at the discretion of the investigator due to safety considerations of inadequately controlled IOP. This is acceptable, assuming that masking to treatment allocation was maintained.

Patients who have not received rescue medication in both eyes were to receive a repeat administration of BIM SR (or Sham administration in Control group study eyes and all fellow eyes) at the Week 16 and Week 32 visits. Patients who have received rescue medication in both eyes were to be followed for at least 12 months following the last administration of bimatoprost SR or sham, at which time they were allowed to exit early at the investigator's discretion.

For the primary and other efficacy analyses, the applicant used MMRMs combining hour 0 and hour 2 data and additionally including an interaction term (timepoint-by-baseline IOP) without justification. Upon request, the applicant re-ran the analyses with simplified models for hour 0 and hour 2. Moreover, a hypothetical and a treatment policy estimand were provided for the primary efficacy analysis. Those additional analyses led to the same conclusion to claim non-inferiority. In addition, these primary analyses were complemented with a tipping point analysis with the simple model specification assuming MNAR, which indicated that the primary analysis can be considered sufficiently robust with respect to deviations from the underlying missing data assumptions and assumptions for imputing for patients receiving rescue treatment.

Other efficacy analyses, in particular, efficacy analysis for cycle 2 and 3 and time to non-study IOP lowering medication or procedure from the 3rd injection, concern a subgroup of participants who had not used non-study lowering IOP medication before and received at least 2 injections. These analyses might be biased due to selection of 'survivors', who endure the time to next injection without rescue medication and might entail bias due to the phenomenon of regression-to-the mean. However, the completion rate of cycle 1 and cycle 2 (most relevant for this application) was high (>90 % with respect to the number of randomized patients per study). In addition, the observation that the IOP-lowering effect in response to study treatment was consistent between treatment cycles is reassuring. Therefore, a potential bias on IOP data due to selection of survivors or regression to the mean in subsequent treatment cycles seems unlikely.

Study 1698-304-007

Study 1698-304-007 was a multicentre, open-label, Phase 3b study in subjects with OAG or OHT. The purpose of this study was to obtain data on the 24-hour IOP-lowering effect at Week 8 of BIM SR 10 µg treatment, with safety assessed until Month 12. Subjects in the bimatoprost SR cohort received a 10µg implant in the study eye on Day 1. At 1 site, an additional cohort of subjects was enrolled to receive bimatoprost eye drops in the study eye (once daily, at 20:00 ± 1 hour). The primary efficacy endpoint was the time-matched IOP change from the Baseline Sleep Lab visit at the Week 8 Sleep Lab Visit in bimatoprost SR-treated eyes. The secondary endpoint was the change from baseline in the range of IOP in eyes treated with bimatoprost SR at the Week 8 Sleep Lab Visit. The IOP fluctuation was defined as the range of IOP over 24 hours (maximum minus minimum).

Efficacy data and additional analyses

Study 192024-093

In total, 183 subjects (ITT population) were randomized to receive treatment (BIM SR 10 µg or SLT), 155 completed the study and 28 discontinued prematurely from the study (15 subjects (16.3%) and 13 subjects (14.3%) in SLT and BIM SR 10 µg arm, respectively). 3 subjects were not treated. 180 eyes received SLT and 175 eyes received BIM SR 10µg (89 eyes according to the fixed schedule and 86 eyes according to the flexible schedule).

Of the 180 subjects who entered Cycle 1, 169 completed Cycle 1 and of those, 126 subjects entered Cycle 2, and 112 subjects completed Cycle 2. 43 subjects had completed the study after receiving only 1 implant.

In the Bim SR fixed arm (second administration due on Week 16), 89 eyes received ≥1 administrations, and 70 eyes received 2 administrations, i.e. 78.7% of treated eyes received the second implant.

In the Bim SR flexible arm (flexible second administration), 86 eyes received ≥1 administrations, and 56 eyes received 2 administrations, i.e. 65.12% of treated eyes received the second implant.

For patients who did not receive the second administration in the Bim SR fixed arm and the Bim SR flexible arm, the applicant should clarify how many did not receive it due to safety concerns (e.g., implant residue/ECL) and how many did not receive it because the IOP criterion was not met (i.e., IOP < 17 mmHg). Additionally, the applicant should provide the IOP values at Week 16 for these patients (**OC**).

The most common reason for study discontinuation was withdrawal of consent (n=6 SLT, n=6 Bim 10µg). No subject discontinued due to an ocular adverse event. Overall, subject disposition and study discontinuations are acceptable, however, it needs to be noted that the total number of subjects enrolled (n=183) is considered rather limited.

As for the 43 subjects who completed the study after receiving 1 implant, 11 subjects discontinued after receiving the implant and prior to starting Cycle 2 due to the following reasons: non-ocular adverse event, withdrawal of consent, lost to follow-up, protocol violation, and other.

As for the 112 subjects who completed the study after receiving 2 implants, 14 subjects discontinued after receiving the implant due to the following reasons: non-ocular adverse event, withdrawal of consent, lost to follow-up, and other.

23.5% of subjects in the ITT population experienced a significant protocol deviation; of those, 13 subjects were excluded from the PP population because the protocol deviations affected the primary efficacy analysis. Given the reasons the subjects were excluded and the small number of total exclusions with similar numbers across SLT and bimatoprost SR-treated eyes, any impact to overall efficacy results is considered unlikely.

The study population is considered to reflect the population for the intended indication. Baseline demographics appear balanced across treatment groups in both studies and do not give rise to concern. The majority of patients had diagnosis of primary OAG in the study eyes (77.6% in the SLT group and 77.0% in the BimSR 10µg group). The proportion of study eyes with OHT was 21.3% and 21.9% in the SLT and the BimSR 10µg group respectively. Overall, ocular baseline characteristics were balanced between SLT and BimSR 10µg groups, no concern arises in that regard.

The most common reason for not being adequately managed with topical IOP-lowering medication was forgetfulness, followed by tolerability/fear of potential side effects and physical inability to administer medication.

Regarding the **primary outcome**, the change from baseline in mean IOP for BimSR 10µg and SLT was similar at Week 4, 12 and 24. Bim SR 10µg met the pre-specified criteria for non-inferiority (statistical: upper limit of the 95% CI ≤ 1.5 mm Hg at Week 4, 12 and 24; clinical: upper limit of the 95% CI ≤ 1.0 mm Hg at 2 of the 3 visits). The reduction in mean IOP from baseline was numerically in favour for Bim SR 10 µg treated eyes compared with SLT-treated eyes at all 3 timepoints. The least square (LS) mean for the treatment difference between Bim SR 10 µg and SLT in IOP change from baseline was **-0.6 mmHg** (95% CI=-1.03, -0.08), **-0.4 mmHg** (95% CI=-1.04, 0.18), and **-0.4 mmHg** (95% CI=-0.97, 0.17), **at Week 4, 12 and 24 respectively**. It is critically noted that results are presented cumulatively regardless of administrations (1 or 2) and regardless of dosing scheme (fixed or flexible). At week 4 and week 12 data were combined for patients who were on fixed and flexible regimen, but since all subjects received only 1 dose this is not considered critical. Week 24 combines data for 1 and 2 administrations (the latter in fixed and flexible regimen), hence, interpretation is problematic. To further evaluate the effect of a single BimSR implant, the applicant was asked to perform primary efficacy analysis at Week 16 before the second implant was administered. The mean difference at Week 15 was 0.2 with 95% CI (-0.44, 0.75), therefore the upper bound of 95% confidence interval at Week 15 fell below the noninferiority margins of 1.5 mmHg for statistical and 1.0 mmHg for clinical justification. However, it is unclear why the newly submitted 95% CIs for the primary endpoint with 1 implant at Weeks 4 and 12 differ from the originally submitted 95% CIs. Furthermore, no Week 24 results were presented for patients who were administered 1 implant, although not all patients in the flexible BIM SR arm received the second implant by Week 24. This needs to be provided (**OC**).

Exclusion of IOP values from eyes that received the second Bim SR 10 µg implant after Week 16 but before Week 24 did not impact noninferiority of bimatoprost SR 10 µg vs SLT. The least square (LS) mean for the treatment difference between Bim SR 10 µg and SLT in IOP change from baseline was **-0.6 mmHg** (95% CI= -1.06, -0.10, p=0.0175), **-0.4 mmHg** (95% CI= -1.05, 0.15, p=0.1436), and **-0.2 mmHg** (95% CI= -0.78, 0.32, p=0.4109), in favour of BimSR 10µg at **Week 4, 12 and 24** respectively. Hence, masking inferior efficacy towards week 24 is not expected. However it needs to be noted that hardly any impact was observed since values of only 12/145 (8.3%) patients were excluded at week 24. Further sensitivity analyses, including those requested by the Rapporteurs, are overall supporting the robustness of the primary efficacy outcome.

Secondary endpoints appear to a large extent similar between groups (SLT vs. BimSR 10µg). The median time from initial administration of Bim SR 10 µg to initial use of rescue treatment was 594 days, regardless of number of administrations (1 or 2). The cumulative probability of not requiring rescue treatment in the study eye at D90, D180 and D360 (regardless of the number of administrations) was similar between Bim SR 10 µg and SLT. To analyse the durability of the effect after 1 administration and after 2 administrations in the flexible re-administration regimen, the applicant provided Kaplan-Meier analyses for time from the first administration to the second administration or rescue, and time from the second administration to rescue treatment. Most of bimatoprost SR-treated eyes in the flexible administration regimen were readministered by 120 days, per protocol requirements (for retreatment at Week 16 if IOP is >17 mmHg). The median time to second administration or non study IOP-lowering treatment was 144 days.

Presented analysis concerning the time to non-study IOP-lowering treatment after the second implant are difficult to interpret and especially assuming that subjects who drop out of the study use rescue at the same frequency as the subjects remaining in the study, which is not considered plausible.

The percentage of eyes that achieved ≥ 20% reduction in IOP was comparable between the SLT and BimSR 10µg groups through Week 12 (W12, Cycle 1: 71.8% vs. 71.1% in the BimSR 10µg vs. SLT respectively). Results are similar between Cycle 1 and Cycle 2. At week 24, the percentage of eyes that achieved ≥ 20% reduction in IOP was slightly higher in the SLT group compared to the BimSR 10µg group (84.8% vs. 71.1%, respectively).

Eyes that received non-study IOP-lowering medication were censored at the time of the first rescue. The percentages of eyes achieving ≥ 15%, ≥ 20% and ≥ 30% reductions from baseline IOP by visit are summarized for all IOP data included regardless of non-study IOP lowering treatment and IOP data excluded after non-study IOP-lowering treatment. The results including and excluding IOP data after non-study IOP-lowering treatment are very similar till Week 36, however differences seem to increase over time till Month 24 (part of Table 200-2.1 and 200-2.2 is only shown in the appendix). Comparing the proportions of eyes achieving 15%, 20% and 30% reduction at each visit (Tables 200-2.1 and 200-2.2), the same pattern seems to emerge independent of including and excluding IOP data after non-study IOP-lowering treatment: First Bim SR seems to outperform SLT, but the difference diminishes and reverses around week 31 including IOP data after non-study IOP-lowering medication and around week 24 excluding IOP data after non-study IOP-lowering medication with SLT outperforming Bim SR afterwards till Month 24. This is probably due to the reduced efficacy of Bim SR over time requiring a re-administration or rescue medication. Per the Glaucoma Research Foundation, the effect of a single SLT treatment generally lasts between 1 to 5 years. If the effect of SLT wears off after a successful period of control, a retreatment may be effective.

An analysis was performed on the time to first achieving ≥ 20% IOP reduction using a competing risk model by treating the use of non-study IOP-lowering medication as a competing event. Bimatoprost SR has a faster onset of treatment effect compared to SLT. Time to achieving ≥ 20% IOP reduction occurred sooner in bimatoprost SR treated eyes than the SLT-treated eyes. At 5 months both treatments reached a similar response level at around 90% and no large changes can be expected afterwards due to the low number of eyes at risk. Most patients have a 20% IOP reduction within the first 5 months from treatment. The number of eyes that received non study IOP-lowering medication as a competing event was the same between bimatoprost SR and SLT-treated eyes, with 17 eyes for each arm prior to achieving ≥ 20% IOP reduction. The IOP change from baseline should be plotted against time for the whole study duration of 24 months including and excluding IOP data after non-study IOP-lowering treatment for both treatment groups.

IOP values and mean IOP change from baseline by treatment were summarized by analysis cycle for week 8, 15 and 20. Bim SR 10 µg-treated eyes and SLT-treated eyes showed similar reductions from baseline in mean IOP across week 8, 15 and 20 (Cycle 1); -6.1, -6.0, -5.9 in the BimSR 10µg group and -6.8, -6.0, -6.4 in the SLT group, respectively. Mean IOP reductions from baseline were largely similar between Cycle 1 and 2. Overall, these results are considered to support data obtained in the primary efficacy analysis.

A subgroup analysis for the **flexible dosing regimen** was performed. The change from baseline in mean IOP for BimSR 10µg and SLT was similar at Week 4, 12 and 24. Bim SR 10 µg met the noninferiority criteria with the upper limit of the 95% CI for the LS mean difference ≤ 1.0 mmHg at all 3 visits. The least square (LS) mean for the treatment difference between Bim SR 10 µg and SLT in IOP change from baseline was **-0.3 mmHg** (95% CI=-0.98, 0.31, p=0.3084), **-0.6 mmHg** (95% CI=-1.47, 0.34, p=0.2165), and **-0.6 mmHg** (95% CI=-1.34, 0.14, p=0.1087), at **Week 4, 12 and 24** respectively. Overall, it was shown that regardless of Bim SR 10 µg re-administration regimen i.e. fixed and flexible combined vs. flexible only, BimSR 10µg was non-inferior to SLT at all 3 visits.

A further subgroup analysis was performed by disease diagnosis (OAG vs. OHT). In both the OAG and OHT subgroups, baseline IOP was comparable between the 2 treatment groups (SLT vs Bim SR 10 µg).

For both subgroups the reduction in mean IOP was numerically in favour for Bim SR 10 µg-treated eyes compared with SLT-treated eyes at Weeks 4, 12, and 24, indicating a similar efficacy profile for both subgroups.

Overall, primary and secondary outcome data demonstrated that up to two BimSR 10µg administrations provide a reduction in IOP through week 24 that is noninferior to a single SLT therapy. This effect is overall supported by sensitivity analyses.

Rescue treatment

Rescue was initiated at investigators' discretion and no IOP criteria triggering rescue have been specified in the study protocol. It is noted that the investigator chose the rescue medication in accordance with the treatment arm. No data on the actual triggers for rescue have been presented. It would be reassuring to know that situations leading to the rescue were the same across arms. Therefore, the applicant should provide the last IOP measurements that triggered the initiation of the rescue for all treatment arms.

After rescue medication was initiated, IOP from the rescued eye was considered confounded and censored from analysis. In this regard some discrepancies have been detected in the information provided in tables that should be further clarified.

The use of concomitant nonstudy IOP-lowering medications (rescue medications) was reported for a significant number of patients receiving SLT and BIM SR 10 µg (fixed and flexible regimen), and was reported at a higher frequency in eyes that received BIM SR 10 µg; i.e., 36.7% (66/180), 48.9% (43/88) and 39.1% (36/92) for eyes receiving SLT, BimSR 10 µg in the flexible regimen and BimSR 10 µg in the fixed regimen, respectively. In the data presented in the table 14.1-4.3.4 of CSR-192024-093, in the arm of the Bim 10 µg treatment a concomitant use with medication indicated in the treatment of OAG is reported; specifically, 17.5% of the eyes in the active arm used Beta blocking agent, 9.8% Carbonic anhydrase inhibitors, 0.5% Other antiglaucoma preparations, 26.2% used prostaglandin analogues and 93.4 % used Sympathomimetics in glaucoma therapy. The applicant should discuss this concomitant use in more detail considering that this was a prohibition criterion. As it may affect the long-term efficacy data it should be clarified whether the use of these medications has been only done from a rescue viewpoint.

Moreover, a significant imbalance was identified for carbonic anhydrase inhibitors between SLT (3.8%) and BimSR (9.8%) groups. The applicant clarified that more carbonic anhydrase inhibitors were used as rescue medication for the BimSR 10µg group to add a different class of medication rather than another prostaglandin. This assumes that investigators knew the treatment assignment before administering rescue medication. The applicant should clarify if the investigator knew of the treatment assignment before the decision to apply rescue medication or after the decision to apply rescue medication for selecting appropriate rescue medication (**OC**).

The rationale to provide topical eye drops as rescue medication to patients that are considered 'unsuitable for treatment with topical medication' was challenged. Topical medications remain a mainstay of IOP lowering therapy at any stage of the patient's treatment journey. This seems in contradiction to the claim of the applicant that bimatoprost SR is not intended to be a replacement for topical IOP-lowering medication, but for patients who have reached the point in disease progression where incisional surgical intervention is the next treatment step to achieve optimal and sustained IOP reduction. As per study 192024-093 around 16.1% of subjects (18.2% and 14.1% for the flex and fixed regimen, respectively) will require rescue medication during the first cycle with Durysta and around 39.7% (48.2% and 32.9% for the flex and fixed regimen, respectively) will require rescue medication during the second cycle with Durysta.

The applicant should clarify if the data from one eye was excluded after rescue medication, then the valid data from the other eye were included OR if all IOP values for that subject were excluded from all efficacy analyses.

Study 1698-301-007

At the responses to D12o LoQ the applicant has provided an update with the available results for the latest data cutoff (15 September 2023)

A total of 441 had received 1 implant, 179 subjects had received 2 implants and 56 had received 3 implants.

After entering Cycle 1, 41 subjects discontinued Cycle 1, 5 subjects discontinued Cycle 2 and 1 subject discontinued Cycle 3. The study is still ongoing. Subject disposition and study withdrawals are acceptable. The median follow-up duration overall was 542 days, with a range of 2 to 1477 days. The median duration of follow-up from the first administration for the study eye was 337 days, with a range of 2 to 1477 days. The median duration of follow-up for the second administration for the study was 288 days, with a range of 2 to 1193 days. The median duration of follow-up for the third administration of bimatoprost SR for the study eye was 319 days, with a range of 2 to 1015 days.

The original protocol was amended twice. In AM1, the 15 µg dose strength was discontinued. With AM2 the PRN treatment period was extended up to and including month 36. No concerns arise from the conduct of the study.

The study population is considered to reflect the population for the intended indication. Study population demographics are comparable to demographics in the Phase III study 093 and do not give rise to concern, however, the applicant should indicate how many EU patients were involved in the study (a concern was already raised in the discussion of study 093). The majority of subjects (81.5%) had a diagnosis of OAG in the study eye. The proportion of subjects with OHT was 18.5%.

The most common reasons for not being adequately managed with topical IOP-lowering medication for study eyes were memory loss (49.2%) and intolerant/side effects of drop therapies (24.9%). Other reasons were physical inability to administer medication and other.

Rescue medications were reported for 22.7% of study eyes in the Bim SR 10 µg group; 12.8% received permanent rescue treatment and 12.1% received intermittent rescue treatment. A concern was raised in study 093 regarding the feasibility of topical rescue medication considering the intended patient population (not suitable for topical IOP-lowering medication).

The mean (SD) duration of intermittent rescue for study eyes was 121.6 (127.86) days during Cycle 1 and 205.3 (107.50) days during Cycle 2, which appears to be rather long.

Regarding the primary outcome, of the 313 study eyes that received a first administration of BimSR 10 µg, 131 study eyes (41.9%) had received a second administration or initiated rescue treatment by the data cutoff date. The **median time** from initial administration of Bim SR 10 µg to **requiring a second administration or rescue treatment** (intermittent or permanent) in the study eye on a PRN re-administration regimen was **377 days (> 1 year**) with 95% CI of 330.0 to 512.0 days, based on data from all subjects regardless of follow-up time. The cumulative probability of not requiring a second administration of BimSR 10 µg or rescue treatment at 360 days was calculated to be 55.1% with 95% CI of (48.2%, 61.4%). Results were confirmed by a sensitivity analysis in a subgroup of study eyes that either had at least 12 months of exposure to Bim SR 10 µg or had an event (bimatoprost SR re-administration, rescue treatment, or study discontinuation) prior to month 12. However, interpretation of this data is obscured by lack of criteria for rescue medication, and it is therefore questioned how this reflects clinical practice. A concern regarding criteria for initiation of rescue medication was raised in study 093 and also applies to study 007.

Regarding secondary variables, four additional time-to event endpoints were investigated: 1) Time to second administration of BimSR in the study eye regardless of intermittent rescue, 2) Time to third administration of BimSR or first rescue treatment in the study eye after the second administration, 3) Time to third administration of BimSR in the study eye regardless of intermittent rescue, 4) Time to first rescue treatment after third administration of BimSR in the study eye.

Of note, results of analyses that did not consider intermittent rescue are not relevant for the proposed indication.

The **median time to requiring a third administration or initiating rescue treatment (intermittent or permanent) after the second administration** of BimSR 10 µg in the study eye was **297 days** (approximately **10 months,** 95 % CI = 258.0, 357.9). The cumulative probability of not receiving a third administration of BimSR 10 µg or rescue treatment after the second administration in the study eye at 360 days was 35.1%. However, it needs to be noted that interpretation of results might be limited due to the rather small cohort size (n=39 eyes) and the phenomenon of regression to the mean, since only participants without rescue medication receiving a second treatment are considered.

Of the 22 eyes that had received a third administration, 9 eyes had initiated rescue treatment.

In conclusion, results of primary and secondary endpoints comprising study 093 and study 007 indicate a sustained IOP-lowering effect after up to two BimSR 10µg administrations. Durability of the IOP-lowering effect appears crucial for the treatment in a chronic disease. Given the chronic nature of the disease, as foreseen in the label, t is however questionable how beneficial such IOP-lowering effect is in a chronic disease setting. This poses a major concern and needs to be further elaborated. Moreover, safety data have shown, that safety signals increase with repeated BimSR 10µg use, which is of major concern (please refer to safety MOs). Given that, the benefit in a chronic disease is even more uncertain, when only a single or maximal two administrations are considered possible.

Studies 192024-091 and 192024-092

Results for studies -091 and -092 were presented individually for each study and pooled together. Based on the similar designs and similar results, the pooling of these studies is considered acceptable. The focus of the assessment was put on the results from individual studies, apart from data on demographics and disposition, which are pooled. The results from the integrated efficacy analysis are in line with results from individual studies.

According to the pooled data from 091 and 092, a total of 1122 patients were randomized in both studies (374 in each arm); and 1111 (99.0%) patients were treated. The overall proportion of subjects who completed the study was slightly higher in pooled BIM SR 10 µg arms (90.65) compared to pooled timolol arms (87.4%). The proportion of subjects for whom protocol deviations (PD) were reported was overall very high in both studies (70% and 66.7% in -091 and -092, respectively). In both studies, a higher percentage of protocol deviations was reported in the BIM 10 ug group (i.e. 149 (75.3%)/120 (68.2%)) compared to the timolol group (127 (64.1%)/110 (62.5%)). In contrast to a high number of PD, but only a small number of subjects was excluded from the PP analysis (9 and 10 subjects in -091 and -092, respectively). Upon request, the applicant discussed that the remaining protocol deviations did not have an impact on the efficacy results of the primary endpoint at Weeks 2, 6 and 12, which was agreed. A total of 22.5% (252/1122) subjects had a diagnosis of OHT, and 74.7% (838/1122) had a diagnosis of primary OAG. The number of patients with Pseudoexfoliation and pigmentary OAG was very low [(8/1122 (0.7%)] and 24/1122 (2.1%), respectively]. As subjects were treated with an intracameral injection of sustained release of bimatoprost, the treatment compliance was not an issue for bimatoprost arms, but it was unclear for timolol eyedrops. Upon request, the applicant clarified how timolol compliance was monitored throughout the studies, but no specific data on timolol treatment

compliance was presented or seems to be available, which can be considered an uncertainty. However, data on timolol performance throughout study 091 and 092 and to some extent historical data from the literature provided reassurance that timolol treatment compliance was sufficiently high to allow a valid comparison between study arms.

The primary efficacy variable was time-matched IOP (mm Hg) change from baseline at each hour evaluated (Hours 0 and 2) of Cycle 1 Week 12, however results for Weeks 2 and 6 were also taken into consideration in order to assess consistency of results.

For study -091, in the ITT analysis set (all randomized patients), the difference between treatments (BIM SR 10 µg vs timolol BID) in change from baseline in mean IOP (mmHg) was: at Week 2: -0.80 (95% CI -1.47, -0.13) at Hour 0, and -0.90 (95% CI -1.50, -0.31) at Hour 2 at Week 2; at Week 6: -0.82 (95% CI -1.46, -0.19) at Hour 0, and -0.66 (95% CI -1.27, -0.04) at Hour 2; at Week 12: -0.33 (95% CI -1.09, 0.43) at Hour 0, and -0.21 (95% CI -0.90, 0.47) at Hour 2.

For study -092, in the ITT analysis set, the difference between treatments (BIM SR 10 µg vs timolol BID) in change from baseline in mean IOP (mmHg) was: at Week 2: -0.58 (95% CI -1.29, 0.14) at Hour 0, and -0.71 (95% CI -1.38, -0.05) at Hour 2; at Week 6: -0.59 (95% CI -1.34, 0.17) at Hour 0, and -0.65 (95% CI -1.36, 0.06) at Hour 2; at Week 12: -0.08 (95% CI -0.88, 0.73) at Hour 0, and -0.36 (95% CI -1.12, 0.41) at Hour 2.

