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Study ID: 192024-092

Title: The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

Protocol Date: June 5, 2018

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The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

Protocol Number:	192024-092 Amendment 3
EudraCT Number:	2014-003186-24
Phase:	3
Name of Investigational Product:	Bimatoprost SR
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Approval Date: 05-Jun-2018

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Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page: name and contact information of Allergan study personnel and emergency telephone numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing institutional review board (IRB); US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations
- Maintain all information supplied by Allergan in confidence, and when this information is submitted to an institutional review board (IRB), independent ethics committee (IEC) or another group, it will be submitted with a designation that the material is confidential
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

Table of Contents

List of Tables

List of Figures

Protocol Summary

Study Compound: Bimatoprost sustained-release (SR) biodegradable implants containing preservative-free AGN-192024 (bimatoprost)

Phase: 3

Study Objectives:
To evaluate the intraocular pressure (IOP)-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) after initial and repeated administrations

Clinical Hypotheses:

At least 1 dose strength (10 µg or 15 µg) of Bimatoprost SR will have an IOP-lowering effect that is noninferior to that of topically administered timolol maleate 0.5% (hereafter referred to as timolol) eye drops in patients with OAG or OHT following single and repeat administration.

Bimatoprost SR administered intracamerally in dose strengths of 10 µg or 15 µg will have an acceptable safety profile in patients with OAG or OHT following single and repeat administration.

Study Design

Structure: Phase 3, multicenter, randomized, masked, parallel-group comparison (2 dose strengths of Bimatoprost SR versus active control), repeat administration

Duration: Approximately 22 months, 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

Study Treatment Groups: Bimatoprost SR dose groups: 10 µg and 15 µg

Control: Timolol eye drops plus Sham needleless procedure (that involves touching the eye at the area of insertion with a needleless applicator).

Dosage/Dose Regimen: Patients will receive 1 of 2 dose strengths of Bimatoprost SR or Control treatment in the study eye on Day 1 (with repeat administration of the same dose strength or Sham at Week 16 and Week 32).

Bimatoprost SR-treated patients will receive intracameral administration of Bimatoprost SR in the study eye using a prefilled applicator. Timolol vehicle eye drops will be used twice daily (BID; in the morning and evening) to mask the treatment of patients receiving Bimatoprost SR in the study eye. The fellow eye will receive a Sham needleless procedure (hereafter called Sham administration or Sham administration procedure) plus topical timolol eye drops, BID. Control group patients will receive a Sham administration plus timolol in both eyes.

All patients will be masked to their treatment group. Treatment groups are shown in Table 1.

Table 1 Treatment Groups

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

The patients will begin self-administration of the study-provided eye drops (vehicle or timolol) in both eyes, starting with the evening dose on the first administration (Bimatoprost SR or Sham administration) day visit. Patients will continue self-administration of the study-provided eye drops in the morning (08:00 ± 1 hour) and in the evening (20:00 ± 1 hour) approximately 12 hours apart throughout the study, with the exception of the morning of a subsequent visit, on which the morning eye drop administration will be performed at the study site.

Randomization/Stratification: Randomization to treatment groups will use a 1:1:1 ratio (Bimatoprost SR 10 µg:Bimatoprost SR 15 µg:Control). Randomization will be stratified by baseline study eye Hour 0 IOP (≤ 25 mm Hg or > 25 mm Hg).

Visit Schedule: Patients who complete the entire study without receiving nonstudy IOP-lowering medication in both eyes will have a minimum of 25 visits and 6 phone calls. The schedule includes:

- Screening (up to 28 days); Washout period of up to 42 days for both eyes (which may begin once screening procedures have been completed); Baseline (up to 3 days)
- Treatment period
    - Cycle 1: Day 1 Administration Day; Day 2; phone call on Days 4 and 8; and visits at Weeks 2, 6, 12, and 15
    - Cycle 2: Week 16 Administration Day; Cycle 2 Day 2; phone call on Cycle 2 Days 4 and 8; and visits at Weeks 18, 22, 28, and 31
    - Cycle 3: Week 32 Administration Day; Cycle 3 Day 2; phone call on Cycle 3 Days 4 and 8; and visits at Weeks 34, 38, 44, 48, and 52
- Extended Follow-up
    - Visits at Months 14, 16, 18, and 20/Exit

Intraocular pressure evaluations will occur at 2 timepoints: Hour 0 (08:00 ± 1 hour) and Hour 2 (Hour 0 + 2 hours [± 30 minutes]).