The change from baseline in mean IOP for BIM SR and timolol were similar for both trials at Week 2, 6 and 12. Both dose strengths of bimatoprost SR met the pre-specified criteria for non-inferiority (upper limit of the 95% CI ≤ 1.5 mm Hg at Week 12 of Cycle 1 (both Hour 0 and 2) in both studies. However, as mentioned earlier, there are limitations to the interpretation of the primary analysis as described earlier in this section and additional analyses are requested which should lead to the same conclusion to claim non-inferiority. The change from baseline in mean IOP (point estimates) was numerically greater for bimatoprost SR 10 µg compared to timolol at each hour evaluated (Hours 0 and 2) at Weeks 2, 6, and 12 of Cycle 1, although the corresponding 95% CIs included unity at several time points.

Mean IOP change from baseline findings for the PP population (the subset of patients in the ITT population who had the primary efficacy variable measured) also confirmed noninferiority. Results from the sensitivity analysis on IOP change from baseline at each hour evaluated (Hours 0 and 2) at Weeks 2, 6, and 12 of Cycle 1 using ANCOVA model with LOCF imputation as well as the sensitivity analysis using ANCOVA model with multiple imputation were similar to the primary analysis. Superiority to timolol was not shown.

Duration of effect: bimatoprost SR 10 µg demonstrated IOP lowering effect comparable to timolol eyedrops BID at Weeks 2, 6 and 12 following each administration. A decrease in effect was observed at Week 12 and was more pronounced at Week 15 of each cycle (before the next dose was administered at Week 16 of each cycle). The last IOP measurements were carried out at Month 20 i.e. approximately 12 months after the injection of the third implant. At Month 20 mean IOP values were 18.6 mmHg and 17.5 mmHg at Hour 0 and 17.9 mmHg and 16.8 mmHg at Hour 2 in BIM 10 µg and timolol group, respectively. This demonstrates that after 3 administration of BIM SR implant, with a fixed time interval of 4 months between two injections, the IOP-lowering effect of BIM SR exists over the timespan of 12 months since the last administered dose, however the effect starts diminishing at Week 12 post-injection. While the IOP values at Month 20 were still markedly lower compared to the baseline IOP values (around 23-25 mm Hg), around 20% of patients had to resort to rescue medication. The interpretation of these results depends on the use of rescue treatment, which needs further clarification (see below). IOP reduction after the injection of first implant and after re-administration were similar, suggesting there is no cumulative IOP-lowering effect of previous implants, although the residua of implants were still detected in the eye. The lack of a cumulative effect suggests that the

active substance is used up before the next implant is injected, which justifies re-administration. However, the degradation of implant itself takes much longer than that of the active substance, which poses concerns (see multidisciplinary MO).

The use of rescue treatment was higher in BIM SR 10 µg compared to timolol group in each cycle; in both studies the utilisation of rescue medication in BIM SR 10 µg group increased with each following cycle. During Cycle 3, the percentage of patients who received rescue treatment were 11.9% (21/176) vs. 1.7% (3/173) in study -091; and 11.1% (17/153) vs. 5.8% (9/154) in study -092 in BIM SR 10 µg and timolol group, respectively. Since in each cycle only participants who had not used rescue medication remain, an increase in use of rescue treatment might be observed based on the phenomenon of regression-to-the-mean and its possible impact needs to be further discussed. In the extended safety follow-up (up to Month 20), the percentage of patients who received rescue treatment was also markedly higher in BIM SR 10 µg group compared to timolol group [10.0% (15/150) vs 4.9% (8/163) in study -091; and 16.4% (22/134) vs. 3.5% (5/142) in study -092].

The applicant provided pooled results from studies 091, 092, and 093 (patients in fixed schedule) on the utilisation of rescue medication. The lowest number of patients receiving rescue medication were in the timolol group (7/370 [1.9 %] in cycle 1, 9/347 [2.6 %] in cycle 2), followed by the BimSR 10 ug group (21/463 [4.5 %] in cycle 1, 28/422 [6.6 %] in cycle 2) and the SLT group (16/146 [11.0 %] in cycle 1, 20/112 [17.9 %] in cycle 2). Of note, the SLT group did not receive any retreatment, which needs to be considered when assessing these results. Nevertheless, when considering the flexible BimSR group, the need for rescue in the BimSR 10 ug group increased considerably (according to Table 200-5.1): during Cycle 1 rescue was administered to 17.8% of eyes followed under SLT treatment for a mean duration of 249 days (median 148 days) in study 192024-093. In the same cycle, 16.1% of eyes treated with the BimSR regimen required rescue therapy for a mean of 288 days (median 241 days). During cycle 2, the greatest need for rescue treatment was reported for the flexible regimen of BimSR (48.2% of eyes in the group) which differs from the fixed regimen of Bim SR (32.9% of eyes in the group) and SLT (31.7% of eyes in the group).

Upon request, a subgroup analysis by underlying ocular disease (OHT and OAG) was presented within the pooled efficacy data analysis (091 and 092), for Weeks 2, 6 and 12 of each treatment cycle for BIM SR 10 µg. An IOP-lowering effect was apparent in both subgroups throughout treatment cycles with a trend indicating an decreased IOP-lowering effect in the BimSR arm with respect to the timolol arm at Week 12 in the OHT subgroup. However, confidence intervals were overlapping with the OAG subgroup and the study is also not powered to show non-inferiority in subgroups. Therefore, no concern was raised. Further, the efficacy profile was similar between ocular disease subgroups in study 192024-093, although it has to be kept in mind that the control treatment was SLT and that the overall study population (not adequately managed with topical IOP lowering medication for reasons other than medication efficacy) may have been different.

Study 1698-304-007

A total of 31 subjects were treated with bimatoprost SR 10 µg and 6 subjects were treated with Lumigan 0.01% in the study eye. The lack of randomisation and the small size of the reference cohort (N=6)) pose limitations to the interpretation of study results. In addition, there were imbalances between the BIM SR and Lumigan in important baseline characteristics, such as diagnosis and baseline IOP etc. The observed mean time-matched 24-hour habitual IOP change from baseline ranged from -3.7 to -1.7 mmHg in the bimatoprost SR treated eyes (diurnal IOP ranged from -3.7 to -1.8 mmHg and nocturnal IOP ranged from -2.4 to -1.7 mmHg) at the Week 8 Sleep Lab visit. The IOP was reduced from baseline (post-washout) at each individual time point. The mean range of IOP (max minus min) measured over a 24-hour period was 9.9 mmHg at Baseline and 8.3 mmHg at the Week 8 Sleep Lab Visit for eyes treated with bimatoprost SR, with a mean change from baseline of IOP range over the

24-hour period at Week 8 of -1.6 mmHg. This reduction in IOP fluctuation on BIM SR treatment is considered very modest considering the washout period patients had to go through before baseline and that at baseline patients could be considered untreated. It is unknown which type of IOP parameter – IOP (average or peak value) or IOP fluctuations contributes more to glaucoma progression (Zhai R et al., 2021). Ideally, IOP-lowering treatment should also reduce circadian IOP fluctuations – this effect appears very modest with BIM SR. Along with long-term IOP fluctuations observed in studies -091 and -092 to a greater extent than with timolol (for which the IOP was more or less constant through Month 20), circadian fluctuations could contribute more to glaucoma progression.

3.3.6. Conclusions on clinical efficacy

The IOP lowering effect of BIM SR 10µg has been demonstrated across different studies. The product is theoretically approvable from the efficacy perspective. Nevertheless, the exact wording of the indication in the PI needs to be agreed on.

3.3.7. Clinical safety

The safety profile of bimatoprost SR has been evaluated in 9 clinical studies. The main safety data of flexible/PRN re-administration of bimatoprost SR 10 µg derive from the ongoing pivotal Phase 3 Study 192024-093 and Phase 3b Study 1698-301-007. Data from these 2 studies are also included in the integrated safety analyses, along with data from Phase 3 Study 192024-095.

Completed **Phase 3 Study 192024-093** and ongoing **Phase 3b Study 1698-301-007** (as of the data cutoff date of 29 July 2022) evaluate bimatoprost SR 10 µg in subjects with OAG or OHT not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence) and incorporate the flexible re-administration regimen (Study 192024-093) or PRN re-administration regimen (Study 1698-301-007) for bimatoprost SR.

Completed 20-month **Phase 3 Studies 192024-091** and **192024-092** as supportive safety information for evaluation of bimatoprost SR (10 µg and 15 µg) versus timolol in subjects with OHT or OAG. Subjects randomized to bimatoprost SR received up to 3 implants on a fixed re-administration regimen of every 16 weeks. Pooled safety data from these studies are summarized.

Completed **Phase 3 Study 192024-095**, in subjects with OAG or OHT who were not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence), as supportive safety information for evaluation of bimatoprost SR (15 µg) versus SLT. Subjects received up to 3 bimatoprost SR 15 µg implants on the fixed re-administration regimen of every 16 weeks.

Completed **Phase 1/2 Study 192024-041D**. Results from this study informed the choice of the bimatoprost SR dose strengths used in subsequent Phase 3 studies. Subjects could receive up to 2 bimatoprost SR implants (≤ 15 µg) on the flexible re-administration regimen. Bimatoprost SR 10 µg (Durysta) in the open-label Phase 4 Study MED-MA-EYE-0648 and completed (or exited early from) Study MED-MA-EYE-0648 with no ongoing safety concerns. No subjects from Study MED-MA-EYE-0648 were enrolled in Study 1698-302-007 as of the data cutoff date (15 June 2022).

Completed Phase **3b Study 1698-304-007**, which evaluated the safety and the 24-hour IOP-lowering effect of bimatoprost SR 10 µg (a single administration sleep laboratory study).

Safety data (as of the data cutoff date of 01 September 2022) from the ongoing **Phase 4 Study MED-MA-EYE-0648**, an observational study of subjects with OAG or OHT who were scheduled for administration of bimatoprost SR 10 µg (Durysta) in 1 or both eyes.

Data from ongoing Phase 3 long-term extension **Study 1698-302-007** as supportive information for subjects who completed 1 of the 4 lead-in Phase 3 bimatoprost SR studies (192024-091, 192024-092, 192024-093, or 192024-095).

3.3.7.1. Patient exposure

Table 52: Number of eyes after 1 or at least 2 implants administration of bimatoprost SR 10 µg in studies 192024-093 and 1698-301-007 (Safety Population)

	Study 192024-093	Study 1698-301-007[a]	Total
	Bim SR 10 µg n (%)	Bim SR 10 µg n (%)	Bim SR 10 µg n (%)
Total number of eyes with at least 1 implant	175	441	616
Minimum of 12-month follow-up period after initial implant	146	312	458
Number of eyes with only 1 implant	49	262	311
Number of eyes with at least 2[b] implants with any follow-up period[c]	126	179	305
Minimum of 3-month follow-up period after 2 implants	126 (100.0)	163 (91.1)	289 (94.8)
Minimum of 6-month follow-up period after 2 implants	124 (98.4)	139 (77.7)	263 (86.2)
Minimum of 12-month follow-up period after 2 implants	78 (61.9)	102 (57.0)	180 (59.0)

a. For Study 1698-301-007, only Bimatoprost SR 10 µg study eyes are included.
b. At the time of data cutoff, 56 subjects in Study 1698-301-007 had received 3 implants.
c. The number of eyes with at least 2 implants were used as the denominator for calculating the percentage at each follow-up timepoint.

Follow-up after initial implant is calculated as the date of last visit minus date of first implant administration +1.
Follow-up after second implant is calculated as the date of last visit minus date of second implant administration + 1.
For subjects who completed the study or prematurely discontinued, the last visit date is taken to be the study exit date.
For subjects ongoing in the study the last visit date is taken to be the data cutoff date, 15 September 2023 for Study 1698-301-007.
Cross reference: Study 192024-093 and Study 1698-301-007 ISS Table 101-1.1

Study 192024-093

Of the 183 subjects in the ITT population who were randomized to receive treatment (bimatoprost SR 10 µg or SLT), 155 completed the study and 28 discontinued prematurely from the study. The most common reason for study discontinuation was withdrawal of consent. Of the 4 subjects who discontinued from the study due to AEs, all subjects discontinued due to nonocular AEs. A total of 180 subjects entered Cycle 1, and 169 subjects completed Cycle 1. Of the subjects who completed Cycle 1, 126 subjects entered Cycle 2 and 112 subjects completed Cycle 2.

Study 1698-301-007

Of the 319 subjects who were randomized or enrolled to receive bimatoprost SR 10 µg, 313 (98.1%) were treated with bimatoprost SR 10 µg in the study eye, 12 (3.8%) completed the study, 26 (8.2%) discontinued from the study, and 281 (88.1%) were still ongoing in the study as of the data cutoff date (29 July 2022). The most frequently reported reasons for study discontinuation were AEs and withdrawal by subject. A total of 7 subjects (2.2%) discontinued from the study due to AEs, including 2 subjects (0.6%) who discontinued due to ocular AEs and 5 subjects (1.6%) who discontinued due to nonocular AEs. Of the 313 subjects who entered Cycle 1, 20 subjects discontinued the study during Cycle 1. The most common reasons for study discontinuation during Cycle 1, were AEs, lost to follow-up, and withdrawal by subject. Of the 96 subjects who entered Cycle 2, 1 subject discontinued the study during Cycle 2 due to "other." As of the data cutoff date, 22 subjects entered Cycle 3 and were ongoing.

Study 192024-041D

109 subjects received study treatment and were included in the safety population. The number of study days was similar across treatment groups, with means ranging from 670.1 to 687.3 days for subjects who received the Generation 2 implant (6 µg [18 subjects], 10 µg [21 subjects], 15 µg [21

subjects], and 20 µg [2 × 10 µg; 15 subjects]). For the 24 subjects who received re-administration (Generation 2 implant only, excluding the bimatoprost SR 20 µg [2 × 10 µg] dose strength), the mean number of days in the first administration cycle ranged from 414.9 to 495.0 days before re-administration. For all subjects who received the Generation 2 bimatoprost SR implant (either initially and/or with re-administration), approximately 40% did not receive rescue medication in the bimatoprost SR-treated eye by Month 12 of the study.

Pooled Studies 192024-091 and 192024-092

In total 1111 subjects received study treatment, 369 subjects in the bimatoprost SR 15 µg group, 372 in the bimatoprost SR 10 µg group, and 370 in the timolol group. In total, 88.2% of subjects (980/1111) completed the study and 11.8% of subjects (131/1111) discontinued the study. The most common reason for discontinuation was AE (4.3% of subjects [48/1111]). More subjects discontinued from the study (mainly due to a higher incidence of ocular AEs) in the bimatoprost SR 15 µg group compared with both the bimatoprost SR 10 µg and timolol groups. In general, there were no other clinically meaningful differences in disposition between subjects in the bimatoprost SR 15 µg, bimatoprost SR 10 µg, and timolol groups. Mean study duration for subjects was 556.4 days in the bimatoprost SR 15 µg group, 575.2 days in the bimatoprost SR 10 µg group, and 562.6 days in the timolol group. A total of 79.4% of bimatoprost SR 15 µg study eyes (293/369) received 3 implants and 87.6% of bimatoprost SR 10 µg study eyes (326/372) received 3 implants.

Study 1698-304-007

All 31 subjects enrolled into the bimatoprost SR cohort received bimatoprost SR in the study eye and standard of care in the fellow eye. All subjects in the bimatoprost SR cohort completed the study. A total of 6 subjects were enrolled into the Lumigan cohort and all 6 subjects received Lumigan 0.01% in the study eye and standard of care in the fellow eye. One (16.7%) subject in the Lumigan cohort discontinued the study due to taking an excluded medication and 5 subjects (83.3%) in the Lumigan cohort completed the Week 8 visit and exited the study. Mean study duration was 361.7 days for subjects in the bimatoprost SR cohort and 57.5 days for subjects in the Lumigan 0.01% cohort.

3.3.7.2. Adverse events

Study 192024-093

Nonocular TEAEs

Nonocular TEAEs occurred in 59.4% of subjects (107/180) in the bimatoprost SR 10 µg-treated safety population. The most common (≥ 5% of subjects) nonocular TEAEs were COVID-19, headache, and hypertension.

Ocular TEAEs

Overall, ocular TEAEs occurred with a similar frequency in bimatoprost SR 10 µg-treated eyes and SLT-treated eyes. For both treatments, the majority of ocular TEAEs were reported in the SOC of eye disorders and were mild to moderate in severity. Overall, severe nonocular TEAEs were reported for 10.6% of subjects in the bimatoprost SR 10 µg-treated safety population. Severe ocular TEAEs were reported for 6.3% of bimatoprost SR 10 µg-treated eyes and 3.3% of SLT-treated eyes (6/180). Of those, conjunctival hyperaemia, visual field defect, conjunctival haemorrhage, corneal oedema, iritis, uveitis, and foreign body in eye occurred only for bimatoprost SR 10 µg-treated eyes (all PTs: 0.6% [1/175]). Other severe ocular TEAEs occurred with the same frequency between bimatoprost SR 10 µg-treated eyes and SLT-treated eyes. In both Cycles 1 and 2, the majority of ocular TEAEs were mild or moderate in severity in both groups. For bimatoprost SR 10 µg-treated eyes, the frequency of

severe ocular TEAEs was 4.6% (8/175) in Cycle 1 and 2.4% (3/126) in Cycle 2. For SLT-treated eyes, the frequency of severe ocular TEAEs was 2.8% (5/180) in Cycle 1 and 0.8% (1/126) in Cycle 2.

The frequency of ocular TEAEs was numerically lower for eyes treated on the flexible bimatoprost SR 10 µg re-administration regimen, as compared with eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen. The most common ocular TEAEs (≥ 10% of eyes) were conjunctival hyperaemia, dry eye, punctate keratitis, and IOP increased for bimatoprost SR 10 µg-treated eyes; and dry eye, punctate keratitis, conjunctival hyperaemia, and IOP increased for SLT-treated eyes. Photophobia was also reported for ≥ 10% of eyes on the flexible bimatoprost SR 10 µg re-administration regimen. The incidence of conjunctival hyperaemia, which is known to be associated with the implant administration procedure, was higher for bimatoprost SR 10 µg-treated eyes than for SLT-treated eyes. In the bimatoprost SR 10 µg-treated eyes, the incidences of conjunctival haemorrhage and eye irritation were lower beyond the immediate 2-day post-administration period compared to within the 2-day post-administration period, which is indicative of these TEAEs being temporally associated with the administration procedure.

Corneal ECL and corneal oedema were reported more frequently for bimatoprost SR 10 µg-treated eyes than for SLT-treated eyes. Overall, ocular TEAEs were reported at a greater frequency in Cycle 2 than Cycle 1 for bimatoprost SR 10 µg-treated eyes. Corneal events, such as corneal ECL and corneal oedema, were reported more frequently in Cycle 2 than Cycle 1 for bimatoprost SR 10 µg-treated eyes. For SLT-treated eyes, the frequency of ocular TEAEs was overall similar between cycles; however, anterior chamber cell was reported more frequently in Cycle 1 than Cycle 2.

Table 53: Ocular TEAEs reported for ≥3 % of treated eyes in any treatment group presented by SOC and PT bimatoprost SR 10 µg/SLT (Safety Population) – study 192024-093

System Organ Class Preferred Term	SLT (N=180) n (%)	Bim SR 10 µg Flexible (N=86) n (%)	Bim SR 10 µg Fixed (N=89) n (%)	Bim SR 10 µg Total (N=175) n (%)
Any Term	114 (63.3)	57 (66.3)	66 (74.2)	123 (70.3)
Eye disorders	102 (56.7)	50 (58.1)	60 (67.4)	110 (62.9)
Conjunctival hyperaemia	22 (12.2)	16 (18.6)	19 (21.3)	35 (20.0)
Dry eye	22 (12.2)	9 (10.5)	16 (18.0)	25 (14.3)
Punctate keratitis	19 (10.6)	10 (11.6)	11 (12.4)	21 (12.0)
Visual field defect	18 (10.0)	7 (8.1)	11 (12.4)	18 (10.3)
Photophobia	2 (1.1)	10 (11.6)	6 (6.7)	16 (9.1)
Eye pain	4 (2.2)	9 (10.5)	6 (6.7)	15 (8.6)
Corneal endothelial cell loss	6 (3.3)	7 (8.1)	5 (5.6)	12 (6.9)
Foreign body sensation in eyes	2 (1.1)	8 (9.3)	4 (4.5)	12 (6.9)
Conjunctival haemorrhage	2 (1.1)	2 (2.3)	7 (7.9)	9 (5.1)
Corneal oedema	0	4 (4.7)	4 (4.5)	8 (4.6)
Anterior chamber cell	10 (5.6)	3 (3.5)	4 (4.5)	7 (4.0)
Vision blurred	4 (2.2)	3 (3.5)	4 (4.5)	7 (4.0)
Cataract	3 (1.7)	3 (3.5)	4 (4.5)	7 (4.0)
Cataract cortical	6 (3.3)	3 (3.5)	3 (3.4)	6 (3.4)
Erythema of eyelid	2 (1.1)	3 (3.5)	3 (3.4)	6 (3.4)
Cataract nuclear	6 (3.3)	1 (1.2)	4 (4.5)	5 (2.9)
Visual acuity reduced	2 (1.1)	2 (2.3)	3 (3.4)	5 (2.9)
Conjunctivitis allergic	4 (2.2)	3 (3.5)	2 (2.2)	5 (2.9)
Iritis	0	3 (3.5)	2 (2.2)	5 (2.9)
Lacrimation increased	3 (1.7)	1 (1.2)	3 (3.4)	4 (2.3)
Infections and infestations	6 (3.3)	8 (9.3)	6 (6.7)	14 (8.0)
Conjunctivitis	5 (2.8)	6 (7.0)	3 (3.4)	9 (5.1)

System Organ Class Preferred Term	SLT (N=180) n (%)	Bim SR 10 µg Flexible (N=86) n (%)	Bim SR 10 µg Fixed (N=89) n (%)	Bim SR 10 µg Total (N=175) n (%)
Investigations	33 (18.3)	19 (22.1)	26 (29.2)	45 (25.7)
Intraocular pressure increased	33 (18.3)	17 (19.8)	26 (29.2)	43 (24.6)

Adverse event terms were coded using the dictionary: MedDRA 26.0.

SOC sorted alphabetically. Within each SOC, PTs are sorted by descending incidence in treatment groups from right to left (Total of fixed and flexible combined, fixed, flexible, and SLT).

Cross reference: Study 192024-093 Final CSR Table 14.3-2.2.1

Analysis Cycle 1

System Organ Class Preferred Term	SLT (N=180) n (%)	Bim SR 10 µg Flexible (N=86) n (%)	Bim SR 10 µg Fixed (N=89) n (%)	Bim SR 10 µg Total (N=175) n (%)
Infections and infestations	5 (2.8)	6 (7.0)	3 (3.4)	9 (5.1)
Conjunctivitis	4 (2.2)	5 (5.8)	1 (1.1)	6 (3.4)
Injury, poisoning and procedural complications	2 (1.1)	3 (3.5)	3 (3.4)	6 (3.4)
Device placement issue	0	2 (2.3)	0	2 (1.1)
Investigations	18 (10.0)	8 (9.3)	11 (12.4)	19 (10.9)
Intraocular pressure increased	18 (10.0)	6 (7.0)	11 (12.4)	17 (9.7)

Analysis Cycle 2

N1 [1]	126	56	70	126
Any Term	56 (44.4)	35 (62.5)	43 (61.4)	78 (61.9)
Eye disorders	47 (37.3)	27 (48.2)	37 (52.9)	64 (50.8)
Conjunctival hyperaemia	8 (6.3)	3 (5.4)	10 (14.3)	13 (10.3)
Visual field defect	11 (8.7)	4 (7.1)	8 (11.4)	12 (9.5)
Eye pain	1 (0.8)	5 (8.9)	5 (7.1)	10 (7.9)
Dry eye	6 (4.8)	3 (5.4)	6 (8.6)	9 (7.1)
Corneal endothelial cell loss	2 (1.6)	5 (8.9)	4 (5.7)	9 (7.1)
Photophobia	1 (0.8)	6 (10.7)	2 (2.9)	8 (6.3)
Foreign body sensation in eyes	1 (0.8)	3 (5.4)	3 (4.3)	6 (4.8)
Corneal oedema	0	3 (5.4)	3 (4.3)	6 (4.8)

Ocular TEAEs With Onset Within and Beyond the Immediate Bimatoprost SR/Sham Bimatoprost SR Post-Administration Period

Ocular TEAEs with onset within 2 days following the bimatoprost SR/Sham bimatoprost SR administration procedure (considered the immediate post-administration period) and those with onset beyond the immediate post-administration period were evaluated to distinguish between ocular TEAEs that were more likely related to the administration procedure and/or procedure preparation (ocular TEAEs with onset within the immediate post-administration period) versus the bimatoprost SR implant (ocular TEAEs with onset beyond the immediate post-administration period).

Ocular TEAEs with onset within the immediate post-administration period were reported for 32.0% of bimatoprost SR 10 µg-treated eyes (54/175) compared with 13.9% of Sham bimatoprost SR-treated eyes (25/180). Ocular TEAEs with onset within this period reported for ≥ 3% of eyes were conjunctival hyperaemia, dry eye, photophobia, eye pain, and foreign body sensation in eyes for bimatoprost SR 10 µg-treated eyes and dry eye for Sham bimatoprost SR-treated eyes. Ocular TEAEs with onset beyond the immediate post-administration period were reported for 66.3% of bimatoprost SR 10 µg-treated eyes compared with 53.9% of Sham bimatoprost SR-treated eyes. Conjunctival haemorrhage and eye irritation were numerically reduced in frequency for bimatoprost SR 10 µg-treated eyes beyond the immediate post-administration period, which is indicative of these TEAEs being temporally associated with the administration procedure.