Patients who have not received nonstudy IOP-lowering medication (prohibited prior to Week 52) in both eyes will 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. Administration should not occur if the investigator believes that there are any safety concerns. Patients who have received nonstudy IOP-lowering medication in both eyes will be followed for at least 12 months following the last administration of Bimatoprost SR or Sham, at which time they may exit early at the investigator's discretion.

Study Population Characteristics

Number of Patients: Approximately 510 patients will be enrolled in the study.

Condition/Disease: Patients with OAG (primary OAG, pseudoexfoliative glaucoma, or pigmentary glaucoma) or OHT who require IOP-lowering medications in both eyes. The eye that meets the entry criteria will be selected as the study eye. If both eyes meet the entry criteria, the eye with the higher IOP at baseline Hour 0 will be selected as the study eye. If both eyes have the same IOP at Hour 0, then the right eye will be designated as the study eye.

Key Inclusion Criteria:

- Written informed consent has been obtained
- Diagnosis of either OAG (ie, primary, pseudoexfoliation, or pigmentary glaucoma) or OHT in each eye and both eyes require IOP-lowering treatment (Note: diagnosis does not have to be the same in both eyes)
- In the investigator's opinion, either eye can be treated adequately with topical ophthalmic beta-blocker (eg, timolol) eye drops as the sole therapy

- In the investigator's opinion, either eye can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy
- The iridocorneal angle in the study eye 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.
- At the Baseline visit: Hour 0 IOP in the study eye of ≥ 22 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≤ 32 mm Hg
- At the Baseline visit: Hour 2 IOP in the study eye of ≥ 19 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≤ 32 mm Hg
- By the Baseline visit, the final central endothelial cell density in both eyes must be confirmed as being qualified by Reading Center assessment, with at least one eye qualified for inclusion as the study eye

Key Exclusion Criteria:

- The following surgical history:
    a. History or evidence of complicated cataract surgery in the study eye: 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 in the study eye
- In the investigator's opinion, patient is nonresponsive to topical ophthalmic beta-blockers and/or topical prostamides, prostaglandins, or prostaglandin analogs (eg, LUMIGAN, Xalatan, Travatan)
- Contraindications to beta-blocker therapy

Response Measures

Efficacy: Intraocular pressure measured by Goldmann applanation tonometry

Safety: Adverse events; ocular parameters as determined through assessment of visual acuity and visual field; evaluation of macroscopic bulbar conjunctival hyperemia and iris color; assessment of endothelial cell density and corneal thickness; IOP measurement, biomicroscopic and ophthalmoscopic examinations (including gonioscopy with Bimatoprost SR implant assessment, optic disc examination, and dilated fundus examination); and optical coherence tomography (OCT) of the macula

General Statistical Methods and Types of Analyses:

The intent-to-treat population (ITT) is defined as all randomized patients and will be used for demographic and efficacy analyses. The per protocol (PP) population will consist of the subset of the ITT population with no protocol deviations affecting the primary efficacy analysis and will be used to confirm the primary efficacy analysis. A list of patients excluded from the PP population will be finalized prior to database lock. The safety population is defined as all patients who received study drug treatment and will be used for safety analyses. Analyses in the ITT population will be based on the treatment to which a patient was randomized, and analyses in both the PP and safety populations will be based on the actual treatment a patient received.

Continuous variables will be summarized by descriptive statistics including sample size, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency and percentage.

The primary efficacy variable is study eye time-matched IOP change from baseline. Mean IOP change from baseline will be compared between each Bimatoprost SR dose strength and timolol for each hour (Hours 0 and 2) using the ITT population. The comparisons at Week 12 will be considered the primary analysis.

Intraocular pressure change from baseline will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The model will include 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 effects. Unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance matrix fails to converge, multiple imputation (MI) will be implemented before MMRM.

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 will be provided for each hour (Hours 0 and 2) at each visit. The formal noninferiority test will be performed at Week 12 for each Bimatoprost SR dose strength versus timolol using a noninferiority margin of 1.5 mm Hg. A gatekeeping procedure will be 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 for a given hour at Week 12 is valid only if the noninferiority of Bimatoprost SR 15 µg to timolol is demonstrated for the same timepoint. Bimatoprost SR 15 µg (or 10 µg) will be declared noninferior to timolol if the upper limit of the 95% confidence interval is ≤ 1.5 mm Hg for both Hours 0 and 2 at Week 12.