Conjunctival hyperaemia (bimatoprost SR 10 µg-treated eyes 7.4% vs SLT-treated eyes 1.7%), dry eye (5.1% vs 4.4%), photophobia (4.6% vs 0), and eye pain (4.6% vs 1.1%) were the most commonly reported TEAEs during the immediate post-administration period. Intraocular pressure increased was reported by 1.1% bimatoprost SR 10 µg-treated eyes vs 2.8% SLT-treated eyes.

Conjunctival hyperaemia (14.9% vs. 10.6%), visual field defect 12 (10.3% vs 10.0%), dry eye (8.0% vs 6.1%), corneal endothelial cell loss (6.9% vs. 3.3%), photophobia (5.1% vs. 1.1%), conjunctivitis (5.1% vs. 2.2%) were the most commonly reported TEAEs beyond the immediate post-administration period. Intraocular pressure increased was reported by 24.6% bimatoprost SR 10 µg-treated eyes vs 17.2% SLT-treated eyes.

Related AEs

Treatment-related ocular TEAEs occurred with a greater frequency for bimatoprost SR 10 µg-treated eyes (40.0%) than for SLT-treated eyes (22.8%) The most common (≥ 5% of eyes) treatment-related ocular TEAEs were conjunctival hyperaemia, punctate keratitis, and photophobia for bimatoprost SR 10 µg-treated eyes and punctate keratitis and anterior chamber cell for SLT-treated eyes. Corneal ECL and corneal oedema occurred with a greater frequency for bimatoprost SR 10 µg-treated eyes compared with SLT-treated eyes.

The frequency of treatment-related ocular TEAEs was lower for eyes treated on the flexible bimatoprost SR 10 µg re-administration regimen (29.1%) compared with eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen (50.6%) and was similar to SLT. The frequency of treatment-related ocular TEAEs was similar between Cycles 1 and 2 for bimatoprost SR 10 µg-treated eyes (26.9% [47/175] and 31.7% [40/126], respectively). For SLT-treated eyes, the frequency of treatment-related ocular TEAEs was greater in Cycle 1 than Cycle 2 (19.4% [35/180] versus 7.1% [9/126]). Punctate keratitis occurred with a greater incidence in Cycle 1 than Cycle 2 for both bimatoprost SR 10 µg-treated eyes (8.0% [14/175] versus 0.8% [1/126]) and SLT-treated eyes (7.2% [13/180] versus 0/126). For SLT-treated eyes, anterior chamber cell was also reported with a higher incidence in Cycle 1 than Cycle 2 (5.0% [9/180] vs 0/126). Corneal events of special interest were generally more common in Cycle 2 than Cycle 1 for bimatoprost SR 10 µg-treated eyes. All other events were generally consistent between cycles.

Corneal TEAEs of Special Interest

Over the duration of the study, corneal TEAEs of special interest were reported for a greater percentage of bimatoprost SR 10 µg-treated eyes than SLT-treated eyes. The frequency of corneal TEAEs of special interest was similar for eyes treated on the flexible bimatoprost SR 10 µg re-administration regimen and eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen.

Overall, the most frequently reported corneal TEAEs of special interest (≥ 2.0%) were corneal ECL and corneal oedema for bimatoprost SR 10 µg-treated eyes and corneal ECL for SLT-treated eyes. For both groups, the majority of corneal TEAEs of special interest were mild or moderate in severity. Severe corneal oedema was reported for 1 bimatoprost SR 10 µg-treated eye on the flexible bimatoprost SR 10 µg re-administration regimen; no other severe corneal TEAEs of special interest were reported in either group. The majority of corneal TEAEs of special interest were considered related to study treatment for both bimatoprost SR 10 µg- and for SLT-treated eyes. There was a total of 31 corneal TEAEs of special interest in 18 eyes treated with bimatoprost SR 10 ug. Out of these 18 eyes, 18 corneal TEAEs of special interest resolved in 11 eyes. There was a total of 9 corneal TEAEs of special interest in 9 eyes treated with SLT. Among these 9 eyes, 3 corneal TEAEs of special interest resolved in 3 eyes. The majority of TEAEs of corneal oedema resolved as of the end of the study.

The frequency of corneal TEAEs of special interest was similar between bimatoprost SR 10 µg-treated eyes and SLT-treated eyes in Cycle 1 (2.9% [5/175] versus 2.8% [5/180]); among bimatoprost SR 10 µg-treated eyes, the incidence was lower for the flexible re-administration regimen compared with the fixed re-administration regimen (2.3% [2/86] versus 3.4% [3/89]). All of the corneal TEAEs of special interest reported in Cycle 1 were considered mild or moderate in severity. In Cycle 2, corneal TEAEs of special interest were more frequently reported for bimatoprost SR 10 µg-treated eyes than for SLT-treated eyes (10.3% versus 3.2%). Among bimatoprost SR 10 µg-treated eyes, the incidence was higher for the flexible re-administration regimen compared with the fixed re-administration regimen (12.5% [7/56] versus 8.6% [6/70]), which may be attributed to differences in duration of study follow-up between these groups. Corneal TEAEs of special interest were reported more frequently for bimatoprost SR-treated eyes in Cycle 2 than in Cycle 1 (10.3% [13/126] versus 2.9% [5/175]). The majority of the corneal TEAEs of special interest reported in Cycle 2 were considered mild or moderate in severity; the only severe corneal TEAE of special interest was corneal oedema reported for 1 bimatoprost SR 10 µg-treated eye (already mentioned above).

Table 54: Corneal TEAEs of Special Interest: Number (%) of Treated Eyes by SOC and PT – Bimatoprost SR 10 µg/SLT (Safety Population) – Study 192024-093

	SLT	Bim SR 10 ug		
System Organ Class Preferred Term	(N=180) n (%)	Flexible (N=86) n (%)	Fixed (N=89) n (%)	Total (N=175) n (%)
Any Term	9 (5.0)	9 (10.5)	9 (10.1)	18 (10.3)
Eye disorders	9 (5.0)	9 (10.5)	9 (10.1)	18 (10.3)
Corneal endothelial cell loss	6 (3.3)	7 (8.1)	5 (5.6)	12 (6.9)
Corneal oedema	0	4 (4.7)	4 (4.5)	8 (4.6)
Corneal thickening	2 (1.1)	1 (1.2)	2 (2.2)	3 (1.7)
Corneal touch	0	0	1 (1.1)	1 (0.6)
Corneal opacity	1 (0.6)	0	0	0

Adverse event terms were coded using the dictionary: MedDRA 26.0.

SOC sorted alphabetically. Within each SOC, PTs are sorted by descending incidence in treatment groups from right to left (Total of fixed and flexible combined, fixed, flexible, and SLT).

Cross reference: Study 192024-093 Final CSR Table 14.3-3.4.1

Anterior Segment Inflammatory TEAEs of Special Interest

Over the duration of the study through data cutoff date (21 June 2022), anterior segment inflammatory TEAEs of special interest were reported for a similar percentage of bimatoprost SR 10 µg-treated eyes and SLT-treated eyes. Overall, the most frequently reported anterior segment

inflammatory TEAEs of special interest (≥ 2.0%) were anterior chamber cell and iritis for bimatoprost SR 10 µg-treated eyes and anterior chamber cell for SLT-treated eyes. For both treatment groups, the majority of anterior segment inflammatory TEAEs of special interest were mild or moderate in severity and were generally transient in duration (lasting < 2 months); none were serious. Severe iritis and severe uveitis were reported for 1 bimatoprost SR 10 µg-treated eye each; no other severe anterior segment inflammatory TEAEs of special interest were reported in either treatment group. The aforementioned severe uveitis occurred in Cycle 1 and the severe iritis occurred in Cycle 2. For both groups, the majority of anterior segment inflammatory TEAEs of special interest were considered related to study treatment. The majority of anterior segment inflammatory TEAEs of special interest had resolved by the end of the study.

In Cycle 1, the frequency of anterior segment inflammatory TEAEs of special interest was lower for bimatoprost SR 10 µg-treated eyes than for SLT-treated eyes (1.7% [3/175] versus 5.6% [10/180]). In Cycle 2, anterior segment inflammatory TEAEs of special interest were more frequently reported for bimatoprost SR 10 µg-treated eyes than for SLT-treated eyes (7.9% [10/126] versus 0.8% [1/126]).

Table 55: Anterior segment inflammatory TEAEs of special interest: number (%) of treated eyes by SOC and PT – bimatoprost SR 10 µg/SLT (Safety Population) – study 192024-093

System Organ Class Preferred Term	SLT (N=180) n (%)	Bim SR 10 ug (N=175) n (%)
Any Term	11 (6.1)	13 (7.4)
Eye disorders	11 (6.1)	13 (7.4)
Anterior chamber cell	10 (5.6)	7 (4.0)
Iritis	0	5 (2.9)
Anterior chamber flare	1 (0.6)	3 (1.7)
Iris adhesions	0	3 (1.7)
Uveitis	0	1 (0.6)
Iridocyclitis	1 (0.6)	0

Adverse event terms were coded using the dictionary: MedDRA 26.0.

SOC sorted alphabetically. Within each SOC, PTs are sorted by descending incidence in treatment groups from right to left.

Cross reference: Study 192024-093 Final CSR Table 14.3-3.5.1

Corneal endothelial cell loss

A CECD loss of ≥ 15% represents a clinically meaningful change, whereas a CECD loss below this threshold may be due to variability in measurements or other factors. The analysis is mainly focused on the ≥ 15% threshold, additionally, confirmed ECL, defined as the first of 2 assessments of ECLs that met the threshold at 2 consecutive visits, was assessed to reduce the chance of spurious readings and provide more reliable results. Since Studies 192024-093 and 1698-301-007 are ongoing, clinical conclusions are based on data available at the respective data cutoff date for each study.

The SLT-treatment data for these analyses are from SLT-treated eyes from both the bimatoprost SR 10 µg-treated safety population and bimatoprost SR 15 µg-treated safety population for Study 192024-093. At baseline (regardless of analysis cycle, before treatments were administered), the mean (SD) central CECD, as evaluated by specular microscopy, was 2492.7 (310.95) cells/mm2 and 2507.6 (324.48) cells/mm2 for eyes treated with bimatoprost SR 10 µg on the flexible re-administration regimen (86/86) or fixed re-administration regimen (89/89), respectively. The mean (SD) central CECD at baseline was 2529.5 (317.20) cells/mm2 for SLT-treated eyes (236/236).

By Week 52 (regardless of analysis cycle), in eyes treated with bimatoprost SR 10 µg on the flexible re-administration regimen with data for baseline and Week 52 (77/86), mean (SD) central CECD change from baseline was –92.6 (282.38) cells/mm2 with a mean (SD) percent change from baseline in central CECD of –3.5% (9.74); mean (SD) central CECD change from baseline was –78.0 (228.63) cells/mm2 with a mean (SD) percent change from baseline in central CECD of –3.3% (10.25) for eyes treated with bimatoprost SR 10 µg on the fixed re-administration regimen with data for baseline and

Week 52 (85/89). For SLT-treated eyes (207/236), mean (SD) central CECD change from baseline was −65.3 (142.52) cells/mm2 with a mean (SD) percent change from baseline in central CECD of −2.5%

(5.53).The SLT-treatment data for these analyses are from SLT-treated eyes from the bimatoprost SR 10 µg-treated safety population from Study 192024-093. At baseline (before treatments were administered), the mean (SD) central CECD as evaluated by specular microscopy was similar between bimatoprost SR 10 µg-treated eyes (2500.3 cells/mm2 [317.08]; 175/175) and SLT-treated eyes (2512.7 cells/mm2 [307.87]; 180/180). The mean percent loss in CECD through Month 24 of Cycle 1 and Month 20 of Cycle 2 ranged from −6.4% to -0.2% and from −11.0% to −0.3%, respectively for bimatoprost SR 10 µg-treated eyes, and from −3.8% to −2.1% and from −5.3% to 1.1% for SLT-treated eyes. The mean percent CECD change from baseline (regardless of administration cycle) was -1.0% versus -2.2% at Week 24, -3.4% versus -2.3% at Week 52, and -6.2% versus -3.1% at Month 24 for bimatoprost SR 10 µg-treated and SLT-treated eyes, respectively.

By category, overall, a central CECD loss of ≥ 15% was more frequently observed for bimatoprost SR 10 µg-treated eyes than for SLT-treated eyes (Table 29). The higher incidence for bimatoprost SR 10 µg-treated eyes was only observed during Cycle 2; in Cycle 1, the incidence of ≥ 15% CECD loss was the same in bimatoprost SR 10 µg-treated eyes and SLT-treated eyes. A similar pattern was observed for ≥ 20% CECD loss.

Eyes treated on the flexible bimatoprost SR 10 µg re-administration regimen had a numerically similar incidence of ≥ 15% observed central CECD loss compared with eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen; however, eyes treated on the flexible bimatoprost SR 10 µg re-administration regimen had a numerically lower incidence of ≥ 20% CECD loss compared with the fixed bimatoprost SR 10 µg re-administration regimen.

Overall, the confirmed ECL incidence and ECL rates were higher for bimatoprost SR 10 µg-treated eyes than for SLT-treated eyes. For bimatoprost SR 10 µg-treated eyes, confirmed ECL incidence and ECL rates were lower on the flexible re-administration regimen compared with the fixed re-administration regimen.

In Cycle 1, the incidence of ≥ 15% central CECD loss was the same between bimatoprost SR 10 µg-treated eyes and SLT-treated eyes. The incidence of ≥ 15% central CECD loss was numerically higher for eyes treated on the flexible bimatoprost SR 10 µg re-administration regimen compared with eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen. The incidence of ≥ 50% central CECD loss was low and only observed in bimatoprost SR 10 µg-treated eyes (2.4% of eyes [2/85] treated on the flexible re-administration regimen and no eyes [0/89] treated on the fixed re-administration regimen) (Study 192024-093 Final CSR Table 14.3-7.2).

In Cycle 2, the incidence of ≥ 15% central CECD loss was higher for bimatoprost SR 10 µg-treated eyes compared with SLT-treated eyes. The incidence of ≥ 15% central CECD loss was numerically lower for eyes treated on the flexible bimatoprost SR 10 µg re-administration regimen compared with eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen. The incidence of ≥ 50% central CECD loss was low and only observed in bimatoprost SR 10 µg-treated eyes (1.8% of eyes [1/56] treated on the flexible re-administration regimen and 2.9% of eyes [2/70] treated on the fixed re-administration regimen).

A similar pattern was observed for ≥ 20% central CECD loss as for ≥ 15% central CECD loss.

Table 56: Specular microscopy – central CECD average (cells/mm2): Number (%) of treated eyes and visit change from baseline – bimatoprost SR 10 µg/SLT (Safety Population) - study 192024-093

Study Period/Visit [1]	Category	SLT (N=180) n (%)	Bim SR 10 µg Flexible (N=86) n (%)	Bim SR 10 µg Fixed (N=89) n (%)	Bim SR 10 µg Total (N=175) n (%)
Overall [1]	N1	178	85	89	174
	>=10% Gain	0	0	0	0
	-10% < and < 10%	161 (90.4)	71 (83.5)	75 (84.3)	146 (83.9)
	>=10% Loss	17 (9.6)	14 (16.5)	14 (15.7)	28 (16.1)
	>=15% Loss	8 (4.5)	8 (9.4)	8 (9.0)	16 (9.2)
	>=20% Loss	6 (3.4)	6 (7.1)	8 (9.0)	14 (8.0)
	>=30% Loss	2 (1.1)	6 (7.1)	8 (9.0)	14 (8.0)
	>=40% Loss	0	4 (4.7)	4 (4.5)	8 (4.6)
	>=50% Loss	0	3 (3.5)	2 (2.2)	5 (2.9)
Analysis Cycle 1 Overall [1]	N1	178	85	89	174
	>=10% Gain	0	0	0	0
	-10% < and < 10%	166 (93.3)	78 (91.8)	87 (97.8)	165 (94.8)
	>=10% Loss	12 (6.7)	7 (8.2)	2 (2.2)	9 (5.2)
	>=15% Loss	6 (3.4)	4 (4.7)	2 (2.2)	6 (3.4)
	>=20% Loss	5 (2.8)	2 (2.4)	2 (2.2)	4 (2.3)
	>=30% Loss	2 (1.1)	2 (2.4)	2 (2.2)	4 (2.3)
	>=40% Loss	0	2 (2.4)	2 (2.2)	4 (2.3)
	>=50% Loss	0	2 (2.4)	0	2 (1.1)
Analysis Cycle 2 Overall [1]	N1	125	56	70	126
	>=10% Gain	0	0	0	0
	-10% < and < 10%	114 (91.2)	49 (87.5)	58 (82.9)	107 (84.9)
	>=10% Loss	11 (8.8)	7 (12.5)	12 (17.1)	19 (15.1)
	>=15% Loss	6 (4.8)	4 (7.1)	6 (8.6)	10 (7.9)
	>=20% Loss	4 (3.2)	4 (7.1)	6 (8.6)	10 (7.9)
	>=30% Loss	0	4 (7.1)	6 (8.6)	10 (7.9)
	>=40% Loss	0	2 (3.6)	2 (2.9)	4 (3.2)
	>=50% Loss	0	1 (1.8)	2 (2.9)	3 (2.4)

N1: Number of eyes with baseline and postbaseline endothelial cell assessments.

[1] For overall summary in any cycle and analysis cycle, the greatest decrease from baseline was used for the category summary during each study period.

Cross reference: Study 192024-093 Final CSR Table 14.3-7.2

Table 57: First observed and first confirmed ECL rate by threshold, exposure-adjusted analysis, and cumulative probabilities of ECL – bimatoprost SR 10 µg/SLT (Safety Population)

Treatment Group	SLT (N = 178)	Bim SR Flexible (N = 85)	Bim SR Fixed (N = 89)	Bim SR Total (N = 174)
ECL Overall Incidence (number (%) of eyes with ECL meeting the ≥ 15% threshold)				
Observed Loss[a]	8 (4.5)	8 (9.4)	8 (9.0)	16 (9.2)
Confirmed Loss[b]	6 (3.4)	6 (7.1)	7 (7.9)	13 (7.5)
ECL Overall Incidence (number (%) of eyes with ECL meeting the ≥ 20% threshold)				
Observed Loss[a]	6 (3.4)	6 (7.1)	8 (9.0)	14 (8.0)
Confirmed Loss[b]	2 (1.1)	5 (5.9)	7 (7.9)	12 (6.9)
Exposure-Adjusted ECL Rate[c] ≥ 15% (per 100 patient-years)				
Observed Loss[a]	2.88	5.27	6.52	5.83
Confirmed Loss[b]	2.15	3.90	5.71	4.70
Exposure-Adjusted ECL Rate[c] ≥ 20% (per 100 patient-years)				
Observed Loss[a]	2.14	3.93	6.49	5.07
Confirmed Loss[b]	0.70	3.23	5.68	4.32
Cumulative Probabilities of ECL ≥ 15% at Month 24 (%)[d]				
Observed Loss[a]	4.6	8.7	11.8	10.0
Confirmed Loss[b]	3.4	6.2	9.7	7.7
Cumulative Probabilities of ECL ≥ 20% at Month 24 (%)[d]				
Observed Loss[a]	3.4	7.4	13.0	9.5
Confirmed Loss[b]	1.1	6.2	10.9	8.1

a. Observed loss: ECL reported at least at one time point during the study.

b. Confirmed loss: at least 2 ECLs meeting the specified threshold at 2 consecutive visits (scheduled or unscheduled) with CECD assessment done on different days. One subject experienced the 1st ECL assessment after study exit and was excluded from this analysis.

c. Exposure-Adjusted ECL Rate = 100 *[number of eyes that experienced the ECL event]/total exposure time in person-years for the treatment group.

d. Cumulative probability for time to the 1st ECL ≥ 15% or 1st ECL ≥ 20% estimated by Kaplan-Meier method.

Cross reference: Study 192024-093 Final CSR Table 14.3-7.5.1, Table 14.3-7.5.2, Table 14.3-7.5.3, Table 14.3-7.5.4, Table 14.3-7.6.1, Table 14.3-7.6.2

Study 1698-301-007

Nonocular TEAEs

Nonocular TEAEs were reported for 38.7% of subjects (121/313) in the bimatoprost SR 10 µg group. The most frequently reported (≥ 5% of subjects) nonocular TEAEs in the bimatoprost SR 10 µg group were COVID-19 (6.7% [21/313]) and hypertension (6.1% [19/313]).

Ocular TEAEs

The majority of ocular TEAEs were reported in the SOC of eye disorders and were mild or moderate in severity for bimatoprost SR 10 µg study eyes and bimatoprost SR 10 µg-treated fellow eyes (i.e., fellow eyes that received 1 administration of bimatoprost SR). Severe nonocular TEAEs were reported for 8.0% of subjects (25/313) in the bimatoprost SR 10 µg group. Severe ocular TEAEs were reported for 1.9% of bimatoprost SR 10 µg study eyes [6/313]. Severe ocular TEAEs reported for bimatoprost

SR 10 µg study eyes were corneal ECL, conjunctival hyperaemia, eye irritation, corneal oedema, scleral hyperaemia, and drug hypersensitivity. During Cycles 1 and 2, the majority of ocular TEAEs were mild or moderate in severity for bimatoprost SR 10 µg study eyes. Among the bimatoprost SR 10 µg study eyes, 1.3% (4/313) had severe ocular TEAEs in Cycle 1 (conjunctival hyperaemia, eye irritation, corneal ECL, scleral hyperaemia, and corneal oedema [reported for 1 study eye each]) and 2.1% (2/96) in Cycle 2 (corneal ECL and drug hypersensitivity [reported for 1 study eye each]).

The most frequently reported ocular TEAE for bimatoprost SR 10 µg study eyes was conjunctival hyperaemia (13.7% [43/313]), which is known to be associated with the implant administration procedure. Other ocular TEAEs reported for ≥ 5% of bimatoprost SR 10 µg study eyes were IOP increased and dry eye. Of the bimatoprost SR 10 µg-treated fellow eyes, 38.0% (35/92) had at least 1 ocular TEAE. The most frequently reported (≥ 5%) ocular TEAEs for bimatoprost SR 10 µg-treated fellow eyes were IOP increased (10.9% [10/92]), visual field defect (6.5% [6/92]), conjunctival hyperaemia (5.4% [5/92]), and scleral hyperaemia (5.4% [5/92]). The incidence of ocular TEAEs for bimatoprost SR 10 µg study eyes was 38.7% (121/313) in Cycle 1 and 44.8% (43/96) in Cycle 2. For these eyes, the most frequently reported (≥ 5%) ocular TEAEs were conjunctival hyperaemia (12.8% [40/313]) and intraocular pressure increased (8.3% [26/313]) during Cycle 1 and conjunctival hyperaemia (12.5% [12/96]), intraocular pressure increased (11.5% [11/96]), corneal ECL (6.3% [6/96]), and dry eye and scleral hyperaemia (5.2% [5/96] each) during Cycle 2.

Ocular TEAEs With Onset or Worsening Within and Beyond the Immediate Post-Administration Period

Ocular TEAEs with onset or worsening within the 2 days following the bimatoprost SR administration procedure (considered the immediate post-administration period) were reported for 21.7% of bimatoprost SR 10 µg study eyes (68/313). Conjunctival hyperaemia was the only ocular TEAE with onset or worsening within this period reported for ≥ 2% of bimatoprost SR 10 µg study eyes. Ocular TEAEs with onset or worsening beyond the immediate post-administration period were reported for 32.3% of bimatoprost SR 10 µg study eyes (101/313). Onset or worsening of conjunctival hyperaemia was reported with less frequency for bimatoprost SR 10 µg study eyes beyond the immediate post-administration period (4.8% [15/313]) compared to within the immediate post-administration period (11.2% [35/313]), which is indicative of this ocular TEAE being temporally associated with the administration procedure.

Conjunctival hyperaemia (11.2%), eye irritation, eye pain and photophobia (1.6% each) were the most commonly reported TEAEs in bimatoprost SR 10 µg-treated eyes during the immediate post-administration period. No patients reported intraocular pressure increased was reported by 9.9% bimatoprost SR 10 µg-treated eyes.

Conjunctival hyperaemia (4.5%), dry eye (4.5%) and corneal endothelial cell loss (4.5%) were the most commonly reported TEAEs in bimatoprost SR 10 µg-treated eyes beyond the immediate post-administration period. Intraocular pressure increased was reported by 9.9% bimatoprost SR 10 µg-treated eyes.

Related AEs

At least 1 treatment-related ocular TEAE was reported for 25.9% (81/313) of bimatoprost SR 10 µg study eyes. The most frequently reported treatment-related ocular TEAE (> 3%) for bimatoprost SR 10 µg study eyes was conjunctival hyperaemia (11.8% [37/313]). Of the 37 study eyes with TEAEs of conjunctival hyperaemia, the event was considered related to the injection procedure in 35 eyes and related to study drug in 3 eyes. The incidence of treatment-related ocular TEAEs for bimatoprost SR 10 µg study eyes was 23.0% (72/313) in Cycle 1 and 22.9% (22/96) in Cycle 2. In Cycles 1 and 2, most of the treatment-related ocular TEAEs were reported as injection procedure-related (16.0% [50/313]

in Cycle 1 and 17.7% [17/96] in Cycle 2). Conjunctival hyperaemia was the most frequently reported treatment-related ocular TEAE in both cycles (10.9% [34/313] in Cycle 1 and 10.4% [10/96] in Cycle 2). The incidence of treatment-related ocular TEAEs was 16.3% for bimatoprost SR 10 µg-treated fellow eyes (15/92). The most frequently reported (≥ 3%) treatment-related ocular TEAEs for bimatoprost SR 10 µg-treated fellow eyes were conjunctival hyperaemia, photophobia, and scleral hyperaemia (4.3% [4/92] each). One fellow eye receiving standard of care in the bimatoprost SR 10 µg group had a treatment-related ocular TEAE of conjunctival hyperaemia.

Corneal TEAEs of Special Interest

Overall, the most frequently reported (≥ 2.0%) corneal TEAEs of special interest were corneal ECL and corneal oedema for bimatoprost SR 10 µg study eyes. Most corneal TEAEs of special interest for bimatoprost SR 10 µg study eyes were considered related to study treatment and were mild to moderate in severity. Of the bimatoprost SR 10 µg study eyes, 2 had severe events of corneal ECL and 1 had a severe event of corneal oedema. Corneal TEAEs of special interest were reported for 4.3% of bimatoprost SR 10 µg-treated fellow eyes (4/92). The events were corneal ECL and corneal oedema (4.3% [4/92] and 1.1% [1/92], respectively). Two of the events of corneal ECL and the event of corneal oedema were considered treatment-related, and 1 event of corneal ECL was reported as severe.

The incidence of corneal TEAEs of special interest for bimatoprost SR 10 µg study eyes was 4.2% (13/313) in Cycle 1 and 8.3% (8/96) in Cycle 2. In Cycle 1, severe corneal ECL and severe corneal oedema were reported for 1 bimatoprost SR 10 µg study eye each; and in Cycle 2, severe corneal ECL was reported for 1 bimatoprost SR 10 µg study eye. There were no corneal TEAEs of special interest reported for fellow eyes (0/313) receiving standard of care in the bimatoprost SR 10 µg group.

Table 58: Corneal TEAEs of special interest: Number (%) of subjects by system organ class and preferred term – overall (Safety Analysis Set) – study 1698-301-007

System Organ Class Preferred Term	Bim SR 10ug SE (N=313) n (%)	FE [1] (N=313) n (%)
Subjects with at least one Corneal TEAE	20 (6.4)	0
Eye disorders	20 (6.4)	0
Corneal endothelial cell loss	14 (4.5)	0
Corneal oedema	11 (3.5)	0
Corneal disorder	2 (0.6)	0
Corneal opacity	1 (0.3)	0

[1] Includes data for events occurring prior to FE being treated with Bim SR or FE never treated with Bim SR.

Note: Adverse event terms are coded using the MedDRA version 25.0.
Table presents data from the Bimatoprost SR 10 µg group only.

Cross reference: Study 1698-301-007 Interim 1 CSR Table 14.3-9.1

Anterior Segment Inflammation TEAEs of Special Interest

Overall, the most frequently reported (≥ 1.0%) anterior segment inflammation TEAEs of special interest were anterior chamber cell, iritis, and iris adhesions for bimatoprost SR 10 µg study eyes. The majority of anterior segment inflammation TEAEs of special interest for bimatoprost SR 10 µg study eyes were considered related to study treatment, and all were nonserious and were mild to moderate in severity. Anterior segment inflammation TEAEs of special interest were generally short in duration, with the majority resolved within approximately 30 days of onset.

The incidence of anterior segment inflammation TEAEs of special interest for bimatoprost SR 10 µg study eyes was 3.2% (10/313) in Cycle 1 and 3.1% (3/96) in Cycle 2. There were no anterior segment inflammation TEAEs of special interest reported for bimatoprost SR 10 µg-treated fellow eyes. There

were no anterior segment inflammation TEAEs of special interest reported for fellow eyes receiving standard of care in the bimatoprost SR 10 µg group.

Table 59: Anterior segment information TEAEs of special interest: Number (%) of subjects by system organ class and preferred term – overall (Safety Analysis Set) – study 1698-301-007

System Organ Class Preferred Term	Bim SR 10ug SE (N=313) n (%)	FE [1] (N=313) n (%)
Subjects with at least one Anterior Segment Inflammation TEAE	14 (4.5)	0
Eye disorders	14 (4.5)	0
Anterior chamber cell	5 (1.6)	0
Iritis	5 (1.6)	0
Iris adhesions	3 (1.0)	0
Anterior chamber flare	2 (0.6)	0
Anterior chamber inflammation	1 (0.3)	0
Iridocyclitis	1 (0.3)	0

[1] Includes data for events occurring prior to FE being treated with Bim SR or FE never treated with Bim SR.

Note: Adverse event terms are coded using the MedDRA version 25.0.
Table presents data from the Bimatoprost SR 10 µg group only.

Cross reference: Study 1698-301-007 Interim 1 CSR Table 14.3-10.1

Corneal endothelial cell loss

At baseline, reading centre central CECD values ranged from 1026.7 to 3285.8 cells/mm2 with a mean (SD) of 2439.6 (396.98) cells/mm2 for bimatoprost SR 10 µg study eyes and values ranged from 633.2 to 3400.2 cells/mm2 with a mean (SD) of 2439.1 (406.94) cells/mm2 for fellow eyes receiving standard of care. Fellow eyes receiving standard of care includes data for assessments occurring prior to the fellow eye being treated with bimatoprost SR 10 µg or fellow eye never treated with bimatoprost SR 10 µg. At Month 12, the mean percent change in central CECD was –4.6 for bimatoprost SR 10 µg study eyes and –0.7 for fellow eyes receiving standard of care.

In the last non-missing assessment prior to bimatoprost SR administration (taken as baseline for these eyes), the central CECD values for bimatoprost SR 10 µg-treated fellow eyes ranged from 494.0 to 3141.8 cells/mm2 with a mean (SD) of 2457.4 (414.24) cells/mm2. For bimatoprost SR 10 µg-treated fellow eyes, the mean percent change in central CECD was –3.0 cells/mm2 at Month 12.

Overall, the majority of bimatoprost SR 10 µg study eyes (91.2% [217/238]) and bimatoprost SR 10 µg-treated fellow eyes (96.9% [62/64]) did not have ≥ 15% ECL during the study. ECL of ≥ 15% was observed in 8.8% of bimatoprost SR 10 µg study eyes (21/238) and confirmed in 6.3% (15/238). Analyses were performed overall and by cycle for the first ECL event and for all ECL events.

The first observed ECL ≥ 15% occurred during Cycle 1 for 5.9% of bimatoprost SR 10 µg study eyes (14/237) and during Cycle 2 for 9.4% of bimatoprost SR 10 µg study eyes (6/64). Two subjects with first observed ECL ≥ 15% in Cycle 1 entered into Cycle 2; these subjects were not included in the Cycle 2 calculation of first observed ECL ≥ 15%. Of the fellow eyes receiving standard of care in the bimatoprost SR 10 µg group, 0.9% (2/230) had ≥ 15% ECL. By Month 12 and Month 20, the cumulative probability of first observed ECL ≥ 15% in bimatoprost SR 10 µg study eyes was 5.6% and 14.3%, respectively, and the corresponding first confirmed ECL ≥ 15% was 4.4% and 9.8%, respectively. Overall, of the 21 first observed ≥ 15% ECL events in bimatoprost SR 10 µg study eyes, there were 15 confirmed as of the data cutoff date.

At Month 8, the cumulative probability of first observed ECL ≥ 15% in bimatoprost SR 10 µg-treated fellow eyes was 4.1% and was unchanged through Month 28, which was the last study visit for which there were eyes at risk at the data cutoff date for this report. In bimatoprost SR 10 µg-treated fellow eyes there were 2 observed ≥ 15% ECL events both of which were confirmed.

Reported corneal TEAEs for bimatoprost SR 10 µg study eyes with CECD loss of ≥ 15% were corneal ECL (reported for 7 study eyes), corneal oedema (6 study eyes), corneal disorder (1 study eye), and corneal dystrophy (1 study eye). Of the 3 bimatoprost SR 10 µg study eyes with ≥ 15% ECL and implant removals, all 3 study eyes had TEAEs of corneal oedema and corneal ECL. The TEAEs of corneal oedema resolved in all 3 study eyes. The TEAEs of corneal ECL were ongoing as of the data cutoff date.

One bimatoprost SR 10 µg-treated fellow eye had implant removal and ≥ 15% ECL. TEAEs of corneal oedema and corneal ECL were reported. The event of corneal oedema resolved, and the event of corneal ECL was ongoing as of the data cutoff date. The majority of eyes with ECL ≥ 15% had no clinically meaningful change (> 2 lines from baseline) in visual acuity at the last study visit.

Supportive Studies

Study 192024-041D

Overall, 81.7% of subjects (89/109) had TEAEs, and the percentage was similar across treatment groups. The most common TEAEs were in the SOC of eye disorders. The only nonocular event with ≥ 5% of subjects reporting was nasopharyngitis (7.3% [8/109]).

The overall frequency of ocular TEAEs was greater for the bimatoprost eye (64.0% for all Generation 2 dose strengths) than for the Lumigan eye (48.0%). Similar frequencies of ocular TEAEs were reported across all Generation 2 dose strengths. Common ocular TEAEs in the bimatoprost eye reported for > 10% of Generation 2 subjects were conjunctival hyperaemia, foreign body sensation in eyes, conjunctival haemorrhage, eye pain, lacrimation increased, punctate keratitis, intraocular pressure increased, photophobia, and vision blurred.

TEAEs potentially related to PGA use

The following TEAEs were included: conjunctival hyperaemia, erythema of eyelid, eyelid oedema, growth of eyelashes, iris hyperpigmentation, orbit atrophy, and blepharitis. Of note, conjunctival hyperaemia can be caused by both the bimatoprost SR administration procedure and topical PGA use.

A potential PGA use-related ocular TEAE reported in the immediate post-administration period of each treatment cycle in Generation 2 subjects was conjunctival hyperaemia. Consistent with the expectation that conjunctival hyperaemia due to the administration procedure will usually arise within the immediate post-administration period (i.e., within approximately 2 days of the administration procedure), a higher percentage of conjunctival hyperaemia was reported for the bimatoprost SR eye compared with the Lumigan eye.

Potential PGA use-related ocular TEAEs reported during the study with onset beyond the immediate post-administration period of each treatment cycle included conjunctival hyperaemia, blepharitis, erythema of eyelid, eyelid oedema, iris hyperpigmentation, orbit fat atrophy and growth of eyelashes. In all treatment groups, a higher percentage of potential PGA use-related ocular TEAEs were reported for the Lumigan eye (18.2% to 40.0% of subjects in each group) than in the bimatoprost SR eye (9.1% to 26.7%) beyond the immediate post-administration period of each treatment cycle, suggesting that bimatoprost SR treatment resulted in fewer PGA use-related ocular adverse reactions compared with Lumigan (bimatoprost eyedrops).

Pooled Studies 192024-091 and 192024-092

All TEAEs and Nonocular TEAEs

The most common TEAEs overall were in the SOC of eye disorders and included conjunctival hyperaemia, eye irritation, conjunctival haemorrhage, corneal ECL, eye pain, and foreign body sensation in eyes.

The most frequently reported severe TEAEs were in the SOC of eye disorders and included conjunctival hyperaemia, eye pain, corneal ECL, and photophobia. The most common nonocular TEAEs were nasopharyngitis, hypertension, and headache, all of which were reported with a similar frequency across groups. Headache was the only treatment-related nonocular TEAE reported for ≥ 1% of subjects in any group.

Ocular TEAEs

The most common ocular TEAEs included conjunctival hyperaemia, corneal ECL, foreign body sensation in eyes, eye pain, and eye irritation. Many of these transient ocular surface TEAEs were expected given that a conservative, aseptic preparation procedure for intraocular surgery (including the use of topical povidone-iodine antiseptic) was used. This preparation has the propensity to cause ocular surface irritation and other ocular surface AEs.

Ocular TEAEs with onset or worsening within the first 2 days following the bimatoprost SR/Sham administration procedure (considered the immediate post-administration period), and those arising or worsening beyond the immediate post-administration period were evaluated to distinguish between AEs that were more likely related to the procedure and/or procedure preparation (which would more likely be reported within the first few days post-administration) versus events which were reported over the longer term and more likely to be bimatoprost SR implant-related.

The incidence of conjunctival hyperaemia was higher for bimatoprost SR 15 µg study eyes and bimatoprost SR 10 µg study eyes compared with timolol study eyes and pooled timolol-treated fellow eyes. However, beyond the immediate post-administration period, the incidence of conjunctival hyperaemia was reduced across groups. This reduction in incidence indicates a temporal relationship with the administration procedure.

The most common (> 5% in any study eye group) ocular TEAEs reported within the immediate post-administration period were conjunctival hyperaemia, foreign body sensation in eyes, eye pain, photophobia, eye irritation, punctate keratitis, and conjunctival haemorrhage.

The most common (> 5% in any study eye group) ocular TEAEs reported beyond the immediate post-administration period were conjunctival hyperaemia, corneal ECL, corneal oedema, and intraocular pressure increased. Comparison of the percentage of specific TEAEs in any group within the immediate post-administration period versus beyond that period suggest a temporal relationship between some TEAEs and the study treatment administration procedure. These included conjunctival hyperaemia, foreign body sensation in eyes, eye pain, photophobia, eye irritation, conjunctival haemorrhage, and lacrimation increased, all of which either reduced in frequency or were not reported 2 or more days after study administration. Many of these AEs that were not exclusively reported within the immediate post-administration period are likely to have been related to the procedure preparation and/or the administration procedure, as they are commonly reported with the use of the required procedure materials.

Related TEAEs

The majority of treatment-related TEAEs were ocular, reported under the SOC of eye disorders. Overall, treatment-related ocular TEAEs for the entire study were reported for 60.7% of bimatoprost SR 15 µg study eyes (224/369), 51.3% of bimatoprost SR 10 µg study eyes (191/372), and 20.8% of timolol study eyes (77/370), compared with 20.3% of pooled timolol-treated fellow eyes (226/1111). The most common treatment-related ocular TEAE was conjunctival hyperaemia for all group study eyes and all pooled timolol-treated fellow eyes.

Corneal TEAEs of Special Interest

Overall, at least 1 corneal TEAE of special interest was reported for 26.8% of bimatoprost SR 15 µg study eyes (99/369), 12.1% of bimatoprost SR 10 µg study eyes (45/372), 1.4% of timolol study eyes (5/370); and 1.3% of timolol-treated fellow eyes (14/1111). The most common corneal TEAEs of special interest for ≥ 5% of study eyes in any group were corneal ECL and corneal oedema; the majority of subjects who reported at least 1 corneal TEAE of special interest reported events of mild or moderate severity. All other corneal TEAEs of special interest for the study eye were reported at an incidence of ≤ 2.4% in any group. All corneal TEAEs of special interest for the timolol-treated fellow eye were reported at an incidence of ≤ 0.4%.

Study 192024-091

Table 60: Corneal TEAEs of special interest: Number (%) of patients by system organ class and preferred term (Safety Population)

System Organ Class Preferred Term	Study Eye BimSR 15 ug (N=193) n(%)	Study Eye BimSR 10 ug (N=197) n(%)	Study Eye Tim BID (N=197) n(%)	Fellow Eye All Patients (N=587) n(%)
Entire Study				
Any term	42 (21.8)	23 (11.7)	3 (1.5)	5 (0.9)
Eye disorders	42 (21.8)	23 (11.7)	3 (1.5)	5 (0.9)
Corneal endothelial cell loss	31 (16.1)	17 (8.6)	0	0
Corneal oedema	14 (7.3)	7 (3.6)	2 (1.0)	1 (0.2)
Corneal opacity	6 (3.1)	1 (0.5)	1 (0.5)	2 (0.3)
Corneal touch	3 (1.6)	5 (2.5)	0	0
Corneal disorder	2 (1.0)	2 (1.0)	0	2 (0.3)
Corneal thickening	2 (1.0)	0	1 (0.5)	0
Cycle 1				
n [1]	193	197	197	587
Any term	5 (2.6)	1 (0.5)	0	0
Eye disorders	5 (2.6)	1 (0.5)	0	0
Corneal oedema	2 (1.0)	0	0	0
Corneal endothelial cell loss	1 (0.5)	0	0	0
Corneal opacity	1 (0.5)	0	0	0
Corneal thickening	1 (0.5)	0	0	0
Corneal touch	1 (0.5)	0	0	0
Corneal disorder	0	1 (0.5)	0	0
Cycle 2				
n [1]	172	191	187	550
Any term	11 (6.4)	6 (3.1)	1 (0.5)	3 (0.5)
Eye disorders	11 (6.4)	6 (3.1)	1 (0.5)	3 (0.5)
Corneal endothelial cell loss	6 (3.5)	3 (1.6)	0	0
Corneal oedema	3 (1.7)	3 (1.6)	1 (0.5)	1 (0.2)
Corneal opacity	2 (1.2)	1 (0.5)	0	2 (0.4)
Corneal disorder	2 (1.2)	1 (0.5)	0	0
Corneal touch	1 (0.6)	3 (1.6)	0	0

System Organ Class Preferred Term	Study Eye BimSR 15 ug (N=193) n(%)	Study Eye BimSR 10 ug (N=197) n(%)	Study Eye Tim BID (N=197) n(%)	Fellow Eye All Patients (N=587) n(%)
Cycle 3				
n [1]	158	183	177	518
Any term	17 (10.8)	8 (4.4)	2 (1.1)	2 (0.4)
Eye disorders	17 (10.8)	8 (4.4)	2 (1.1)	2 (0.4)
Corneal endothelial cell loss	11 (7.0)	6 (3.3)	0	0
Corneal oedema	8 (5.1)	3 (1.6)	1 (0.6)	0
Corneal opacity	2 (1.3)	0	1 (0.6)	0
Corneal touch	1 (0.6)	2 (1.1)	0	0
Corneal thickening	1 (0.6)	0	1 (0.6)	0
Corneal disorder	0	0	0	2 (0.4)
Extended Safety Follow-up				
n [1]	152	178	170	500
Any term	15 (9.9)	10 (5.6)	0	0
Eye disorders	15 (9.9)	10 (5.6)	0	0
Corneal endothelial cell loss	14 (9.2)	9 (5.1)	0	0
Corneal oedema	2 (1.3)	1 (0.6)	0	0

AE dictionary: MedDRA Version 22.0
Patients are counted only once within each system organ class and preferred term.
Corneal AEs of interest were identified separately prior to database lock.
Entire Study includes the entire period during which each patient is in the study.
[1] Includes all treated patients in the corresponding study period and is used as the denominator for percentage calculations.
Source: Tables 14.3-5.1.1,14.3-5.1.2, 14.3-5.1.3, 14.3-5.1.4, 14.3-5.1.5

Anterior Segment Inflammation TEAEs of Special Interest

Overall, at least 1 anterior segment inflammation TEAE of special interest was reported for 19.8% of bimatoprost SR 15 µg study eyes (73/369), 13.2% of bimatoprost SR 10 µg study eyes (49/372), 3.2% of timolol study eyes (12/370); and 2.0% of timolol-treated fellow eyes (22/1111). The most common anterior segment inflammation TEAEs of special interest reported for ≥ 5% of study eyes in

any group were iritis and anterior chamber cell; the majority of subjects who reported at least 1 anterior segment inflammation TEAE of special interest in the study eye reported events of mild or moderate severity. All other anterior segment inflammation TEAEs of special interest for the study eye were reported at an incidence of ≤ 2.7% in any group. All anterior segment inflammation TEAEs of special interest for the timolol-treated fellow eye were reported at an incidence of ≤ 0.6%.

Study 1698-304-007

All TEAEs and Nonocular TEAEs

At least 1 TEAE was reported for 71.0% of subjects (22/31) in the bimatoprost SR cohort and 83.3% of subjects (5/6) in the Lumigan cohort. The most frequently reported SOC for either eye was eye disorders (51.6% of subjects [16/31] in the bimatoprost SR cohort and 66.7% of subjects (4/6) in the Lumigan cohort). The most common (≥ 5% of subjects) TEAEs reported for the bimatoprost SR cohort were conjunctival hyperaemia, IOP increased, conjunctival haemorrhage, visual field defect, cataract, dry eye, foreign body sensation in eyes, punctate keratitis, and COVID-19. The only ocular TEAE reported for the Lumigan cohort was conjunctival hyperaemia.

The most common (≥ 5% of subjects) nonocular TEAE was COVID-19, which was reported for 2 subjects (6.5%) in the bimatoprost SR cohort. All other nonocular TEAEs were reported for 1 subject each in any cohort and included TEAEs in the following SOCs: blood and lymphatic system disorders; gastrointestinal disorders; infections and infestations; injury, poisoning, and procedural complications; nervous system disorders; respiratory, thoracic, and mediastinal disorders; and vascular disorders.

Ocular TEAEs

Ocular TEAEs were reported for 61.3% of bimatoprost SR study eyes (19/31). The most common (≥ 5% of study eyes) ocular TEAEs for bimatoprost SR study eyes were conjunctival hyperaemia, IOP increased, conjunctival haemorrhage, foreign body sensation in eye, and punctate keratitis. Ocular TEAEs were reported for 66.7% of Lumigan study eyes (4/6). Conjunctival hyperaemia was the only ocular TEAE reported for the Lumigan study eyes. The incidence of ocular TEAEs for the pooled fellow eyes that received standard of care was 43.2% (16/37). The most common (≥ 5% of fellow eyes) ocular TEAEs reported for the pooled fellow eyes that received standard of care were conjunctival hyperaemia, IOP increased, visual field defect, cataract, and dry eye.

Corneal TEAEs of Special Interest and Anterior Segment Inflammation TEAEs of Special Interest

One subject (3.2% [1/31]) in the bimatoprost SR cohort had a corneal TEAE of special interest (corneal ECL) in the study eye that was nonserious and considered not related to study treatment.

One subject (3.2%) reported 1 TEAE each of anterior chamber cell and anterior chamber flare in the bimatoprost SR study eye.

3.3.7.3. Serious adverse events, deaths, and other significant events

Deaths

Study 192024-093

Two subjects died during the study. Both subjects received SLT in the primary eye and bimatoprost SR 10 µg in the contralateral eye. The first subject had a fatal TEAE of COVID-19 and the other subject had fatal TEAEs of bladder cancer and oesophageal cancer. None of the events was considered to be related to study treatment.

Study 1698-301-007

As of the data cutoff date (29 July 2022), 3 deaths were reported for subjects in the bimatoprost SR 10 µg group (causes of death: sudden death, pancreatic carcinoma, pulmonary embolism) and 1 death was reported for a subject in the bimatoprost SR 15 µg group (causes of death: intestinal perforation and rectal perforation). The events were not considered to be related to study treatment.

Study 192024-041D

One death was reported in for a subject who received bimatoprost SR 15 µg (cause of death: mantle cell lymphoma; Generation 1). The event was not considered to be related to study treatment or procedures.

Study 192024-091

Four deaths were reported: 2 deaths in the bimatoprost SR 15 µg group (causes of death: bowel obstruction and cardiac arrest; cerebrovascular accident), 1 death in the bimatoprost SR 10 µg group (causes of death: femur fracture, hypotension, cardiac failure, renal failure, and acute pulmonary oedema), and 1 death in the timolol group (causes of death: joint instability, fall, and head injury). None of the events were considered related to study treatment or procedures.

Study 192024-092

Two deaths were reported: 1 death in the bimatoprost SR 15 µg group (causes of death: ascites, metastases to liver, metastases to lung, and prostate cancer) and 1 death in the timolol group (cause of death: related to complications of hip fracture). The events were not considered related to study treatment or procedures.

Study 192024-095

No deaths were reported.

Study 1698-304-007

No deaths were reported.

Study 1698-302-007

As of the data cutoff date (15 June 2022), 2 deaths were reported for subjects who had received bimatoprost SR 10 µg during lead-in Study 192024-091 and 1 death was reported for a subject who had received bimatoprost SR 15 µg during lead-in Study 192024-093.

Serious adverse events

Study 192024-093

Nonocular TESAEs

Nonocular TESAEs were reported for 10.0% of subjects in the bimatoprost SR 10 µg-treated safety population. Atrial fibrillation, which was reported for 2 subjects (1.1%), was the only nonocular TESAE that occurred in > 1 subject. None of the nonocular TESAEs were considered related to study treatment.

Ocular TESAEs

Ocular TESAEs were reported for 2.3% of bimatoprost SR 10 µg-treated eyes and no SLT-treated eyes. One subject had a total of 4 ocular TESAEs in the same eye (corneal oedema, corneal thickening, photophobia, and vision blurred); all other eyes (for which a TESAE was reported) had 1 ocular TESAE each. All ocular TESAEs occurred in eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen. For bimatoprost SR 10 µg-treated eyes, the overall frequency of ocular TESAEs was similar

between Cycles 1 (1.1% [2/175]) and 2 (1.6% [2/126]). All ocular TESAEs reported in the bimatoprost SR 10 µg-treated safety population were considered related to study treatment.

Table 61: Ocular TESAEs: Number (%) of treated eyes by SOC and PT – bimatoprost SR 10 µg/SLT (Safety Population)

System Organ Class Preferred Term	SLT (N=180) n (%)	Bim SR 10 ug Flexible (N=86) n (%)	 Fixed (N=89) n (%)	 Total (N=175) n (%)
Any Term	0	0	4 (4.5)	4 (2.3)
Eye disorders	0	0	4 (4.5)	4 (2.3)
Cataract subcapsular	0	0	1 (1.1)	1 (0.6)
Corneal endothelial cell loss	0	0	1 (1.1)	1 (0.6)
Corneal oedema	0	0	1 (1.1)	1 (0.6)
Corneal thickening	0	0	1 (1.1)	1 (0.6)
Episcleritis	0	0	1 (1.1)	1 (0.6)
Photophobia	0	0	1 (1.1)	1 (0.6)
Vision blurred	0	0	1 (1.1)	1 (0.6)

SOC sorted alphabetically. Within each SOC, PTs are sorted by descending incidence in treatment groups from right to left (Total of fixed and flexible combined, fixed, flexible, and SLT).
Cross reference: Table 14.3-3.1.1

Study 1698-301-007

Nonocular TESAEs

Nonocular TESAEs were reported for 11.5% of subjects (36/313) in the bimatoprost SR 10 µg group. Nonocular TESAEs reported for ≥ 2 subjects in the bimatoprost SR 10 µg group were myocardial infarction, coronary artery disease, COVID-19, pneumonia, road traffic accident, hypertension, and cerebrovascular accident. No nonocular TESAE was considered to be treatment-related.