For the United States Food and Drug Administration (US FDA), the primary efficacy variable will be the study eye IOP. The primary analysis will be based on Weeks 2, 6, and 12 using the ITT population. Specifically, the following analysis will be performed: IOP will be analyzed using an MMRM approach based on the same model as described for the primary efficacy analysis of time-matched IOP change from baseline. Within the framework of this model, the mean difference between each Bimatoprost SR dose strength and timolol group and the corresponding 95% confidence interval will be provided for each hour (Hours 0 and 2) and each visit (Weeks 2, 6, and 12). A gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level for each timepoint, testing Bimatoprost SR 15 µg against timolol first and followed by the comparison between Bimatoprost SR 10 µg and timolol. The test for Bimatoprost SR 10 µg versus timolol for a given hour at a visit is valid only if the noninferiority of Bimatoprost SR 15 µg to timolol has been demonstrated for the given timepoint. Each Bimatoprost SR dose strength that shows noninferiority to timolol at all 6 timepoints with a 1.5 mm Hg margin (ie, the upper limit of the 95% confidence interval is ≤ 1.5 mm Hg) will be declared clinically noninferior to timolol if the upper limit of the 95% confidence interval is ≤ 1.0 mm Hg for 3 or more timepoints.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized for all events regardless of causality and for treatment-related adverse events. Ocular adverse events and safety variables will be tabulated by study eye and fellow eye within each treatment dose strength or group, and nonocular safety variables will be summarized by patient.

Sample Size Calculation: The sample size calculation is based on the primary efficacy analysis of the IOP for US FDA review because the sample size based on the primary efficacy analysis for other regions is expected to be smaller. Based on simulations, a sample size of 486 patients (162 per group) will provide approximately 95.1% and 83.5% power to show noninferiority (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. Assuming a premature discontinuation rate of 5% within 12 weeks (before the primary database lock), approximately 510 patients (170 per group) are to be enrolled into this study.