Ocular TESAEs

Ocular TESAEs were reported for 1.3% of bimatoprost SR 10 µg study eyes (4/313). Ocular TESAEs reported for bimatoprost SR 10 µg study eyes were corneal ECL and corneal oedema (reported for 2 eyes each), and cataract and glaucoma (reported for 1 eye each). Of these, the events of corneal ECL and corneal oedema were considered related to treatment, and all but 1 event of corneal ECL led to discontinuation of study drug.

The incidence of ocular TESAEs for bimatoprost SR 10 µg study eyes was 0.3% (1/313) during Cycle 1 and 3.1% (3/96) during Cycle 2. Of these, in Cycle 1, corneal oedema and corneal ECL were reported for 1 study eye; and in Cycle 2, corneal oedema was reported in 1 study eye, corneal ECL was reported in 1 study eye and cataract and glaucoma were reported for 1 study eye. One ocular TESAE (corneal ECL) was reported for a bimatoprost SR 10 µg-treated fellow eye (1/92). This ocular TESAE was reported in a subject who also had an ocular TESAE of corneal ECL in the bimatoprost SR 10 µg study eye. The event was considered related to study treatment and the implants were removed from both eyes. There were no ocular TESAEs reported for fellow eyes receiving standard of care in the bimatoprost SR 10 µg group.

Table 62: Ocular TESAEs: Number (%) of subjects by system organ class and preferred term – overall (Safety Analysis Set) – study 1698-301-007

System Organ Class Preferred Term	Bim SR 10ug SE (N=313) n (%)	FE [1] (N=313) n (%)
Subjects with at least one TESAE	4 (1.3)	0
Eye disorders	4 (1.3)	0
Corneal endothelial cell loss	2 (0.6)	0
Corneal oedema	2 (0.6)	0
Cataract	1 (0.3)	0
Glaucoma	1 (0.3)	0

[1] Includes data for events occurring prior to FE being treated with Bim SR or FE never treated with Bim SR.

Note: Adverse event terms are coded using the MedDRA version 25.0.
Table presents data from the Bimatoprost SR 10 µg group only.

Cross reference: Study 1698-301-007 Interim 1 CSR Table 14.3-6.1

Study 192024-041D

19 subjects (17.4%) had TESAEs. Each TESAE PT was reported for only 1 subject. The only ocular TESAE was retinal detachment reported for a Lumigan eye. No TESAEs were considered related to study treatment.

Pooled Studies 192024-091 and 192024-092

Nonocular TESAEs

In the Pooled Studies 192024-091 and 192024-092, nonocular TESAEs were reported for 12.5% of subjects (46/369) in the bimatoprost SR 15 µg group, 9.1% of subjects (34/372) in the bimatoprost SR 10 µg group, and 8.9% of subjects (33/370) in the timolol group. The majority of nonocular TESAEs were reported for 1 subject each in any group. Overall, incidence of nonocular TESAEs was similar across groups.

Ocular TESAEs

Ocular TESAEs of corneal ECL and corneal oedema were reported at a higher incidence for bimatoprost SR 15 µg study eyes compared with bimatoprost SR 10 µg study eyes. All other ocular TESAE PTs were reported for 1 study eye each in any group. Retinal tear was the only ocular TESAE reported for a timolol-treated fellow eye.

Study 1698-304-007

One subject in the bimatoprost SR cohort had a nonocular TESAE of COVID-19 that was considered not related to study treatment. No ocular TESAEs were reported during the study.

Ocular TEAEs Resulting in Implant Removal

Study 192024-093

Implants were removed using the recommended anterior chamber washout procedure as needed. Ocular TEAEs leading to implant removal were reported for 2.3% of bimatoprost SR 10 µg-treated eyes (4/175). One eye had 4 TEAEs leading to implant removal, 2 eyes had 2 TEAEs leading to implant removal each, and 1 eye had 1 TEAE leading to implant removal. The majority of ocular TEAEs leading to implant removal were corneal events. Corneal ECL and corneal oedema were the ocular TEAEs leading to implant removal that occurred in > 1 bimatoprost SR 10 µg-treated eye. Ocular TEAEs leading to implant removal were reported for 1.2% of eyes (1/86) treated on the flexible bimatoprost SR 10 µg re-administration regimen compared with 3.4% of eyes (3/89) treated on the fixed bimatoprost SR 10 µg re-administration regimen.

All ocular TEAEs leading to implant removal were considered related to study treatment and 6 out of 9 events occurred in Cycle 1; during Cycle 2, 1 event of corneal oedema and iritis was reported for 1 bimatoprost SR 10 µg-treated eye each, and 1 event of corneal ECL was reported for another bimatoprost SR 10 µg-treated eye. The majority of TEAEs leading to implant removal resolved by the end of the study.

Study 1698-301-007

Ocular TEAEs leading to implant removal occurred for 1.6% of bimatoprost SR 10 µg study eyes (5/313) and 1.1% of bimatoprost SR 10 µg-treated fellow eyes (1/92). Events leading to implant removal in 4 bimatoprost SR 10 µg study eyes were corneal TEAEs (corneal oedema and corneal ECL), and 1 bimatoprost SR 10 µg study eye had a TEAE of medical device removal, in which the bimatoprost SR implant was released into the corneal tissue during the administration procedure, prompting implant removal. All ocular TEAEs leading to implant removal were considered related to study treatment.

The incidence of ocular TEAEs leading to implant removal for bimatoprost SR 10 µg study eyes was 1.0% (3/313) during Cycle 1 and 2.1% (2/96) during Cycle 2 (Study 1698-301-007 Interim 1 CSR Table 14.3-8.2); in Cycle 1, corneal oedema was reported in 2 study eyes and medical device removal was reported in 1 study eye; and in Cycle 2, corneal ECL and corneal oedema were reported in 1 study eye each. As of the data cutoff date, 4 of the 6 ocular TEAEs leading to implant removal had

resolved (1 with sequelae). The 2 ongoing events (corneal ECL) were reported for the same subject (1 event each in the bimatoprost SR 10 µg study eye and bimatoprost SR 10 µg-treated fellow eye).

Pooled Studies 192024-091 and 192024-092

Overall, at least 1 ocular TEAE leading to implant removal was reported for 9.5% of bimatoprost SR 15 µg study eyes (35/369) and 3.2% of bimatoprost SR 10 µg study eyes (12/372). The most common ocular TEAEs (≥ 0.5% of study eyes) leading to implant removal were corneal ECL, corneal oedema, corneal touch, conjunctival hyperaemia, corneal abrasion, and product administered at inappropriate site. All other ocular TEAEs leading to implant removal were reported for 1 study eye (0.3%) per treatment group.

Study 1698-304-007

No subject experienced an ocular AE that required implant removal.

3.3.7.4. Laboratory findings

Postbaseline laboratory assessments were only analysed for Study 192024-041D.

In Study 192024-041D, shifts in laboratory parameters were infrequent. The only shifts from normal to low or high in more than 1 subject per treatment group were glucose (1 to 4 subjects per group), creatine kinase (0 to 3 subjects per group), calcium (0 to 2 subjects per group), cholesterol (0 to 2 subjects per group), urea/creatinine (0 to 2 subjects per group), neutrophils (0 to 2 subjects per group), lymphocytes (0 to 2 subjects per group), and reticulocytes/erythrocytes (0 to 2 subjects per group).

Vital signs

Vital signs were collected but not analysed for most of the studies. Analyses of vital signs were limited to the pooled Phase 3 Studies 192024-091 and 192024-092 and the Phase 1/2 Study 192024-041D.

Pooled Studies 192024-091 and 192024-092

Changes from baseline in vital signs were small and similar across groups. Mean changes from baseline in systolic blood pressure ranged from −3.5 to 2.0 mmHg. Mean changes from baseline in diastolic blood pressure ranged from −2.1 to 0.5 mmHg. Mean changes from baseline in body temperature ranged from −0.091 to 0.038°C. Mean changes from baseline in pulse rate ranged from −2.9 to 1.8 bpm.

Study 192024-041D

Changes from baseline in vital signs were small and similar across groups. Mean changes from baseline in systolic blood pressure were ≤ 11.5 mmHg. Mean changes from baseline in diastolic blood pressure were ≤ 10.0 mmHg. Mean changes from baseline in body temperature were ≤ 11.3°C. Mean changes from baseline in pulse rate were ≤ 10.0 bpm. Mean changes from baseline in respiratory rate were ≤ 7.3 resp/min.

Ophthalmic examinations

Specular Microscopy

Please, see information included under "Corneal endothelial loss" above.

Implant assessment

The size of the bimatoprost SR implant was evaluated over time relative to the original implant size by gonioscopy

Study 192024-093 and Study 1698-301-007: The bimatoprost SR 10 µg implants appeared to degrade in 2 stages through Week 52:

- During the first stage (approximately Weeks 4 through 31), the implant generally remained close to its original size (± 25%). Some implants would swell, which is expected.
- During the second stage (after Month 8) a more rapid degradation occurred, with the majority of implants decreasing to ≤ 25% of their original size by Month 12.

Pooled Studies 091-092: Overall, 96.2% of bimatoprost SR 15 µg study eyes and 97.9% of bimatoprost SR 10 µg study eyes had visible implants (implants administered during Cycles 1, 2, and 3) at Week 52. At the Month 20/Exit visit, the percentage of bimatoprost SR study eyes with visible implants decreased to 86.6% for the bimatoprost SR 15 µg study eyes and 87.4% for the bimatoprost SR 10 µg study eyes.

Overall, 31.4% of bimatoprost SR 15 µg study eyes (116/369) and 22.9% of bimatoprost SR 10 µg study eyes (85/371) had implant contact with the corneal endothelium. By the extended safety follow-up, implant contact with the corneal endothelium had decreased to 7.4% of bimatoprost SR 15 µg study eyes (21/284) and 5.3% of bimatoprost SR 10 µg study eyes (17/322).

Best-corrected Visual Acuity

Study 192024-093: The percentage of eyes with worsening BCVA (more than 2-line decrease from baseline) was higher for bimatoprost SR 10 µg-treated eyes (10.3% [18/175]) than for SLT-treated eyes (5.6% [10/179]). For both bimatoprost SR 10 µg-treated eyes and SLT-treated eyes, results were overall consistent by cycle and across timepoints.

Study 1698-301-007: The majority of bimatoprost SR 10 µg study eyes (95.2% [298/313]) and bimatoprost SR 10 µg-treated fellow eyes (96.7% [89/92]) had no change (defined as > 2 lines improvement or worsening) from baseline in BCVA. For fellow eyes receiving standard of care in the bimatoprost SR 10 µg group, 97.1% (304/313) had no change from baseline in BCVA.

Pooled Studies 093-095-301-007:

- Analysis Set 1: Worsening of BCVA from baseline (loss of > 2 lines) in Cycle 1 and Cycle 2 was slightly higher for bimatoprost SR 10 µg-treated eyes (4.1% [20/488] and 6.3% [14/222]) compared with SLT-treated eyes (2.7% [10/375] and 3.6% [11/302]). Worsening of BCVA occurred at a slightly lower incidence in Cycle 1 and Cycle 2 for eyes treated on the flexible/PRN bimatoprost SR 10 µg re-administration regimen (3.8% [15/399] and 5.3% [8/152]) compared with eyes treated on the fixed bimatoprost SR 10 µg re-administration regimen (5.6% [5/89] and 8.6% [6/70]).
- Analysis Set 2: Worsening of BCVA from baseline (loss of > 2 lines) was slightly higher for bimatoprost SR 10 µg-treated eyes (6.3% [14/222]) compared with SLT-treated eyes (3.6% [11/302]) in Cycle 2, while the incidence was similar between the groups in Cycle 1.

  Worsening of BCVA occurred at a slightly lower incidence for eyes treated on the flexible/PRN regimen (5.3% [8/152]) compared with fixed regimen (8.6% [6/70]) in Cycle 2, while the opposite pattern was observed in Cycle 1.

Pooled Studies 091-092: Overall, 86.2% of bimatoprost SR 15 µg study eyes (318/369), 91.9% of bimatoprost SR 10 µg study eyes (342/372), and 95.7% of timolol study eyes (354/370) had no change in BCVA. No change in BCVA was seen in 93.9% of timolol-treated fellow eyes (1043/1111). In Cycle 3, 5.2% of bimatoprost SR 15 µg study eyes (16/305) reported more than a +2-line decrease, compared with 1.8% of bimatoprost SR 10 µg study eyes (6/339), 2.1% of timolol study eyes (7/336), and 2.3% of pooled timolol-treated fellow eyes (23/980).

Visual Field

Study 192024-093: Abnormal visual field findings, including enlargement of blind spot, superior arcuate scotoma, paracentral scotoma, nasal step, central scotoma, generalized depression, or temporal scotoma, were generally consistent between bimatoprost SR 10 µg-treated eyes and SLT-treated eyes overall and by cycle. Inferior arcuate scotoma was reported for a higher percentage of SLT-treated eyes than bimatoprost SR 10 µg-treated eyes (6.8% [12/176] versus 1.7% [3/173]).

Study 1698-301-007: The most frequently reported abnormal visual findings (≥ 5%) were superior arcuate scotoma and nasal step for bimatoprost SR 10 µg study eyes and enlargement of blind spot, superior arcuate scotoma, inferior arcuate scotoma, paracentral scotoma, nasal step, and generalized depression for bimatoprost SR 10 µg-treated fellow eyes. The most frequently reported abnormal visual findings (≥ 5%) were enlargement of blind spot, superior arcuate scotoma, nasal step, and generalized depression for fellow eyes receiving standard of care in the bimatoprost SR 10 µg group.

Pooled Studies 093-095-301-007:

Analysis Set 1: Abnormal visual field findings arising postbaseline were generally similar across bimatoprost SR 10 µg-treated eyes and SLT-treated eyes, both overall and during Cycles 1 and 2 individually. Abnormal visual field findings were generally similar between eyes treated on either the flexible/PRN bimatoprost SR 10 µg re-administration regimen or the fixed bimatoprost SR 10 µg re-administration regimen. Abnormal visual field findings arising postbaseline for fellow eyes receiving standard of care were infrequent.

Analysis Set 2: Similar findings to those described above.

Pooled Studies 091-092: Overall, abnormal visual field findings in the study eye were generally consistent between groups and across cycles. Findings between the study eyes and pooled timolol-treated fellow eyes were also comparable.

Macroscopic Conjunctival Hyperaemia Assessment

Study 192024-093: A 2-grade or greater increase in severity from baseline in macroscopic conjunctival hyperaemia was reported for 23.4% of bimatoprost SR 10 µg-treated eyes and 10.6% of SLT-treated eyes.

Study 1698-301-007: A 2-grade or greater increase in severity from baseline was reported for 17.6% of bimatoprost SR 10 µg study eyes and 3.5% of fellow eyes receiving standard of care (11/313) in the bimatoprost SR 10 µg group.

Pooled Studies 093-095-301-007:

Analysis Set 1: 20.1% of bimatoprost SR 10 µg; 8.5% of SLT; 4.3% fellow eyes receiving standard of care.

Analysis Set 2: 23.4% of bimatoprost SR 10 µg; 8.5% of SLT; 4.0% fellow eyes receiving standard of care.

Pooled Studies 091-092: > 1 grade increase from baseline was reported for 36.0% of bimatoprost SR 15 µg study eyes, 30.6% of bimatoprost SR 10 µg study eyes, and 10.5% of timolol study eyes.

Biomicroscopy and Ophthalmoscopy

Study 192024-093: The most frequently reported (≥ 10.0% of eyes) biomicroscopy findings with a 2-grade or greater increase from baseline were conjunctival hyperaemia and corneal staining for bimatoprost SR 10 µg-treated eyes and corneal staining for SLT-treated eyes. For both, conjunctival hyperaemia was reported with a similar frequency between cycles, whereas corneal staining was more frequently reported during Cycle 1 than Cycle 2.

Study 1698-301-007: The most frequently reported (≥ 10%) biomicroscopy finding with a 2-grade or greater increase from baseline for bimatoprost SR 10 µg study eyes was conjunctival hyperaemia and the incidence was generally consistent across cycles. No unexpected observations were made for bimatoprost SR 10 µg-treated fellow eyes.

Pooled Studies 093-095-301-007:

Analysis Set 1: The most frequently reported (≥ 5.0% of eyes) biomicroscopy findings with a 2-grade or greater increase from baseline were conjunctival hyperaemia and vital dye staining cornea present for both bimatoprost SR 10 µg-treated eyes and SLT-treated eyes; additionally, anterior chamber cell met this threshold for SLT-treated eyes.

Analysis Set 2: The most frequently reported (≥ 5.0% of eyes) biomicroscopy findings with a 2-grade or greater increase from baseline were conjunctival hyperaemia and vital dye staining cornea present for both bimatoprost SR 10 µg-treated eyes and SLT-treated eyes; additionally, anterior chamber cell met this threshold for SLT-treated eyes.

Pooled Studies 091-092: At any cycle, > 1 grade increase in examination findings from baseline was reported for 56.4% of bimatoprost SR 15 µg study eyes (208/369), 47.3% of bimatoprost SR 10 µg study eyes (176/372), and 31.9% of timolol study eyes (118/370).

Lens Opacity

No clinically meaningful trends in lens opacity were observed.

Cup/Disc Ratio

The majority of both bimatoprost SR 10 µg-treated eyes or bimatoprost SR 10 µg-treated eyes in the studies had no change in cup/disc ratio.

Corneal Thickness

No clinically meaningful changes in CCT were reported in the patients included in the studies.

3.3.7.5. In vitro biomarker test for patient selection for safety

N/A

3.3.7.6. Safety in special populations

Intrinsic Factors

Subgroup analyses (age, sex, race) were performed for the pooled Phase 3 (192024-093/192024-095) and Phase 3b (1698-301-007) studies and for the pooled Phase 3 (192024-091/192024-092) studies. Subgroup analyses were also performed to assess the safety of bimatoprost SR among subjects with OHT versus subjects with OAG diagnosis. Subgroup analyses of Shaffer grade and lens status were performed for the pooled Phase 3 (192024-093/192024-095) and Phase 3b (1698-301-007) studies and the individual Studies 192024-093 and 1698-301-007.

Pooled Studies 192024-093, 192024-095, and 1698-301-007

Subgroup analyses were performed for all TEAEs, ocular TEAEs, ocular TESAEs, and ocular TEAEs leading to study discontinuation. The following subgroups were analysed: age group (< 45 years, ≥ 45 to ≤ 65 years, > 65 years), sex (male or female), and race (white, Asian, black or African American, or other).

For Analysis Set 1, reports of TEAEs, ocular TEAEs, ocular TESAEs, and ocular TEAEs leading to study discontinuation within each treatment group were overall consistent across age, sex and race subgroups. Within each treatment group, no PTs beyond those commonly reported for the pooled safety population overall emerged as particularly common or clinically meaningful in any age subgroup. Similar results were observed for Analysis Set 2.

Subgroup analyses by diagnosis (OHT or OAG) were performed on Analysis Set 1 (10 µg data) only.

Pooled Studies 192024-093, 192024-095, and 1698-301-007 enrolled mostly eyes diagnosed with OAG compared to OHT (~80% vs ~20% respectively). Reports of ocular TEAEs were higher in eyes with OHT versus OAG within each treatment group. For all eyes treated with bimatoprost SR 10 µg, 50.9% (199/391) experienced an ocular TEAE in eyes with OAG versus 56.7% (55/97) in eyes with OHT. Preferred terms of corneal oedema and corneal ECL were more frequently reported in eyes with OHT versus those with OAG.

With respect to CECD and rates of ECL, a higher percentage of bimatoprost SR 10 µg treated eyes diagnosed with OHT had ECL ≥ 15% (12.7%) compared with eyes diagnosed with OAG (7.5%). The first observed ≥ 15% ECL incidence was 7.5% for bimatoprost SR 10 µg-treated eyes with OAG and 12.7% for bimatoprost SR 10 µg treated eyes with OHT. The first observed exposure-adjusted (per 100 person-years) ≥ 15% ECL rate was 6.63 for bimatoprost SR 10 µg-treated eyes with OAG and 10.79 for bimatoprost SR 10 µg-treated eyes with OHT.

While rates of ocular TEAEs and ECL were higher in eyes with OHT, the analyses did not reveal any clinical explanation for this difference. Given the small sample size of OHT included in the analyses, no conclusive statement can be made regarding the safety profile of bimatoprost SR 10 µg in eyes with OHT versus OAG. The OAG and OHT subgroups were further analysed for ECL ≥ 15% based on Shaffer grade and lens status. The incidence of ECL ≥ 15% was higher for bimatoprost SR 10µg treated eyes with OAG assessed as Shaffer Grade 3 compared to Grade 4 in Study 192024-093 (12.1% [7/58] vs 3.9% [3/77]) and bimatoprost SR 10 µg study eyes with OAG assessed as Shaffer Grade 3 compared

to Grade 4 in Study 1698-301-007 (13.8% [12/87] vs 2.7% [3/111]). Shaffer grade did not appear to be an ECL risk factor for subjects with OHT, though sample sizes were small.

MedDRA Terms	**Age <65** **number (percentage)**	**Age 65-74** **number (percentage)**	**Age 75-84** **number (percentage)**	**Age 85+** **number (percentage)**
Total AEs				
Serious AEs – Total				
- Fatal				
- Hospitalisation/prolong existing hospitalisation				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

3.3.7.7. Immunological events

N/A

3.3.7.8. Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been performed.

3.3.7.9. Discontinuation due to adverse events

Study 192024-093

Nonocular TEAEs

Nonocular TEAEs that led to study discontinuation were reported for 2.2% of subjects in the bimatoprost SR 10 µg-treated safety population. None of the nonocular TEAEs that led to study discontinuation were considered related to study treatment.

Ocular TEAEs

No ocular TEAEs in the bimatoprost SR 10 µg-treated safety population led to study discontinuation.

Study 1698-301-007

Nonocular TEAEs

Nonocular TEAEs leading to study discontinuation were reported for 1.3% of subjects (4/313) in the bimatoprost SR 10 µg group. Nonocular TEAEs leading to study discontinuation were each reported for only 1 subject and were not considered to be related to study treatment.

Ocular TEAEs

The incidence of ocular TEAEs leading to study discontinuation was low for bimatoprost SR 10 µg study eyes (0.6% [2/313]). Ocular TEAEs leading to study discontinuation were IOP increased and corneal oedema for bimatoprost SR 10 µg study eyes and were both considered related to study treatment. No ocular TEAEs leading to study discontinuation were reported for bimatoprost SR 10 µg-treated fellow eyes.

All ocular TEAEs leading to study discontinuation for the bimatoprost SR 10 µg study eyes were reported during Cycle 1. There were no ocular TEAEs leading to study discontinuation reported for fellow eyes receiving standard of care in the bimatoprost SR 10 µg group.

Pooled Studies 192024-091 and 192024-092

Nonocular TEAEs

Overall, 1.6% of subjects (6/369) in the bimatoprost SR 15 µg group, 1.1% of subjects (4/372) in the bimatoprost SR 10 µg group, and 1.4% of subjects (5/370) in the timolol group reported at least 1 nonocular TEAE leading to study discontinuation. All nonocular TEAEs leading to study discontinuation were reported at an incidence of ≤ 0.3% in any group.

Ocular TEAEs

Overall, at least 1 ocular TEAE leading to study discontinuation was reported for 5.7% of bimatoprost SR 15 µg study eyes (21/369), 1.9% of bimatoprost SR 10 µg study eyes (7/372), and 0.8% of timolol study eyes (3/370); and 0.5% of timolol-treated fellow eyes (5/1111). All ocular TEAEs leading to study discontinuation were reported at an incidence of ≤ 1.6% in any group.

Study 1698-304-007

No subject discontinued the study due to a TEAE.

3.3.7.10. Post marketing experience

The first regulatory approval for Durysta was in the US on 04 March 2020; this date is the International Birth Date (IBD). No safety-related changes to the USPI (the safety reference information for Durysta) were made since the initial approval. There were no safety signals identified or closed

during the reporting interval. No new and significant safety findings concerning Durysta were identified in the scientific literature during the reporting interval. During the reporting interval there were 260 case reports received for Durysta from postmarketing sources. Fifty-six cases were serious, of which 54 were medically confirmed and 2 were consumer reported, and 204 cases were nonserious, of which 190 were medically confirmed and 14 were consumer reported. The most commonly reported events in postmarketing for Durysta (top 5) were IOP increased (44 cases), corneal oedema (29 cases), complication of device insertion (29 cases), product administered at inappropriate site (25 cases), and device malfunction (18 cases). The most frequently reported adverse events for Durysta were consistent with the known safety profile of the product and are listed in the Durysta USPI.