Figure 1 **Flowchart of Patient Participation**

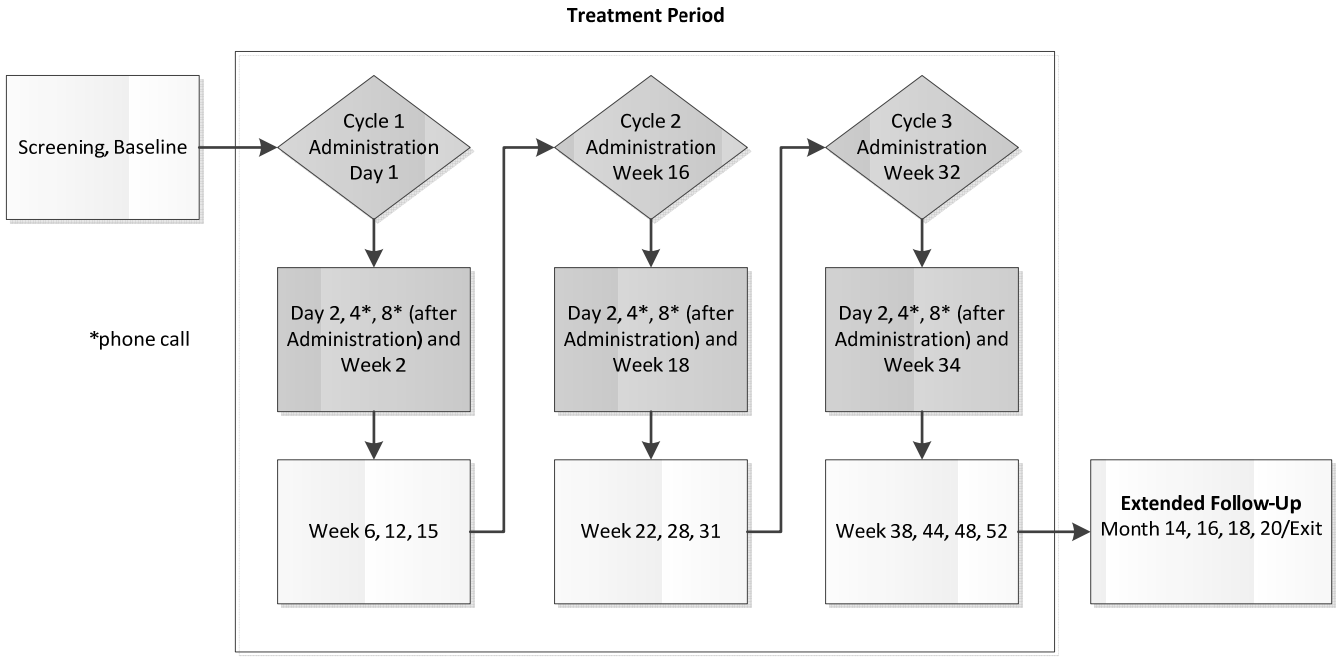


Table 2 Screening through Treatment Day 1

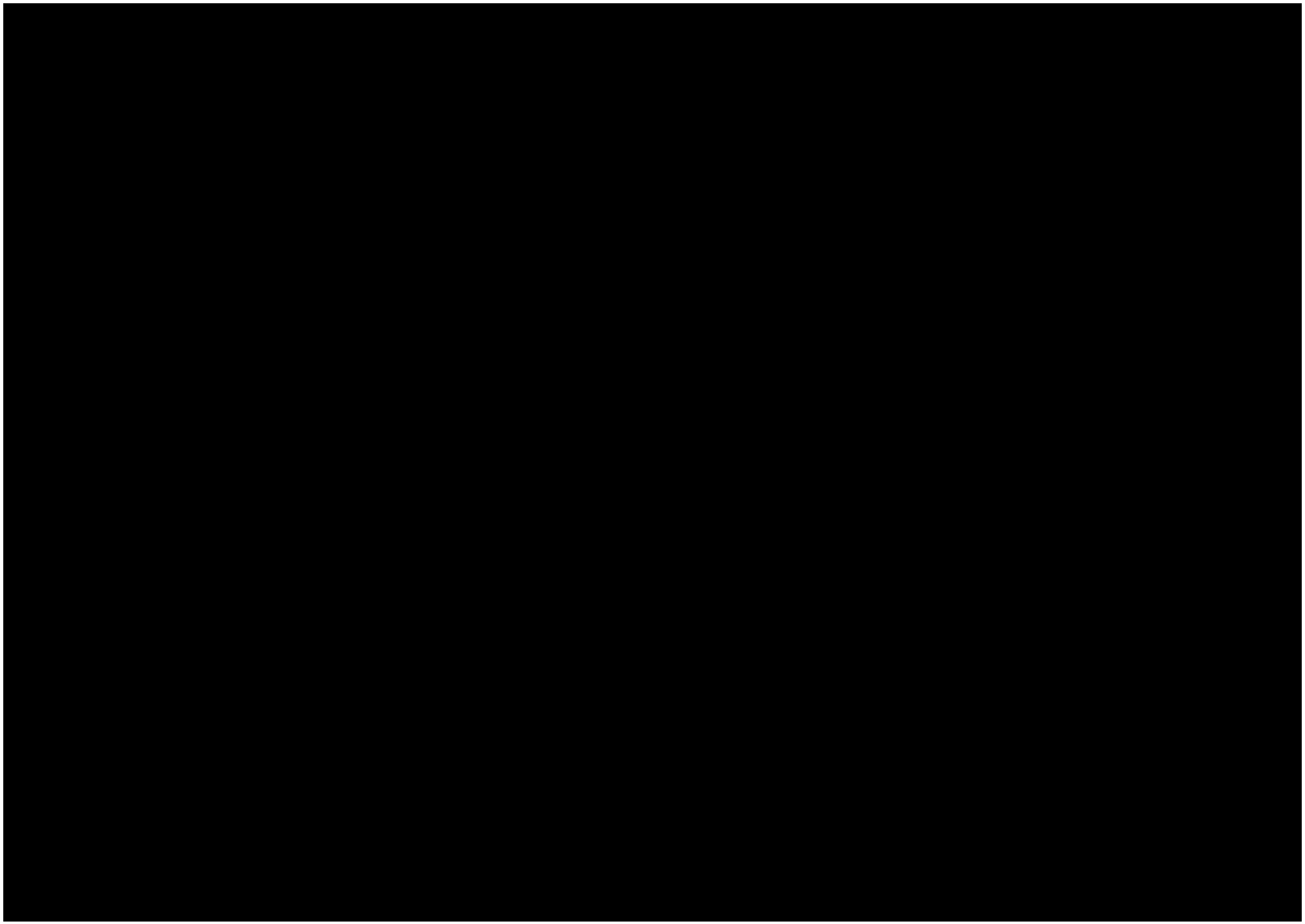


Table 3 Administration Cycle 1 Schedule of Visits and Procedures: Treatment Period Day 2 through Week 12