3.3.8. Discussion on clinical safety

The safety profile of Durysta was evaluated in 9 clinical studies. No overall pooled safety data were available at submission, due to differences in study design, dose and comparator. A pooled summary of safety data for all studies conducted with the intended dose and patient population, irrespective of unsuitability for topical medication, was provided upon request. The main safety data in the intended indication OAG or OHT not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy derive from the ongoing pivotal phase 3 study 192024-093 where 10µg bimatoprost were evaluated and SLT was used as a comparator. Two other studies including an ongoing phase 3b study 1698-301-007 with no comparator and a phase 3 study 192024-095 where only the 15µg dose bimatoprost was used are available. A pooled analysis from phase 3 Studies 192024-093, 192024-095, and Phase 3b study 1698-301-007 is also provided with 2 different analysis sets based on frequency of bimatoprost administration. Pooled data are further available from Phase 3 Studies 192024-091 and 192024-092 where the indication was OAG/OHT and the comparator timolol. Data from phase 1/2 Study 192024-041D in patients with OAG and topical Lumigan (bimatoprost) and phase 3b Study 1698-304-007 in patients with OAG/OHT with no comparator are provided separately. Safety data from the extension study 1698-302-007 (evaluating safety of bimatoprost in subjects who completed 1 of the 4 Phase 3 studies 192024-091, 192024-092, 192024-093, or 192024-095) were provided with a data-cutoff 15-June-2022 in the initial submission. Additional data, including summary tables, follow-up duration, and number of implants were provided with D121 responses.

At submission, the evaluation of safety on eCRFs as well as methods to evaluate ocular safety in the clinical programme were generally considered appropriate and the presentation of safety data was sufficient to allow an assessment. However, for the ongoing studies only AE listings and summaries from the ISS were available and no final CSR with separate analysis of results per study. These data were requested also with regard to the missing 12-month follow up data from studies 192024-093 (which was completed since submission) and 1698-301-007. From the data provided with responses, several follow-up OCs were raised.

Considering the proposed posology, where treatment of a chronic disease is foreseen, data from retreatment as well as long-term safety data were limited. This was seen as a major concern, especially since from the provided analyses, safety signals seemed to increase with repeated use and the safety of the implant remaining in the eye was still of concern. Consequently, two Safety MOs were raised: in one MO additional information on the increased frequencies of endothelial cell loss from Durysta 10µg treated eyes were requested. In a second MO the applicant was asked to elaborate on possible long-term safety, especially with regard to the limited biodegradability of the implant. Briefly, the raised safety MOs could not be resolved after responses. A third MO regarding unacceptability of repeat dosing is raised. This is further discussed below.

Exposure

In the clinical programme about 1435 eyes received at least one dose of 10µg bimatoprost, whereof 156 were re-administrations in study 1698-302-007. While the overall number of subjects who received any bimatoprost dose in the clinical programme could be considered adequate, after completion of study 192024-093, only 616 eyes received at least 1 implant of 10µg bimatoprost and 305 received at least 2 implants 10µg bimatoprost in study 192024-093 and 1698-301-007 in the planned indication. Only 180 eyes had at least 12 month follow up after 2 implants, thereof 78 from pivotal study 093. In the 2 phase 3 studies 192024-091 and 192024-092 372 participants received bimatoprost 10µg and 369 received bimatoprost 15µg. The limited amount of long-term safety data raised concerns. With responses, the applicant provided additional information on available data from eyes with 12 month follow up from studies 192024-093 and 1698-301-007. Taking only eyes into account that received 1 implant in total, >1 year follow-up data were available for a total of 189 eyes from both studies combined. Taking only eyes into account that received 2 implants in total on either a fixed or PRN regimen, at least 1 year follow-up data were available for 209 from both studies combined.

Demographic and baseline data

Demographic and baseline characteristics of the study population are in general comparable between the treatment groups in the respective studies. In study 192024-093 the majority of subjects were female (51.4%), white (69.4), and non-Hispanic (91.3%). Similar demographic data are observed for the other studies. About ~96.7% of eyes randomized to bimatoprost 10µg and SLT in study 192024-093 received concomitant ophthalmic medications. The use of these medication was mostly linked to the SLT or BimSR administration procedure, as outlined in the protocol, and overall balanced between treatments, except for carbonic anhydrase inhibitors (see above section) and corticosteroids. More BimSR treated eyes received corticosteroids with respect to SLT treatment (15/183 (8.2%) and 3/183 (1.6%), respectively). Observed imbalances could be explained due to protocol-defined administration procedures (BimSR vs SLT) and that certain indication for corticosteroid use were reported more frequently as TEAE in BimSR eyes (e.g. photophobia, anterior chamber cell, iritis).

Nonocular TEAEs

In study **192024-093 59.4%** of subjects experienced nonocular TEAEs, with Covid-19, headache and hypertension as the most commonly reported AEs (≥5%). Also in study **1698-301-007 45.4%** of subjects experienced nonocular TEAEs, with Covid-19 and hypertension as the most commonly reported AEs (≥5%). While headache is included in section 4.8 of the SmPC, other nonocular AEs with a lower frequency than 5% were not included. On request, the applicant analysed additional non-ocular AEs for inclusion into the SmPC. Based on this evaluation, headache was added to the SmPC.

Ocular TEAEs

In study **192024-093** the frequency of ocular TEAEs on the **fixed bimatoprost SR 10 µg** re-administration regimen (**74.2%**) was **higher** than on the **flexible bimatoprost SR 10 µg** re-administration regimen (**66.3%**) and **SLT-treated eyes** (**63.3%**). The most common TEAEs for bimatoprost SR 10 µg-treated eyes on flexible and fixed regimen were conjunctival hyperaemia (18.6% and 21.3%), dry eye (10.5% and 18.0%), punctate keratitis (11.6% and 12.4%) and IOP increased (19.8% and 29.2%); and dry eye (12.2%), punctate keratitis (10.6%), conjunctival hyperaemia (12.2%), and IOP increased (18.3%) for SLT-treated eyes. Photophobia was also under the most commonly reported (11.6%) on the flexible bimatoprost SR 10 µg re-administration regimen. The AE of conjunctival hyperaemia reported in the 2-day post-administration period is associated with the implant procedure preparation.. While conjunctival hyperaemia and dry eyes events reported beyond these 2 days are likely related to the injection procedure, the increase of intraocular pressure

reported is attributed by the applicant to loss of efficacy of the implant. Admitting that it could be possible, the incidence of increase of intraocular pressure is rather irregular along the cycles, not clearly suggesting a gradual loss of efficacy. However, the small numbers preclude from achieving any sound conclusion.

Ocular TEAEs were also reported at a **greater frequency in Cycle 2 (61.9%)** than Cycle 1 **(50.3%)** for bimatoprost SR 10 µg-treated eyes, while in the SLT treated eyes frequency of TEAEs between cycle 1 **(45.0%)** and cycle 2 **(44.4%)** was similar except for anterior chamber cell, which was more frequent in the 1st cycle.

The frequency of **ECL in cycle 1** was **similar** between the **bimatoprost (1.7%)** and **SLT (2.2%)** treatment group. In **cycle 2** the frequency of **ECL** was **higher** in the **bimatoprost (7.1%)** compared to **SLT (1.6%)** treatment group. The frequency of ECL in cycle 2 was even higher in the flexible regimen (8.9%) compared to fixed regimen (5.7%).

It is noted that for ocular TEAE frequencies reported analysed by treatment cycle, some uncertainties are raised regarding interpretability of the available data. Since evaluable cycle length depends on the duration before retreatment, a longer follow up is available for the flexible treatment regimen than for the fixed regimen. Therefore, for reported incidences of delayed-onset TEAEs (e.g. corneal ECL), bias due to carry-over into the second treatment cycle, leading to erroneous assignment of these events to the second cycle, is considered likely.

Incidence of **ocular TEAEs** was **higher in eyes with OHT versus OAG** within each treatment group.

In study **1698-301-007**, 50.8% of Subjects treated with bimatoprost SR 10µg had at least one TEAE. The most commonly reported ocular TEAE for bimatoprost SR study eye was conjunctival hyperaemia (17.5%). Other frequent AEs were increased IOP (13.4%), dry eye (6.3%) and corneal endothelial cell loss (7.0%). Compared to this, lower frequencies for ocular TEAEs were reported for the fellow eye treated with standard of care, for which 21.3% reported at least one TEAE. For the fellow eye, the most commonly reported ocular TEAEs was conjunctival hyperaemia (5.0%) and dry eye (2.3%). Notably, increased IOP was reported from only 2.5% and corneal endothelial cell loss from only 0.7%.. Ocular TEAEs in study eyes were reported **more frequently in cycle 2 (46.9%)** compared to **cycle 1 (42.2%)**. 28.6% of study eyes reported at least 1 related ocular AE, with conjunctival hyperaemia as the most common (12.2%).

For the **pooled studies 192024-091** and **192024-092** the overall safety data for 10µg bimatoprost are comparable to data observed in study 192024-093 and study 1698-301-007.

Also the AE profiles of the supportive studies **192024-041D** and **1698-304-007** mainly resemble the safety profile observed in study 192024-093. In study 192024-041D the AEs were in general more frequent in the bimatoprost group (64%) compared to the Lumigan group (48%).

Related TEAEs

The Incidence of **treatment-related** ocular TEAEs was **higher for bimatoprost SR 10 µg-treated eyes (40.0%)** compared with SLT-treated eyes **(22.8%)** in study **192024-093**. In the **fixed** re-administration regimen the frequency was higher **(50.6%)** compared to the flexible re-administration regimen (**29.1%**). In **cycle 2** the frequency of treatment-related ocular TEAEs in bimatoprost SR 10 µg-treated eyes was **higher (31.7%)** compared to cycle 1 **(26.9%)**. In SLT-treated eyes, the frequency of treatment-related ocular TEAEs was greater in Cycle 1 (19.4%) than Cycle 2 (7.1%). In study **1698-301-007** the frequency of related AE was slightly higher in cycle 1 (23.8%) compared to cycle 2 (19.6%).

Anterior segment inflammatory TEAEs of special interest

In study **192024-093** the most common **anterior segment inflammatory TEAEs of special interest** were **anterior chamber cell** and **iritis** for bimatoprost group and anterior chamber cell for SLT group. Most events were mild or moderate in severity and of transient duration. In cycle 1 the frequency was lower in the bimatoprost group (1.7%) compared to SLT (5.6%), whereas in **cycle 2 the frequency was higher** in the bimatoprost group (7.9%) vs SLT group (0.8%).

In study **1698-301-007** the most common anterior segment inflammation TEAEs of special interest were anterior chamber cell, iritis, and iris adhesions for bimatoprost study eyes with the majority considered as related. The frequency was slightly higher in cycle 1 (3.6%) compared to cycle 2 (4.5%).

Corneal TEAEs of special interest

In study **192024-093** the frequency of TEAEs of **special interest** was **higher in the bimatoprost SR 10 µg-treated eyes** than SLT-treated and also **higher in cycle 2**. The most common corneal TEAEs of special interest reported were **corneal endothelial cell loss (ECL)** and **corneal oedema**.

Most cases were mild or moderate in severity and most in the bimatoprost group were considered related to study treatment. The majority of corneal oedema events resolved at the data cutoff date. In cycle 1 the overall frequency of corneal TEAEs of special interest was similar between bimatoprost (2.9%) and SLT treated eyes (2.8%), however in the fixed bimatoprost regimen the frequency was higher (3.4%) to the flexible regimen (2.3%). In **cycle 2** the frequency was **higher** in the bimatoprost group (10.3%) compared to the SLT group (3.2%). Higher frequencies were reported from the flexible (12.5%) compared to the fixed regimen (8.6%).

*Corneal endothelial cell loss (ECL)*Although there is a limited capacity of wound healing of the endothelium occurring by cell enlargement and migration of peripheral corneal endothelium, the corneal endothelial cell layer does not regenerate per se, and corneal endothelial cell loss is considered mostly irreversible. The corneal endothelium plays a critical role in regulating corneal hydration and is therefore necessary for the maintenance of corneal transparency. Therefore, preservation of endothelial cell density is considered most important for patients with chronic eye diseases. In this context the greater loss of corneal endothelial cells reported from the bimatoprost SR treatment groups, with even further increased frequencies reported after the first cycle was of great concern. A major objection was raised due to the substantially higher frequency of corneal endothelial cell loss observed in the bimatoprost SR group compared to the comparator SLT group in the pivotal Study 192024-093, with consistent observations also made in Studies 007, 091, and 092.

According to the applicant, ECL may be caused from physical contact between the implant and the corneal endothelium. This effect was exacerbated by the presence of multiple implants in various stages of biodegradation, which were reported to be "stacking upon each other". Given the very long duration of incomplete biodegradation in patient eyes, this raises major concerns.

Evaluation of ECL frequencies reported from the pivotal clinical programme is hampered by various factors. The delayed onset of corneal ECL, which is typically reported >16 weeks post implantation according to the applicant, leads to difficulties in interpretations, since it is not possible to clearly determine which implant caused the adverse event, e.g. due to carry-over, the occurrence of corneal ECL during the second treatment cycle follow-up might have in fact been caused by the first implant. Similarly, difficulties arise when comparing ECL incidences reported from a fixed regimen vs a flexible regimen. Due to shorter follow-up duration after the first implantation defined by the fixed duration to retreatment (16 weeks in pivotal studies with fixed regimen) the risk for carry-over into the second treatment cycle follow-up duration is considered considerable. Further, the reported ECL frequencies

mainly based on a responder-type endpoint applying a threshold of ≥15% cell loss to define ECL as event, limiting interpretation of the extent/severity of the reported ECL events.

In pivotal study 192024-093, the overall incidence of corneal ECL ≥15% was higher for bimatoprost SR 10 µg-treated eyes (6.9%) than for SLT-treated eyes (3.3%), and was more frequently observed in cycle 2 compared to cycle 1 and more frequent with flexible administration compared to the fixed regimen.

Also in study **1698-301-007** most common TEAEs of special interest are corneal ECL and corneal oedema, with the majority considered as related. 9.1% of bimatoprost study eyes had corneal TEAEs of special interest, compared to 0.7%reported in the fellow eye group treated with standard of care. The incidence of corneal TEAEs of special interest for bimatoprost SR study eyes increased with treatment cycle, with 5.7% reported during cycle 1, 6.1% in cycle 2, and 14.3% in cycle 3.

With regard to endothelial cells, the loss in the pooled studies **192024-091** and **192024-092** seemed to be smaller than in study 093. In study **192024-091,** ECL during cycle 1 was not observed in the 10µg bimatoprost group, whereas in cycle 2 1.6% of study eyes in the 10µg bimatoprost group had a loss of endothelial cells compared to none in the control group of timolol receiving eyes. In cycle 3 the frequency was even higher with 3.3% ECL. In cycle 2 and 3 1.5% (3/197) of study eyes in the bimatoprost 10 µg group reported severe ECL events. In study **192024-092** ECL was only observed in cycle 3 with 3.8% in the 10mg bimatoprost group vs none in the control group.

In summary, **more AEs of endothelial cell loss** were observed in the bimatoprost SR groups compared to the comparator arms and fellow eyes treated with standard of care in pivotal studies **192024-093**, **1698-301-007, 192024-091** and **192024-092**, and seemed to increase with repeat dosing**.**

A risk factor for corneal AESIs was reported to be the morphological characteristics of the patient eye. Subgroup analyses showed a *significantly* increased risk for corneal AESIs including ECL in eyes with narrower iridocorneal angle (Shaffer grade 3), compared to eyes with more open angle (Shaffer grade 4). From pooled analyses (studies 093, 095, 301-007), significantly increased occurrence of corneal AESIs were reported for eyes with Shaffer grade 3 (13.8% [34/246] for flexible/PRN; 15.6% [5/32] for fixed) compared with eyes assessed as Shaffer grade 4 (5.3% [15/281] for flexible/PRN; 7.0% [4/57] for fixed).

However, not only the incidence of corneal ECL seemed to be increased under Durysta treatment compared to SLT, also the *severity* of corneal ECL was substantially worse.

While a threshold of ≥15% cell loss was used to report ECL as event across all pivotal studies, additional analyses of ECL (severity) applying different thresholds for ECL definition were provided with responses as part of the finalised data package from the completed pivotal study 192024-093. In these data, **endothelial cell loss ≥30% was reported for 8.0% of Durysta 10µg treated eyes compared to 1.3%** under SLT treatment. **Severe ECL of ≥40% and ≥50% were reported for 4.6% and 2.9% of Durysta-treated eyes, compared to 0.4% and 0% of SLT-treated eyes.** These new analyses therefore report substantially worse ECL severity under Durysta 10µg treatment compared to comparator SLT. Comparable data were provided for a pooled analysis of studies 192024-093 and 301-007.

Additionally, analysis of these data by Shaffer grade from studies 192024-093 and 301-007 were provided. In line with previous findings, a significantly increased risk for ECL was reported from eyes with Shaffer grade 3 compared to 4. **ECL ≥30%** was reported from **11.8% of Shaffer 3 eyes** (SLT: 1.0%) compared to **5.1% of Shaffer 4 eyes** (SLT: 1.5%). **ECL ≥40%** was reported from **6.6% of Shaffer 3 eyes** (SLT: 0%) compared to **3.1% of Shaffer 4 eyes** (SLT: 0.8%). **Severe ECL ≥50%** cells lost compared to baseline was reported from **3.9% of Shaffer 3 eyes** (SLT: 0%) compared to

2.0% of Shaffer 4 eyes (SLT: 0%). These data report substantially increased severity of ECL for the overall patient population (Shaffer 3 and 4 combined) compared to the comparator SLT. **The risk for severe ECL events reported from patients with narrower irido-corneal angle (Shaffer 3) is considered inacceptable.** The risk for severe ECL events for eyes with **Shaffer grade 4** - while comparably lower than in eyes with Shaffer grade 3 - is still ***substantially*** **higher compared to SLT**, questioning acceptability of Durysta 10µg treatment also in these patients. Comparable data were provided for a pooled analysis of studies 192024-093 and 301-007.

Serious adverse events and death

In study **192024-093** 10.0% of subjects in the bimatoprost group in study 192024-093 experienced a nonocular SAE. Atrial fibrillation occurred in 2 subjects, other SAEs were reported as single cases and none was considered related. **Ocular SAEs** were reported in **2.3%** (4 eyes) of bimatoprost fixed regimen treated eyes vs none in SLT treated eyes. One subject experienced 4 SAEs in the same eye including corneal oedema, corneal thickening, photophobia and vision blurred, other 3 eyes had 1 SAEs each. SAEs were **slightly higher in cycle 2 (1.6%)** compared to cycle 1 (1.1%), all ocular SAEs were considered related. All SAEs were included in the SmPC except corneal thickening. Upon request, the applicant included the related SAE corneal thickening in the SmPC.

In study **1698-301-007** 11.6% of subjects in the bimatoprost group experienced a nonocular SAE. Myocardial infarction, coronary artery disease, COVID-19, pneumonia, road traffic accident, hypertension, and cerebrovascular accident were reported in 2 or more subjects, none was considered related. **1.6%** of subjects reported **ocular SAE**, including corneal ECL and corneal oedema, reported for 3 eyes each, and cataract, corneal touch, glaucoma, and keratopathy in one eye each. ECL, corneal oedema, corneal touch, and keratopathy were considered related. Corneal touch, corneal oedema (3 events), and corneal ECL led to discontinuation of study drug. The incidence of ocular SAEs was also **higher in cycle 2 (1.7%)** compared to cycle 1 (0.5%).

In the summary of safety only limited information is provided for studies other than 192024-093 or 1698-301-007. In studies 192024-041D and 1698-304-007 only one subject each had a SAE (retinal detachment in the control group and Covid-19 in the bimatoprost group), none was considered related. In the pooled analysis of studies 192024-091 and 192024-092 4% of subjects in the bimatoprost 10µg group experienced an ocular SAE. Although the applicant included the AEs macular oedema, corneal decompensation, and cystoid macular oedema in the SmPC under the headline description of selected AE, these AE were also requested to be included in AEs table in 4.8. For other SAE considered related but not included in the SmPC a respective rationale was requested. Consequently, the applicant included corneal thickening, episcleritis, and keratopathy in the SmPC.

18 cases of death were observed during the clinical programme. None was considered related to study treatment or procedure.

Ocular TEAEs Resulting in Implant Removal

In general the number of TEAEs leading to implant removal during the clinical programme was low and all AEs considered related are included in SmPC. In study **192024-093 2.3%** of bimatoprost eyes (4 eyes) had an ocular AE that led to implant removal, 1 eye in the flexible group and 3 eyes in the fixed group. Corneal ECL and corneal oedema occurred in at least 2 eyes and all AE leading to removal were considered related.

In study **1698-301-007 1.4%** of bimatoprost study eyes (6 eyes) and 0.6% of bimatoprost fellow eyes (1 eye) had an ocular AE that led to implant removal. The TEAEs leading to removal were corneal oedema, corneal touch, corneal ECL, and medical device removal due to implant released into the corneal tissue during the administration procedure. All ocular AEs were related to treatment.

In the pooled studies **192024-091** and **192024-092 3.2%** of bimatoprost 10µg eyes (12 eyes) had an ocular AE that led to implant removal.

The applicant was asked to provide an analysis per cycle for AEs leading to implant removal for pooled studies 192024-091 and 192024-092. From the limited sample available, no new cycle-dependent patterns were observed.

Implant assessment

When the size of the bimatoprost SR implant was evaluated over time relative to the original implant size in studies 192024-093 and 1698-301-007 the implant size remained unchanged during the first 8 months, being reduced ≤ 25% of their original size by Week 52 in about 60% of patients. A major objection was raised due to the limited biodegradability of the implants seen in clinical and non-clinical studies. This MO could not be resolved based on the follow-up data on biodegradation of Durysta 10µg across studies provided with responses. While the exact duration for complete biodegradation in the patient eye still remains unknown, the anticipated duration is considered extremely long based on available data. After 60 months of follow-up post first implantation of Durysta 10µg, implant remnants (>0-25% of the original implant size) were still detectable in the majority of study eyes. This is while the actual size of remaining implant residues was however not provided, since an evaluation range of >0-25% of the initial implant size was determined as the smallest evaluable category and no data on implant size were provided. No analytical data from residual implants were available, with consequent uncertainties regarding the qualitative composition of the incompletely degraded implant residues in patient eyes.

In contrast, with responses, a much shorter time frame of ~100 days was presented for the release of the total amount of active substance based on analyses from aqueous humour samples of patients whose implants were removed.

Further, "stacking" of multiple implants in early stages of biodegradation was described by the applicant as an important safety relevant event, causing increased corneal endothelial cell loss, due to the implant getting into physical contact with the corneal endothelium. This effect consequently led to the applicant's decision to move away from repeat dosing >2 administrations of Durysta.

It is unclear whether implant remnants could negatively impact other treatment options after patients completed Durysta treatment (e.g. SLT).

Safety in special populations

Upon, request the applicant submitted pooled safety data separated by age group. The overall safety profile of BimSR seems comparable between age subgroups. However, a trend towards a higher occurrence of corneal endothelial cell loss is noted in eyes receiving BimSR with increasing age, especially pronounced among eyes with 2 implant administration. Considering that this safety signal is already discussed for the overall population, no further concern is raised in this instance. However, the applicant is asked to present pooled safety data per age group according to the suggested format.

Analyses by age, sex, race were performed for the pooled Phase 3 (192024-093/192024-095) and Phase 3b (1698-301-007) studies and for the pooled Phase 3 (192024-091/192024-092) studies and no meaningful differences were observed.

Subgroup analyses were further performed by diagnosis OHT or OAG for bimatoprost 10 µg data. In studies 192024-093, 192024-095, and 1698-301-007 mostly patients with OAG (~80%) compared to OHT (~20%) were included. There was a **higher frequency of ocular TEAEs** in eyes with **OHT** versus OAG within each treatment group. In the bimatoprost group 56.7% experienced an ocular TEAE in eyes with OHT vs. 50.9% in eyes with OAG. Also AEs of corneal oedema and corneal ECL were more

frequently reported in eyes with OHT. 12.7% of bimatoprost eyes diagnosed with OHT had ECL ≥15% compared to 7.5% eyes diagnosed with OAG.

Also in study 192024-091 and 192024-092 the majority of patients had a diagnosis of OAG. In study 192024-091 19.7% of the patients had a diagnosis of OHT and 78.1% had a diagnosis of OAG. In study 192024-091 25.6% of the patients had a diagnosis of OHT and 74.4% had a diagnosis of OAG.

The overall safety profile seems to be even worse in the OHT population. Although overall the difference between SLT and the bimatoprost group seems to be comparable, an analysis per cycle per subgroup (OHT vs OAG) was requested for AE, SAE and AE of ECL for pooled studies 192024-093/192024-095 and 1698-301-007 as well as for pooled studies 192024-091/192024-092 and for the overall pooled safety data. The applicant provided pooled TEAEs analysis per disease group (OHT vs OAG), from studies 192024-041D, 192024-091, 192024-092, 192024-093, 192024 095, 1698-301-007, and 1698-304-007 as well as studies 192024-093 and 1698-301-007 for comparisons between number of implants (1 vs 2). The safety profile among disease subgroups appeared overall consistent. A trend towards an increased incidence of corneal endothelial cell loss in the OHT subgroup was noted, which is however also apparent in SLT-treated eyes. Further, the small number of eyes with OHT has to be considered. Therefore, no concern pertaining to a potential differential safety profile of BimSR between disease subgroups is raised.

Given the low systemic concentrations of bimatoprost achieved after the intracameral implantation of bimatoprost SR the risk of systemic interactions is very unlikely. At request, the applicant has identified four potential risks derived from the concomitant administration of Durysta and other ophthalmic products including intravitreal medicinal products such as anti-VEGF drugs or intravitreal corticosteroids. These risks are IOP increase, corneal oedema secondary to narrowing of the anterior chamber due to intravitreal injection, anterior migration of the intravitreal implant and intraocular inflammation and endophthalmitis. Risk of anterior migration of the implant is already included in the SmPC as a contraindication for patients with absent or ruptured posterior lens capsule. Risks of corneal oedema and intraocular inflammation are described in Section 4.4, Special warnings and precautions for use. This section should also include a warning about the risk of IOP increase in case of coadministration of intravitreal medicinal products. The fact that the information and related recommendations are already reflected in the SmPC of intravitreal antiVEGF and corticoids does not prevent from including it in Durysta SmPC.

From a clinical perspective, the reported presence of stainless steel particles in the implant are very concerning. The limited clinical information provided by the applicant as part of a medical opinion cannot alleviate concerns regarding stainless steel particles in the patient eye. A justification is requested that no adverse events occurred due to these particles and that respective measures ensuring detection of possible adverse events caused by (sub)visible stainless steel particles were implemented into the safety evaluation in the clinical studies.

Postmarketing experience

The most frequently reported events in the postmarketing were related to the administration procedure (complication of device insertion, product administered at inappropriate site and device malfunction).

FDA label includes implant migration as adverse reaction, and "product administered at inappropriate site" is included as information from clinical trials. It is expected that adverse reactions related to administration procedure increase in clinical practice setting, outside the controlled context of clinical trials.

3.3.9. Conclusions on clinical safety

Major issues have been identified in the safety profile of BIM SR 10µg implant pertaining to endothelial cell loss and long persisting residues of the implant in the eye.

Regarding endothelial cell loss, BIM SR was associated with an increased frequency and significantly greater severity of irreversible corneal endothelial cell loss (ECL) events compared to the comparator selective laser trabeculoplasty (SLT). Frequencies of ECL occurrence reported after retreatment are considered inacceptable, and the option for re-administration should be excluded from the SmPC. However, the data available do not clearly indicate whether the increased ECL frequencies observed after retreatment could in fact be caused by the first implant. These uncertainties arise due to the commonly described delayed onset of ECL events >16 weeks post-implantation and potential carry-over into the second treatment cycle. Notably, ECL frequencies reported from patients who received only one implant in total (with consequently longer follow-up durations after first treatment) were similar compared to the overall ECL incidence reported from patients who received two implants in total. Therefore, the acceptability of a single administration is also questioned.

Based on subgroup analyses, the safety profile of Durysta 10µg is considered unacceptable for patients with a narrower iridocorneal angle (Shaffer grade 3) due to a significantly higher frequency and severity of ECL events. Also, in patients with a more open iridocorneal angle (Shaffer grade 4) a substantially increased risk for severe corneal ECL was reported compared to SLT.

Visible Durysta 10µg implant residues were reported in more than 50% of patient eyes after a follow-up of 60 months. It is currently unclear if or when Durysta 10µg implants are completely degraded. Based on the available data, it can be concluded that clinically useless and potentially harmful implant residues of different (yet not clearly described) sizes and of undescribed qualitative composition remain in the eyes for many years in the majority of patient eyes. This risk substantially outlasts the potential benefit as the active substance contained in the implant seems to be released within 3-4 months (based on limited data). Implant remnants were further described to lead to "stacking" with other implants in case of retreatment in the same eye, thought to further increase the risk for irreversible corneal endothelial cell loss.

Three major objections on these important safety relevant findings are raised (increased frequency and severity of ECL with Bim SR 10µg vs comparator SLT, incomplete biodegradation of implants after 60 months in the majority of study eyes, and unacceptable safety profile after retreatment,).

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant initially proposed the following summary of safety concerns in the RMP:

Table 63: Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	Corneal events (corneal endothelial cell loss, corneal oedema, corneal touch) Anterior segment inflammation Macular oedema
Important Potential Risks	Endophthalmitis Implant migration into the posterior segment Reactivation of ocular or periocular infections
Missing Information	Use in pregnancy and lactation

Table 64: The updated summary of safety concerns (RMP version 0.1; April 2024):

Summary of Safety Concerns	
Important Identified Risks	Corneal endothelial cell loss and associated corneal events (corneal oedema and corneal touch)
	Anterior segment inflammation
	Macular oedema
	Endophthalmitis
Important Potential Risks	Implant migration into the posterior segment
	Reactivation of ocular or periocular infections
Missing Information	Long-term safety

3.4.1.1. Discussion on safety specification

The proposed safety concerns were revised, and additional risks and missing information were included.

Endothelial cell loss:

As requested "corneal endothelial cell loss and associated corneal events (corneal oedema and corneal touch)" will be included into the summary of safety concerns of the RMP as an important identified risk.

Endophthalmitis

"Endophthalmitis" is included as an important identified into the RMP risk after an analysis of endophthalmitis reports.

Long-term safety:

"Long term safety" is defined as missing information as there is very limited data in patients and treatment with Durysta could even have risks after the treatment due to the remaining implant. For better characterisation, as proposed by the PRAC rapporteur, the full wording of the risk, "Safety related to long term use of intracameral implant", should be included throughout the RMP. " Since we do not know the safety implications of long term presence of the implant, the clinical outcome cannot be defined more precisely.

Use in pregnancy and lactation:

The missing information "use in pregnancy and lactation" was *deleted* from the RMP summary of safety concerns but will be included in the summary of safety concerns of the PSUR to be monitored via future PSURs.

Off-label use:

"Off label use (more than single re-administration)" is included into the PSUR summary of safety concerns as an important potential risk and thereby detailed reporting of the issue in future PSURs is ensured.

The MAH agrees that Durysta should be classified with additional monitoring status since bimatoprost has not been previously marketed as intracameral implant in the EU.

The RMP has been revised from version 1.0 to 0.1 however the final sign-off date was not revised to format: DD-MM-YYYY. This should be done in the final version of the RMP.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification the updated summary of safety specification of the RMP version 0.1 is adequate. Of note, the applicant agreed to include "Long term safety" as missing information within the RMP. For better characterisation, as proposed by the PRAC rapporteur, the full wording of the risk, "Long term use of intracameral implant", should be included throughout the RMP.

3.4.2. Pharmacovigilance plan

Routine pharmacovigilance activities

Routine PV activities beyond adverse reactions reporting and signal detection include:

Specific adverse reaction follow-up questionnaires for:

- Important Identified risk: Corneal endothelial cell loss and associated corneal events (PT Terms: corneal oedema, corneal endothelial cell loss, corneal touch)
- Important Identified risk: Anterior segment inflammation (PT Terms: anterior chamber cell, anterior chamber flare, iris adhesions. Iritis, iridocyclitis, uveitis)
- Important Identified risk: Macular oedema (PT Terms: cystoid macular oedema, macular oedema)
- Important Identified risk: Endophthalmitis (PT Term: Endophthalmitis)
- Important potential risk: Migration of implant into the posterior segment (PT term: Device dislocation)
- Important Potential risk: Reactivation of ocular/periocular infections viral, bacterial, and fungal (PT terms: related to eye infection viral, bacterial, and fungal)

For each of these identified and potential risks, a follow-up questionnaire (see Annex 4) is being used in the post marketing setting.

The applicant AbbVie has a standardised global process for the use of targeted follow-up questionnaires for safety concerns stated above within the PV system as part of post marketing surveillance for adverse events of special interest in the target population. This process includes contact to the heath care provider/HCP or reporter using the questionnaire via phone, facsimile, or send letter/form. The follow-up to consumer includes an attempt to obtain consent to contact the HCP.

A minimum number of queries are made depending on the seriousness of the case; medical judgment or local regulations are applied to determine if further attempts (above the minimum) should be made.

Other forms of routine PV activities:

No other forms of routine PV activities are planned, implemented, or ongoing for Durysta, besides the aforementioned activities.

Additional pharmacovigilance activities

Long-term safety and risks associated with the use of Durysta, specifically relating to endothelial cell loss, are being evaluated in the ongoing Phase 3 Study 1698-301-007, which has a follow-up time of up to 48 months.

Study 1698-301-007:

Rationale and Study Objectives:

The objective of this study is to evaluate the duration of IOP-lowering effect and safety of up to 3 PRN administrations of 10 µg bimatoprost SR (reduced to up to 2 PRN administrations in Amendment 4) in subjects with OAG or OHT who are not adequately managed with topical IOP-lowering medication. This study will evaluate the long-term safety of 10 µg bimatoprost SR, including implant biodegradation as well as endothelial cell loss, over a study duration of up to 48 months.

Study Design:

This study is a multicentre, open-label, Phase 3b study. See Module SIII for details.

Study Population:

This study included subjects with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence).

Milestones:

{Commercially confidential information deleted}

Summary of planned additional PhV activities from RMP

Table 65: Ongoing and planned additional pharmacovigilance activities

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
1698-301-007 Ongoing	The objective of this study is to evaluate the duration of IOP-lowering effect and safety of up to 3 PRN administrations of 10 µg Bimatoprost SR (reduced to up to 2 PRN administrations in Amendment 4) in subjects with OAG or OHT who are not adequately managed with topical IOP-lowering medication. This study will evaluate the long-term safety of 10 µg Bimatoprost SR, including implant biodegradation as well as endothelial cell loss, over a study duration of up to 48 months.	Long-term safety	{Commercially confidential information deleted}	{Commercially confidential information deleted}

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is currently acceptable to identify and characterise the risks of the product as the applicant has proposed to include the ongoing study 1698-301-007 as additional pharmacovigilance activities to further investigate the risks considered ”longterm use of intracameral implant” and “Corneal endothelial cell loss and associated corneal events (corneal oedema and corneal touch)”. However, further discussion regarding the study is required and the applicant is requested to elaborate further on the study e.g. propose new milestones and further information regarding the statistical analysis that will be conducted.

The proposed routine pharmacovigilance activities are currently considered appropriate. However, the applicant is requested to reconsidered the need for a specific adverse reaction follow-up questionnaire for the risk “macular oedema”, as the risk may be considered well-known at this point in time with regard to the active substance bimatoprost.

Plans for post-authorisation efficacy studies

No efficacy studies have been imposed by competent authorities as a condition of the marketing authorisation or are Specific Obligations in the context of the conditional marketing authorisation or marketing authorisation under exceptional circumstances.

3.4.3. Risk minimisation measures

Routine Risk Minimisation Measures

Table 66: Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Corneal endothelial cell loss and associated corneal events (corneal oedema and corneal touch)	Routine risk communication: SmPC Section 4.2 - Posology and method of administration SmPC Section 4.3 - Contraindications SmPC Section 4.4 - Special warnings and precautions for use SmPC Section 4.8 - Undesirable effects PIL Section 2 - What you need to know before you are given DURYSTA PIL Section 4 - Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to monitor corneal endothelial cell health, and guidance on implant removal in patients, included in SmPC Section 4.4 Recommendation to examine the size and position of the existing implant for sufficient iridocorneal angle space for next implant, included in SmPC Section 4.4. Detailed step-by-step of intracameral injection procedure with pictograms to prevent improper placement included in SmPC Section 6.6 Other routine risk minimisation measures: Pack Size: Applicator containing implant is package for single use only for treatment of a single eye Use only by qualified ophthalmologist experienced in intracameral procedures.
Anterior segment inflammation	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use SmPC Section 4.8 - Undesirable effects

Safety Concern	Routine Risk Minimisation Activities
	PIL Section 2 - What you need to know before you are given DURYSTA PIL Section 4 - Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures: Use only by qualified ophthalmologist experienced in intracameral procedures.
Macular oedema	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use SmPC Section 4.8 - Undesirable effects PIL Section 2 - What you need to know before you are given DURYSTA PIL Section 4 - Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures: Use only by qualified ophthalmologist experienced in intracameral procedures
Endophthalmitis	Routine risk communication: SmPC Section 4.2 - Posology and method of administration SmPC Section 4.3 - Contraindications SmPC Section 4.4 - Special warnings and precautions SmPC Section 4.8 - Undesirable effects PIL Section 2 - What you need to know before you are given DURYSTA PIL Section 4 - Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to instruct patients to contact physician immediately for specific eye events following intracameral administration, included in SmPC Section 4.4 Aseptic technique must always be used for administration and patients should be monitored afterwards, included in SmPC Section 4.4. Detailed step-by-step of intracameral injection procedure with description of aseptic technique included in SmPC Section 6.6 Other routine risk minimisation measures: Use only by qualified ophthalmologist experienced in intracameral procedures.
Implant migration into the posterior segment	Routine risk communication: SmPC Section 4.2 - Posology and method of administration SmPC Section 4.3 - Contraindications PIL Section 2 - What you need to know before you are given DURYSTA Routine risk minimisation activities recommending specific clinical measures to address the risk: Detailed step-by-step of intracameral injection procedure with pictograms to prevent improper placement included in SmPC Section 6.6 Other routine risk minimisation measures: Use only by qualified ophthalmologist experienced in intracameral procedures

Safety Concern	Routine Risk Minimisation Activities
Reactivation of ocular or periocular infections	Routine risk communication: SmPC Section 4.3 - Contraindications PIL Section 2 - What you need to know before you are given DURYSTA Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures: Use only by qualified ophthalmologist experienced in intracameral procedures
Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures: Use only by qualified ophthalmologist experienced in intracameral procedures

Additional risk minimisation measures

Not applicable.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

PRAC outcome

During the plenary meeting held on 10-13 June 2024, the PRAC, having considered the PRAC rapporteur's evaluation, agreed by consensus that Durysta RMP version 0.1 requires revision.

Safety specifications

As proposed by the PRAC rapporteur, it is raised for CHMP attention the suggestion to rephrase the missing information "Long term safety" as "Long-term use of intracameral implant".

Pharmacovigilance Plan

The applicant proposed specific adverse reaction follow-up questionnaires for:

- The important identified risk of
  - Corneal endothelial cell loss and associated corneal events (corneal oedema and corneal touch)
  - Anterior segment inflammation
  - Macular oedema
  - Endophthalmitis
- The important potential risk of
  - Implant migration into the posterior segment
  - Reactivation of ocular or periocular infections (viral, bacterial, and fungal)

PRAC considered that adverse reaction follow-up questionnaires might be justified to collect data elements not otherwise gathered throughout routine follow up activities. Therefore, the applicant should reconsider (and justify) the proposal for each of the follow-up questionnaires above listed.

PRAC also noted the applicant's proposal to include the ongoing open-label, phase IIIb study 1698-301-007 in the PhV Plan as category 3 study, to further investigate the safety concerns of "Long-term use of intracameral implant" (in relation to biodegradability of Durysta implant) and "Corneal endothelial cell loss and associated corneal events (corneal oedema and corneal touch)".

As detailed in the conclusion on clinical safety in the D150 joint assessment report (AR), visible Durysta 10µg implant residues were reported in more than 50% of patient's eyes after a 60-month follow up, and this incomplete implants' biodegradation was raised as a major objection.

Study 1698-301-007 has a follow-up time of up to 48 months, which may not be sufficient to address the concerns related to persistence of Durysta implant in the eye, as well as corneal endothelial cell loss. Therefore, the applicant should discuss the suitability of study 1698-301-007 in the context of follow-up time in relation to the major objection on incomplete biodegradation of implants after 60 months, and in terms of which additional data could be collected about endothelial cell loss and implant's biodegradability.

In addition, the applicant should clarify study 1698-301-007 data analyses methods (with references to specific statistical analyses, to be described in a dedicated statistical analysis plan) and revise accordingly the study milestones (including full protocol submission for PRAC endorsement, upon finalisation of the current procedure).

If study 1698-301-007 is not sufficient to address all the above, the applicant should propose additional alternative PhV activities.

Risk Minimisation measures

The applicant included extensive information in the proposed product information (PI) about risks associated with intracameral injection (e.g. to alert patients about symptoms suggestive of endophthalmitis). However, no additional risk minimisations measures (RMMs) have been proposed, whereas for other medicinal products administered via intravitreal injection (or other comparable route of administration) additional RMMs are in place, particularly to inform patients about signs and symptoms of eye infections. Also in light of Durysta safety profile, PRAC agreed that educational materials for patients are warranted.

3.4.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 required revision.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on differences in formulation and known issues with biodegradability of the implant, the PRAC Rapporteur is of the opinion that a separate entry in the EURD list for Durysta is needed, as it cannot follow the already existing entry for bimatoprost. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 16-03-2002. The new EURD list entry will therefore use the {EBD} {IBD} to determine the forthcoming Data Lock Points.>

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Non-Conformity with agreed Paediatric Investigation Plan

Not applicable

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

Durysta (bimatoprost SR) is intended to be used for the reduction of intraocular pressure (IOP) in adults with open angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medications.

5.1.2. Available therapies and unmet medical need

Treatment options range from non-invasive (such as topical drops and procedures that do not enter the eye, such as laser trabeculoplasty), to more invasive surgical interventions (such as minimally invasive glaucoma surgery [MIGS], trabeculectomy, or tube shunts). Topical drops are typically the first line of treatment for patients with glaucoma or OHT because they are non-invasive. Topical medications also remain a mainstay of IOP lowering therapy at any stage of the patient's treatment journey.

Beyond topical IOP-lowering medications, the non incisional treatment option commonly used before needing to resort to more invasive options is laser trabeculoplasty, a common type of which is selective laser trabeculoplasty (SLT). In clinical practice SLT is used both as initial therapy and as adjunctive therapy in combination with topical medications.

5.1.3. Main clinical studies

The main clinical evidence supporting up to 2 as-needed administration cycles per eye in adults with open angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medicinal product is based on the completed Phase III study 192024-093 (-093) and the ongoing IIIb study 1698-301-007 (-301-007). Data from completed Phase III studies 192024-091, 192024-092, and 192024-095, as well as Phase I/II study 192024-041D and Phase IIIb study 1698-304-007 are considered supportive.

Study 192024-093 was a randomized, subject and efficacy evaluator-masked trial comparing 1 or 2 administration cycles of BIM SR to a single Selective Laser Trabeculoplasty (SLT) therapy in adults with OAG or OHT who are unsuitable for topical IOP-lowering medicinal product. The study was designed as non-inferiority study. The second administration cycle was initially fixed at Week 16, but was later

changed to a more flexible regimen (re-administration after Week 16 and prior to the Month 12 visit if the retreatment criteria were met). Retreatment criteria were based on IOP threshold (> 17 mm Hg) and safety aspects (e.g. endothelial cell density and implant remnants).

In total, 183 subjects were randomized to receive Bim SR in one eye and SLT treatment in the fellow eye. 180 eyes received SLT and 175 eyes received BIM SR 10µg (89 eyes according to the fixed schedule, 86 eyes according to the flexible schedule). Of the 180 subjects who entered Cycle 1, 169 completed Cycle 1 and of those, 126 subjects entered Cycle 2, and 112 subjects completed Cycle 2.

In the Bim SR fixed arm (second administration due on Week 16), 89 eyes received ≥1 administrations, and 70 eyes received 2 administrations, i.e. 78.7% of treated eyes received the second implant. In the Bim SR flexible arm (flexible second administration), 86 eyes received ≥1 administrations, and 56 eyes received 2 administrations, i.e. 65.12% of treated eyes received the second implant.

Study 1698-301-007 is an ongoing, open-label, uncontrolled Phase IIIb study to evaluate the duration of IOP-lowering effect and safety of up to 3 administrations of Bim SR 10 µg. The purpose of this study is to obtain data on a PRN (pro re nata, as needed or flexible) re-administration regimen of Bim SR. As of the data cutoff date (29 July 2022), 319 subjects were randomized, or enrolled to receive Bim SR 10 µg.

Studies 192024-091 and 192024-092 evaluated the IOP-lowering efficacy and safety of 3 administrations of Bimatoprost SR (10 µg and 15 µg) implant with a fixed 4-month interval between two administrations in patients with OAG or OHT. While the dosing regimen investigated in this study in not fully in line with that proposed in the label, these studies provide important evidence for the efficacy and safety of 1 and 2 administrations of Bimatoprost SR 10 µg, when the second implant is injected 4 months after the first implant which is also the minimum interval as proposed by the applicant.

5.2. Favourable effects

Clinical Aspects

The IOP lowering effect of BIM SR 10 µg has been demonstrated across different studies.

Study 192024-093

For up to 2 BIM SR administrations: The change from baseline in mean IOP (primary efficacy outcome) for up to two BIM SR 10µg implants and a single SLT was similar at Week 4, 12 and 24. **Bim SR 10µg met the pre-specified criteria for non-inferiority**. The reduction in mean IOP from baseline was numerically larger and in favour of Bim SR 10 µg treated eyes compared with SLT-treated eyes at all 3 timepoints. The least square (LS) mean for the treatment difference between Bim SR 10 µg and SLT in IOP change from baseline was -0.6 mmHg (95% CI=-1.03, -0.08), -0.4 mmHg (95% CI=-1.04, 0.18), and -0.4 mmHg (95% CI=-0.97, 0.17), at Week 4, 12 and 24 respectively. Further sensitivity analyses overall support sufficient robustness of the primary efficacy outcome.

Results of secondary endpoints 'Time to Initial Use of Rescue Treatment', 'Reduction in IOP of at least 20%' and 'IOP Change from Baseline at Weeks 8, 15, and 20' appear to a large extent similar between the SLT and the BimSR 10µg group.

Subgroup analyses in the **flexible re-administration group** and subgroup analysis by disease diagnosis (OAG vs. OHT) support the overall results.

For a single BIM SR administration: A post-hoc primary efficacy analysis before the second implant was administered was requested by the Rapporteurs to assess the effect of a single administration. The

mean difference at Week 15 was 0.2 with 95% CI (-0.44, 0.75), therefore the upper bound of 95% confidence interval at Week 15 fell below the noninferiority margins of 1.5 mmHg for statistical and 1.0 mmHg for clinical justification.

Duration of effect: the median time to second administration or non-study IOP-lowering treatment was 144 days, based on the pooled analysis for the fixed (re-administration at Week 16) and flexible administration regimen (re-administration possible from Week 16 to prior to Month 12).

Study 1698-301-007

Of the 313 study eyes that received a first administration of BimSR 10 µg, 131 study eyes (41.9%) had received a second administration or initiated rescue treatment by the data cutoff date. The **median time from initial administration of Bim SR 10 µg to requiring a second administration or rescue treatment** in the study eye on a PRN (flexible) re-administration regimen was **377 days (> 1 year**) with a 95% CI of 330.0 to 512.0 days, based on data from all subjects regardless of follow-up time. The cumulative probability of not requiring a second administration of BimSR 10 µg or rescue treatment at 360 days was calculated to be 55.1% with 95% CI of (48.2%, 61.4%).

Results from the sensitivity analysis on duration of IOP-lowering effect in study eyes that had at least 12 months of exposure to Bim SR 10 µg or had any event of Bimatoprost SR re-administration, rescue treatment, or study discontinuation prior to month 12 (n=215) were similar to the primary analysis.

Of the 96 eyes that had received a second BimSR 10 µg administration, 39 eyes had received a third administration or initiated rescue treatment. The **median time to requiring a third administration or initiating rescue treatment after the second administration** of BimSR 10 µg in the study eye was **297 days** (approximately 10 months). The cumulative probability of not receiving a third administration of BimSR 10 µg or rescue treatment after the second administration in the study eye at 360 days was 35.1%.

Subgroup analyses by disease diagnosis (OAG vs. OHT) support the overall results.

Studies 192024-091 and 192024-092

When BIM 10 µg implant was administered three times in a fixed schedule of 4 months between two doses (studies **192024-091** and **192024-092**), IOP-lowering effect was observed after initial and repeated administrations. The primary endpoint - time-matched IOP (mm Hg) change from baseline at each hour evaluated (Hours 0 and 2) of Cycle 1 Week 12 – was met. Bimatoprost SR 10 µg **met** the pre-specified criteria for **non-inferiority** (upper limit of the 95% CI ≤ 1.5 mm Hg at Week 12 of Cycle 1 (both Hour 0 and 2) **in both studies**. In addition, the change from baseline in mean IOP were similar for BIM SR and timolol eye drops BID in both trials at Weeks 2 and 6. The change from baseline in mean IOP (point estimates) was numerically greater for Bimatoprost SR 10 µg compared to timolol at each hour evaluated (Hours 0 and 2) at Weeks 2, 6, and 12 of Cycle 1, although the corresponding 95% CIs included unity at several time points. In addition, Bimatoprost SR 10 µg demonstrated IOP lowering effect comparable to timolol eyedrops BID at Weeks 2, 6 and 12 following each administration (Cycle 1, 2 and 3). At Month 20 (approximately 12 months after the last administration), mean IOP values were 18.6 mmHg and 17.5 mmHg at Hour 0 and 17.9 mmHg and 16.8 mmHg at Hour 2 in BIM 10 µg and timolol group, respectively. Despite an increase compared to earlier time points, IOP values at Month 20 were still markedly lower compared to the baseline IOP values (around 23-25 mm Hg).

5.3. Uncertainties and limitations about favourable effects

Non-clinical aspects

Study TX09066 reveals a slight, but consistent **IOP-lowering effect of the placebo** over the observation period (6 months) (see report TX09066-TX, p. 34, text table 1). Furthermore, in study TX09051, which was conducted in cynomolgus monkeys, the placebo implant elicits a decrease in IOP, which is at least equivalent to the decrease observed in the highest dose group which received 120 µg bimatoprost (see report TX09051-TX, p.39, figure 2). At first, it is emphasized that in the presentation thereof the time axis is not linear but segmented in an arbitrary manner (e.g. the distance between week 2 and week 5 is equivalent to the distance between week 17 and 26). This is misleading as in such a way the placebo effect (which is predominant between weeks 13 and 26) is ostensibly underestimated. Strikingly, in both studies (TX09066 and TX09051) the placebo exerts a robust IOP-lowering effect between three and five months after injection – similar observations were also made in studies PK09109, BIO-09-803, BIO-009-787. In study TX09051 it is considered that the placebo effect on IOP is due to inflammation or even due to chemical results of polymer degradation of the implant. In the latter case, this would suggest a mode of action for IOP-decrease based on polymer degradation and (at least to a certain extent) questions the purpose of the presence of bimatoprost in the implant. Taken together, the conducted non-clinical placebo-implant controlled studies (TX09051, TX09066, PK09109, BIO-09-803 and BIO-009-787) **challenge bimatoprost as the sole cause of the observed IOP-decrease**. The applicant is asked to further substantiate that implant-released bimatoprost (at the reached concentrations in the eye) is key for the IOP-lowering effect of Bim SR.

Clinical Aspects

Patient population

Of note, BIM SR implant is intended for use in a very narrowly defined patient group described as incapable of adhering to topical IOP-lowering medicinal products for tolerability or compliance. It remains unclear in how far this subgroup can in turn resort to topical alternative/rescue medication when required in therapeutical practice, after being considered eligible for the insertion of Durysta. Adherence is likely overestimated in a clinical trial setting.

There is no evidence to suggest that the success or failure of treatment with BIM SR can be predicted based on noncompliance with topical IOP lowering therapy. The indication concerns subjects who were not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence). It is unclear how nonadherence is determined for subjects to render implanting Bimatoprost SR meaningful, i.e. if nonadherence is based on experience or other information. The definition of "unsuitable for topical IOP-lowering medications" and how such patients can be identified should be clarified in the SmPC.

Additionally, considering the invasive nature of the BIM SR treatment and given that the intended treatment means a long-term exposure to bimatoprost, it is important to ensure that patients have an adequate response to bimatoprost or at least to prostaglandin analogues prior to administration of BIM implant. According to published studies up to 66.9% of patients treated with bimatoprost eye drops achieved at least a 20% reduction of IOP at month 1; 60.2% at month 3 and 57.9% at month 6. Therefore, there is still a percentage of non-responder patients. Only the patients who show a response to prostaglandins/prostamides should be treated with Bimatoprost SR, so this should be indicated in section 4.1 of the SmPC.

The duration of the IOP-lowering effect/effect diminishes over time.

In studies -091 and -092, where BIM SR was administered 3 times in a fixed dosing regimen (Q16W), the decrease of effect started at around 3 months after each administration.

The duration of the effect in the flexible dosing regimen is difficult to interpret due to varying retreatment criteria across studies. The treatment effects are further convoluted by unclear criteria for the initiation of the rescue treatment, prolonged concomitant use of rescue treatment and the small number of eyes for which long term data is available.

While a longer treatment effect was observed in some patients, there is high variability in the duration of response. Furthermore, it is not fully understood where the longer effect in some patients is coming from. Limited PK data, from patients in whom aqueous humour samples were collected during the removal of the implant show that bimatoprost/acid was undetectable beyond 100 days post-implantation (last positive sample taken on day 97 post implantation). Although the interpretation of these data is limited, seen in conjunction with findings from the non-clinical studies suggesting an (unexplained) IOP-lowering sham effect of the implant this contributes to the overall uncertainties regarding the long-term effect of BIM SR.

Further clarification is needed regarding the reasons for patients following the flexible regimen not receiving the second administration (safety concerns or the IOP criterion was not met.

Rescue treatment

A high proportion of patients in the studies took topical rescue IOP lowering treatment which contradicts the applicant's positioning of the drug for those patients not being adequately treated with topical IOP lowering medicines. For instance, in study -093 36.7% of patients in the SLT group, 48.9% in the flexible Bim SR group and 39.1% in the fixed Bim SR group) received topical IOP lowering medications concomitantly. Therefore, the promise of not having to use topical IOP-lowering medications with Bim SR might not hold.

Additional clarifications are needed regarding the use of rescue medication and handling IOP measurements following initiation of the rescue treatment.

Additional uncertainties

In non-inferiority studies **192024-091** and **192024-092** timolol eye drops were used as active control. The selection of the NI margin of 1.5 mm Hg has not been justified neither from a clinical nor from a statistical perspective. While the clinical difference between the treatments is considered not relevant based on the results, a 95% confidence interval for the estimated treatment difference is lacking to judge statistical superiority to (a putative) placebo. Furthermore, as timolol had to be administered twice daily over a period of 20 months, the treatment compliance might have been an issue, which is not the case for BIM SR implant.

Analyses of other efficacy endpoints in the subgroups of patients from studies **192024-091 and 192024-092** who had not used non-study lowering IOP medication before and received at least 2 injections bear a similar potential bias due to selection and regression-to-the-mean as in study **1698-301-007**, when investigating.

5.4. Unfavourable effects

Nonclinical aspects

Bim SR-related effects which were frequently observed in non-clinical dog studies were either expected (lower IOP; miosis; hyperpigmentation of the iris) or non-adverse due to low severity and reversibility (hyperaemia, corneal oedema, corneal vascularisation, corneal scars at the injection site, Schwalbe's line cell hypertrophy/hyperplasia, fibrillar matrix deposition, changes in iridocorneal angle width).

With respect to corneal changes (e. g. vascularisation; oedema), the applicant considers transient contact between the (mobile) implant and the corneal endothelium as a cause. Such contacts are possibly the result of postural changes. As humans are presumably more subjected to changes of head orientation (e.g. sleeping position) and lowering their sight (e.g. reading, working or due to frailty), the applicant is encouraged to discuss the probability of such corneal changes based on differences in eye position between dogs and human.
Study TX12012 describes one case of a full thickness iris hole near the pupil margin (iris atrophy) in an eye given 20 µg implants. The applicant considers these findings attributable to intense miosis, an ocular response to prostamides unique to dogs (a statement made several times throughout the dossier). Hence, these adverse events are not expected to occur in humans. The applicant is encouraged to duly corroborate this statement on a weight-of-evidence basis. Therefore, the applicant should provide literature that (i) chronic intense miosis can cause such an event and (ii) such intense miosis upon prostamides would not appear in humans.

During the earlier stages of Bim SR development, a non-GLP single dose toxicity study (TX09051; issued August 2010) on cynomolgus monkeys was performed, which prompted the applicant to conclude that dogs are a more suitable model for Bim SR development, mainly because of the space to accommodate the implant within the inferior part of the anterior chamber (which is larger in dogs). This is supported. However, it must be noted that animals which received one or two implants (4 groups; 4 females per group. 2 × 0 µg [placebo]; 1 × 30 µg; 1 × 60 µg; 2 × 60 µg) into the right eye exhibited adverse events not observed in subsequent dog studies. These events included aqueous flare, anterior chamber cells, corneal thickening and endothelial cell loss. As these findings also appeared in the placebo group they must be attributed to the physical presence of the implants. Although it is agreed that these findings are difficult to extrapolate to humans, the study clearly shows that the implant can elicit adverse reactions upon contact with certain eye regions and the occurrence of such events during human use should not be ruled out.

Clinical aspects

Increased frequency and significantly increased severity of irreversible corneal endothelial cell loss (ECL) events were reported compared to the comparator selective laser trabeculoplasty (SLT) in pivotal study 192024-093.

The exact duration for complete biodegradation in the patient eye is unknown and the anticipated duration is considered extremely long based on available data. After 60 months of follow-up post first implantation of Durysta 10µg, implant remnants (>0-25% of the original implant size) were still detectable in the majority of study eyes.

"Stacking" of multiple implants in early stages of biodegradation was described by the applicant as an important safety relevant event, causing increased corneal endothelial cell loss, due to the implant getting into physical contact with the corneal endothelium.

The main safety data derive from the completed pivotal phase 3 study 192024-093 where 10µg bimatoprost were evaluated and SLT was used as a comparator. While the overall safety data from 9

clinical studies could be considered adequate, only 616 eyes received at least 1 implant of 10µg bimatoprost and 305 received at least 2 implants 10µg bimatoprost with any follow-up period in the main study 192024-093 and study 1698-301-007 in the planned indication. Of these, only 180 eyes had at least 12 month follow up after 2 implants, thereof 78 from pivotal study 093.

With regard to the proposed posology, where treatment of a chronic disease is foreseen, data from retreatment as well as long-term safety data are therefore limited.

In study 192024-093 the frequency of ocular TEAEs on the fixed Bimatoprost SR 10 µg re-administration regimen (74.2%) was higher than on the flexible Bimatoprost SR 10 µg re-administration regimen (66.3%) and SLT-treated eyes (63.3%).

The most common TEAEs for Bimatoprost SR 10 µg-treated eyes on flexible and fixed regimen were conjunctival hyperaemia (18.6% and 21.3%), dry eye (10.5% and 18.0%), punctate keratitis (11.6% and 12.4%) and IOP increased (19.8% and 29.2%); and dry eye (12.2%), punctate keratitis (10.6%), conjunctival hyperaemia (12.2%), and IOP increased (18.3%) for SLT-treated eyes. Photophobia was also under the most commonly reported (11.6%) on the flexible Bimatoprost SR 10 µg re-administration regimen.

Ocular TEAEs were also reported at a greater frequency in Cycle 2 (61.9%) than Cycle 1 (50.3%) for Bimatoprost SR 10 µg-treated eyes, while in the SLT treated eyes frequency of TEAEs between cycle 1 (45.0%) and cycle 2 (44.4%) was similar.

In study **1698-301-007**, the most commonly reported ocular TEAE for Bimatoprost SR study eye was conjunctival hyperaemia (17.5%). Other frequent AEs were increased IOP (13.4%), dry eye (6.3%) and corneal endothelial cell loss (7.0%). Compared to this, lower frequencies for ocular TEAEs were reported for the fellow eye treated with standard of care, for which 21.3% reported at least one TEAE. For the fellow eye, the most commonly reported ocular TEAEs were conjunctival hyperaemia (5.0%) and dry eye (2.3%).

In study 192024-041D the AEs were in general more frequent in the bimatoprost group (64%) compared to the Lumigan group (48%).

The Incidence of treatment-related ocular TEAEs was higher for Bimatoprost SR 10 µg-treated eyes (40.0%) compared with SLT-treated eyes (22.8%) in study 192024-093.

Also anterior segment inflammatory TEAEs of special interest were higher in the bimatoprost group (7.9%) vs SLT group (0.8%) in cycle 2.

Corneal TEAEs of special interest were higher in the Bimatoprost SR 10 µg-treated eyes than SLT-treated and also higher in cycle 2. The most common corneal TEAEs of special interest reported were corneal endothelial cell loss and corneal oedema.

The frequency of ECL in cycle 1 was similar between the bimatoprost SR (1.7%) and SLT (2.2%) treatment group. In cycle 2 the frequency of ECL was higher in the bimatoprost (6.3%) compared to SLT (0.8%) treatment group. However, compared to these numbers, ECL frequencies reported from patient eyes which only received one administration of bimatoprost SR in total were considerably higher and similar to the frequencies reported from patient eyes which received two implants in total.

Also in 1698-301-007, 192024-091 and 192024-092 more AEs of ECL are seen in the bimatoprost group. In addition, the frequency of ECL was higher in patients diagnosed with OHT (12.7%) compared to OAG (7.5%). The greater loss of corneal endothelial cells in the bimatoprost group, especially after cycle 1 is seen as a major concern.

Severity of corneal ECL was substantially worse under Durysta treatment compared to SLT. From study 192024-093, endothelial cell loss ≥30% was reported for 8.0% of Durysta 10µg treated eyes

compared to 1.3% under SLT treatment. Severe ECL of ≥40% and ≥50% were reported for 4.6% and 2.9% of Durysta-treated eyes, compared to 0.4% and 0% of SLT-treated eyes.

Subgroup analyses showed a *significantly* increased risk for corneal AESIs including ECL in eyes with narrower iridocorneal angle (Shaffer grade 3), compared to eyes with more open angle (Shaffer grade 4). From pooled analyses (studies 093, 095, 301-007), significantly increased occurrence of corneal AESIs were reported for eyes with Shaffer grade 3 (13.8% [34/246] for flexible/PRN; 15.6% [5/32] for fixed) compared with eyes assessed as Shaffer grade 4 (5.3% [15/281] for flexible/PRN; 7.0% [4/57] for fixed).

ECL ≥30% was reported from 11.8% of Shaffer 3 eyes (SLT: 1.0%) compared to 5.1% of Shaffer 4 eyes (SLT: 1.5%). ECL ≥40% was reported from 6.6% of Shaffer 3 eyes (SLT: 0%) compared to 3.1% of Shaffer 4 eyes (SLT: 0.8%). Severe ECL ≥50% cells lost compared to baseline was reported from 3.9% of Shaffer 3 eyes (SLT: 0%) compared to 2.0% of Shaffer 4 eyes (SLT: 0%).

Ocular SAEs were generally low and reported only in the bimatoprost group (2.3%) vs none in SLT group in study 192024-093, with a slightly higher frequency in cycle 2 (1.6%) vs cycle 1 (1.1%).

Incidence of ocular TEAEs was higher in eyes with OHT (56.7%) versus OAG (50.9%) within each treatment group in study 192024-093 and similar results are obtained in the other studies.

The reported presence of stainless-steel particles in the implant are very concerning. The limited clinical information provided by the applicant as part of a medical opinion cannot alleviate concerns regarding stainless steel particles in the patient eye.

5.5. Uncertainties and limitations about unfavourable effects

Nonclinical aspects

Intact implants, partially biodegraded implants or implant remnants were found by gonioscopy in each implant toxicity study in a large number of eyes until the very end of the observation period.
Not even an approximate timescale by which the implant definitely undergoes complete biodegradation could be defined. As a consequence, it is unclear how long residual implant material might reside in the eye and represents a potential safety risk in the long term. In fact, study TX12102 reveals that by the end of the observation period (= 18 months) implant remnants are detectable in most, if not all eyes. Importantly, these remnants often deposit within the trabecular meshwork, a structure, which is of fundamental importance for the drainage of the aqueous humour and thus to control the intraocular pressure (IOP). The long-term effect of these deposits (beyond week 78) on the IOP is unclear. Strikingly, right (treated) eyes of dogs in group 3 (treated three times with doses of 20 µg) of study TX12102 show a certain IOP-increase compared to baseline (IOP of the same eyes at study initiation) at the end of the observation period.
Three observations constitute a substantial concern, that the mentioned IOP-increase might be implant-triggered. (i) Only the group which received the highest load of implants (group 3) is affected by the late apparent IOP-increase. It is very possible that a certain amount of remnants accumulates to elicit this effect. (ii) The effect is sufficiently high and robust (similar extent over 2 consecutive timepoints) to consider this a true and non-random IOP-increase. (iii) The depositing implant remnants within the trabecular meshwork are reminiscent of the pathology of pigment dispersion syndrome (PDS)/pigmentary glaucoma, which is characterized by pigment accumulation within the trabecular meshwork disturbing the aqueous outflow.

Irrespective of these concerns raised, the applicant does not provide sufficient data to conclude on the final fate of the implant and on the long-term condition of the test animal's eyes after the implant's entire elimination. As the deposition of implant remnants in the trabecular meshwork appears to be a

very late event, it is very possible that other adverse events (including but not limited to increased IOP) occur on a timescale beyond the observation period of study TX-12102. Of note, limited biodegradability of the implant was also observed over the course of clinical studies. The applicant is advised to thoroughly discuss this matter and to comprehensibly rule out that implant-remnants represent a long-term risk to patients.

Clinical aspects

Evaluation of ECL frequencies reported from the pivotal clinical programme is hampered by various factors. The delayed onset of corneal ECL, which is typically reported >16 weeks post implantation according to the applicant, leads to difficulties in interpretations, since it is not possible to clearly determine which implant caused the adverse event, e.g. due to carry-over, the occurrence of corneal ECL during the second treatment cycle follow-up might have in fact been caused by the first implant.

Similar difficulties arise when comparing ECL incidences reported from a fixed regimen vs a flexible regimen. Due to shorter follow-up duration after the first implantation defined by the fixed duration to retreatment (16 weeks in pivotal studies with fixed regimen) the risk for carry-over into the second treatment cycle follow-up duration is considered considerable.

Across pivotal studies, ECL evaluation was mainly based on a responder-type endpoint applying a threshold of ≥15% cell loss to define ECL as event, limiting interpretation of the extent/severity of the reported ECL events. Additionally presented data in patient listings report substantially increased severity of ECL events occurring under Durysta treatment compared to the comparator SLT. Additional analyses are requested.

"Stacking" of multiple implants in early stages of biodegradation was described by the applicant as an important safety relevant event, causing increased corneal endothelial cell loss, due to the implant getting into physical contact with the corneal endothelium.

The reported presence of stainless-steel particles in the implant are very concerning. The limited clinical information provided by the applicant as part of a medical opinion cannot alleviate concerns regarding stainless steel particles in the patient eye. A justification is requested that no adverse events occurred due to these particles and that respective measures ensuring detection of possible adverse events caused by (sub)visible stainless-steel particles were implemented into the safety evaluation in the clinical studies.

After 60 months of follow-up post first implantation of Durysta 10µg, implant remnants (>0-25% of the original implant size) were still detectable in the majority of study eyes. This is while the actual size of remaining implant residues was however not provided, since an evaluation range of >0-25% of the initial implant size was determined as the smallest evaluable category and no data on implant size were provided. No analytical data from residual implants were available, with consequent uncertainties regarding the qualitative composition of the incompletely degraded implant residues in patient eyes.

The duration required to achieve complete biodegradation in the patient eye is unknown.

It is unclear whether implant remnants could negatively impact other treatment options after patients completed Durysta treatment (e.g. SLT).

Although it has been suggested that safety profile, particularly conjunctival hyperaemia decreased beyond the immediate administration period, patients treated with Bimatoprost SR 10 µg in study 192024-093 reported higher frequency of conjunctival hyperaemia, dry eye and intraocular pressure increased beyond the two-day period after the implantation compared to the immediate postimplantation period, which requires further justification by the applicant.

Given the low systemic concentrations of bimatoprost achieved after the intracam

eral implantation of Bimatoprost SR the risk of systemic interactions is very unlikely. However, no discussion is made by the applicant related to the local risks derived from the concomitant administration of intravitreal medicinal products (anti-VEGF drugs, intravitreal corticosteroids such as dexamentasone [Ozurdex] or fluocinolone acetonide [Iluvien]) and bimatoprost SR.

5.6. Effects Table

Table 67: Effects Table for Durysta 10 micrograms indicated for the reduction of intraocular pressure (IOP) in adults with open angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medications (data cut-off: Study 192024-093: 21 June 2022; Study 1698-301-007: 29 July 2022).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Phase III trial 192024-093			**Bimatoprost SR 10µg**	**SLT**		
IOP Change from baseline (CFB) at week 4, 12, 24	IOP CFB, least square mean	mmHg	(n=183 subject eyes)	(n=183 subject eyes)	<u>Strength of evidence:</u> Non inferiority criteria met for all three timepoints <u>Uncertainties</u> W24 data is presented cumulatively for 1 and 2 BimSR administrations and fixed and flexible dosing regimen – additional analysis requested, MMMR model might be too optimistic – additional analyses requested	Section on clinical efficacy 3.3.4 Primary efficacy endpoint
		W4	-6.8	-6.2	-0.6 with 95% CI (-1.03, -0.08, p=0.0231)	
		W12	-6.9	-6.4	-0.4 with 95% CI (-1.04, 0.18, p=0.1615)	
		W24	-6.9	-6.5	-0.4 with 95% CI (-0.97, 0.17, p=0.1673)	
Phase IIIb trial 1698-301-007			**Bimatoprost SR 10µg** (n=313)	N/A		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
median time from initial administration of Bim SR 10 µg to requiring a second administration or rescue treatment		(time [days] to event)	377 days 95% CI (330.0, 512.0) For the 50% percentile		Uncertainty interpretation of data is obscured by lack of criteria for rescue medication	Primary efficacy endpoint
Phase 3 trials - 091 and - 092						
IOP Change from baseline at Hour 0 and Hour 2 of week 12, Cycle 1	Difference in LS mean change from baseline (BIM SR 10 µg – timolol)	mmHg	BIM SR 10 µg	Timolol BID Hour 0: -6.05 Hour 2: -6.48	Difference vs.TIM (95% CI) NI criteria met; uncertainties regarding the superiority over (a putative) placebo, MMMR model might be too optimistic – additional analyses requested	**co-PEP**
IOP Change from baseline at Hour 0 and Hour 2 of week 12, Cycle 1	Difference in LS mean change from baseline (BIM SR 10 µg – timolol)	mmHg	BIM SR 10 µg	Timolol BID	Difference vs.TIM (95% CI) Hour0: -0.08 (-0.88, 0.73) Hour2: -0.36 (-1.12, 0.41) NI criteria met; uncertainties regarding the superiority over (a putative) placebo, MMMR model might be too optimistic – additional analyses requested	**co-PEP**
Unfavourable Effects						
Ocular TEAEs	Overall higher in bimatoprost group	% of treated eyes	10µg bimatoprost SR 67.4%	SLT 60%	175 patients in bimatoprost group, 180 in SLT group	Section on clinical safety 3.3.7
Related ocular TEAEs	Overall higher in bimatoprost group	% of treated eyes	38.9%	22.2%	Same as above	Same as above
Corneal TEAEs of special interest	Similar in cycle 1	% of treated eyes	2.9%	2.8%	Same as above Carry-over may mask higher frequencies in cycle 1 due to late onset	Same as above

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Corneal TEAEs of special interest	Higher in bimatoprost group in cycle 2	% of treated eyes	8.9%	1.6%	Same as above	Same as above
ECL ≥15%	Similar in cycle 1	% of treated eyes	1.7%	2.2%	Same as above Carry-over may mask higher frequencies in cycle 1 due to late onset	Same as above
ECL ≥15%	Higher in bimatoprost group in cycle 2	% of treated eyes	6.3%	0.8%	Same as above	Same as above
ECL ≥30%	Higher in bimatoprost group	% of treated eyes	8.0%	1.3%	Same as above	Same as above
ECL ≥40%	Higher in bimatoprost group	% of treated eyes	4.6%	0.4%	Same as above	Same as above
ECL ≥50%	Higher in bimatoprost group	% of treated eyes	2.9%	0%	Same as above	Same as above
SAEs	Higher in bimatoprost group	% of treated eyes	2.3%	0%	Same as above	Same as above

Abbreviations: TEAEs: treatment emergent adverse events; SAEs: serious adverse events; IOP: intraocular pressure, SLT: selective laser trabeculoplasty, CI: Confidence interval, ECL ≥40%: ≥40% corneal endothelial cells lost compared to baseline

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

For patients whose intraocular pressure (IOP) is not adequately controlled with topical IOP-lowering agents (eye drops) due to non-adherence, the BIM SR implant offers a viable treatment option that addresses at least partly the issue of non-adherence associated with daily administration of eye drops and may reduce the number of medications a patient is required to self-administer. The IOP-lowering effect of BIM SR is non-inferior to selective laser trabeculoplasty (SLT).

Considering the data on the flexible dosing regimen from studies -093 and -301-007, it appears that for many patients, one administration of BIM SR may provide at least one year of IOP lowering. However, this effect is variable and many patients still need concomitant eye drops as a rescue treatment to control the IOP.

The overall safety profile of Durysta concerning and is worse compared to SLT treatment. Safety events are already more frequently observed after cycle 1 Frequency of ocular TEAEs, related TEAEs, and SAEs are all higher in the bimatoprost group. Frequencies of corneal TEAEs of special interest were comparable between Durysta and SLT treatment in cycle 1. However, due to late onset described for e.g. corneal endothelial cell loss (>16 weeks post implantation), uncertainties remain regarding assignment of these events to treatment cycles. The safety profile after retreatment is significantly worse compared to cycle 1. Although most of the ocular TEAEs are mild or moderate in intensity, especially the corneal TEAEs of special interest during cycle 2 are of great concern.

Corneal endothelial cell loss is reported at higher frequencies and with increased severity (e.g. more cells lost compared to baseline) under Durysta treatment compared to SLT. This cell loss is irreversible, since human endothelial cells are considered to be non-proliferative in vivo, making the preservation of endothelial cell density most important for patients with chronic eye diseases.

After a follow-up duration of 60 months, it is still unclear when Durysta implants are fully degraded in the majority of patient eyes. This issue is further aggravated by reports of "stacking" of implants in patient eyes after retreatment, thought to increase likelihood of endothelial cell loss.

Considering the proposed posology, where treatment of a chronic disease is foreseen, data from retreatment as well as long-term safety data are considered limited. Critical safety signals like ECL increase with repeated use and the safety effects of the implant remaining in the eye are still uncertain.

5.7.2. Balance of benefits and risks

Bimatoprost SR implant is intended for a temporally limited use (i.e. maximum 2-cycles). Therefore, treatment with Bimatoprost SR could account for only a (very small) portion of a patient's ever changing treatment regimen over the course of the disease, and a different treatment option would be necessary once Bimatoprost SR administration is no longer indicated. In this light, especially taking into consideration the considerable safety risks associated with BIM SR the benefit of 1-2 doses of Bim SR implant is considered limited. The safety risk pertaining to endothelial cell loss seems to be more pronounced upon re-administration, however it remains unclear whether some of these events stem from the first implant but are reported only later due to the delayed onset leading to carry-over. The long persistence of the (useless) implant in the eye and "stacking" with other implants in case of retreatment in the same eye, are thought to further increase the risk for irreversible corneal endothelial cell loss.

Considering these concerns, the benefit/risk of re-administration is considered negative. The data so far do not establish the benefit/risk of a single administration. In addition, depending on the applicant's responses on patients with Shaffer grades 3 and 4, the target population might have to be further narrowed. All three safety MOs need to be resolved to conclude a positive B/R balance from a clinical safety perspective. Resolving the MO regarding unacceptability of the safety profile after retreatment is not sufficient to alleviate concerns regarding the overall safety profile of the Bimatoprost SR implant.

In addition, seven quality major objections relating to definition and compliance (MDR) of the integral medical device (applicator), comparability of drug release and particulate contamination of commercial and clinical trial product, novel excipients, sterility of the finished product and process control are raised.

Therefore, the benefit/risk is considered negative.

5.7.3. Additional considerations on the benefit-risk balance

Not applicable.

5.8. Conclusions

The overall benefit /risk balance of Durysta (bimatoprost SR) is negative.