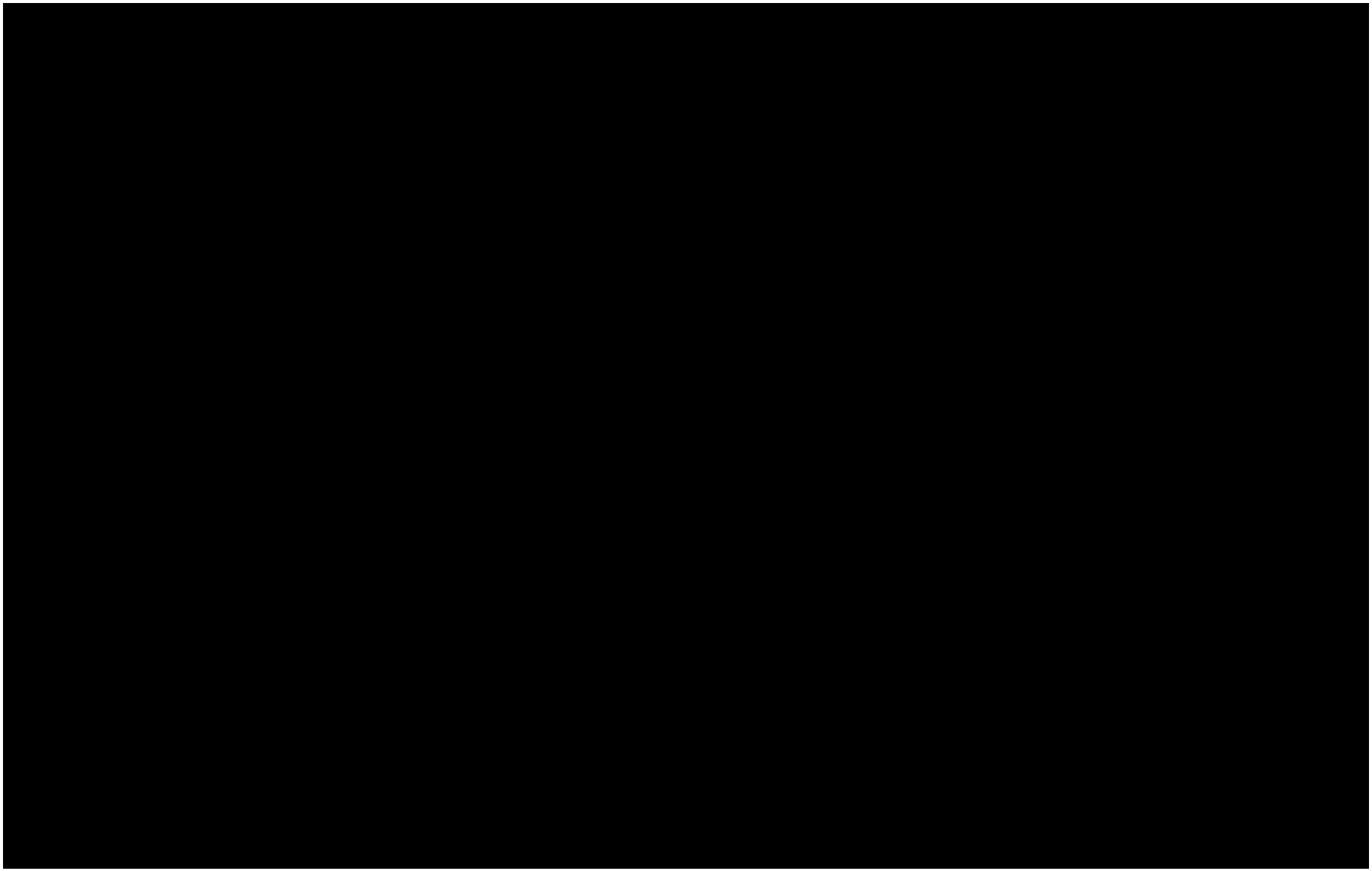
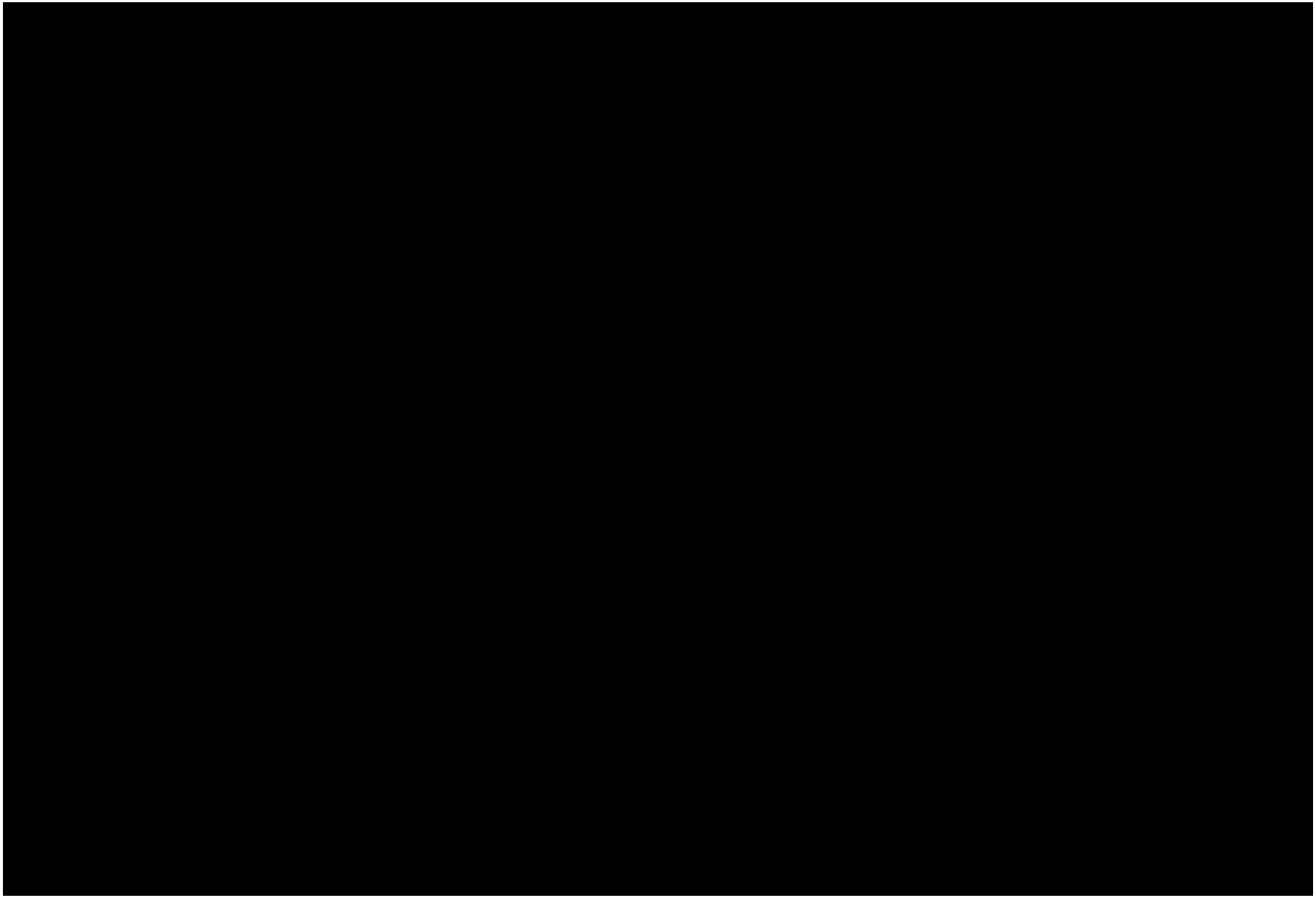


Table 4 Administration Cycle 2 Schedule of Visits and Procedures: Treatment Period Week 15 Through Week 28



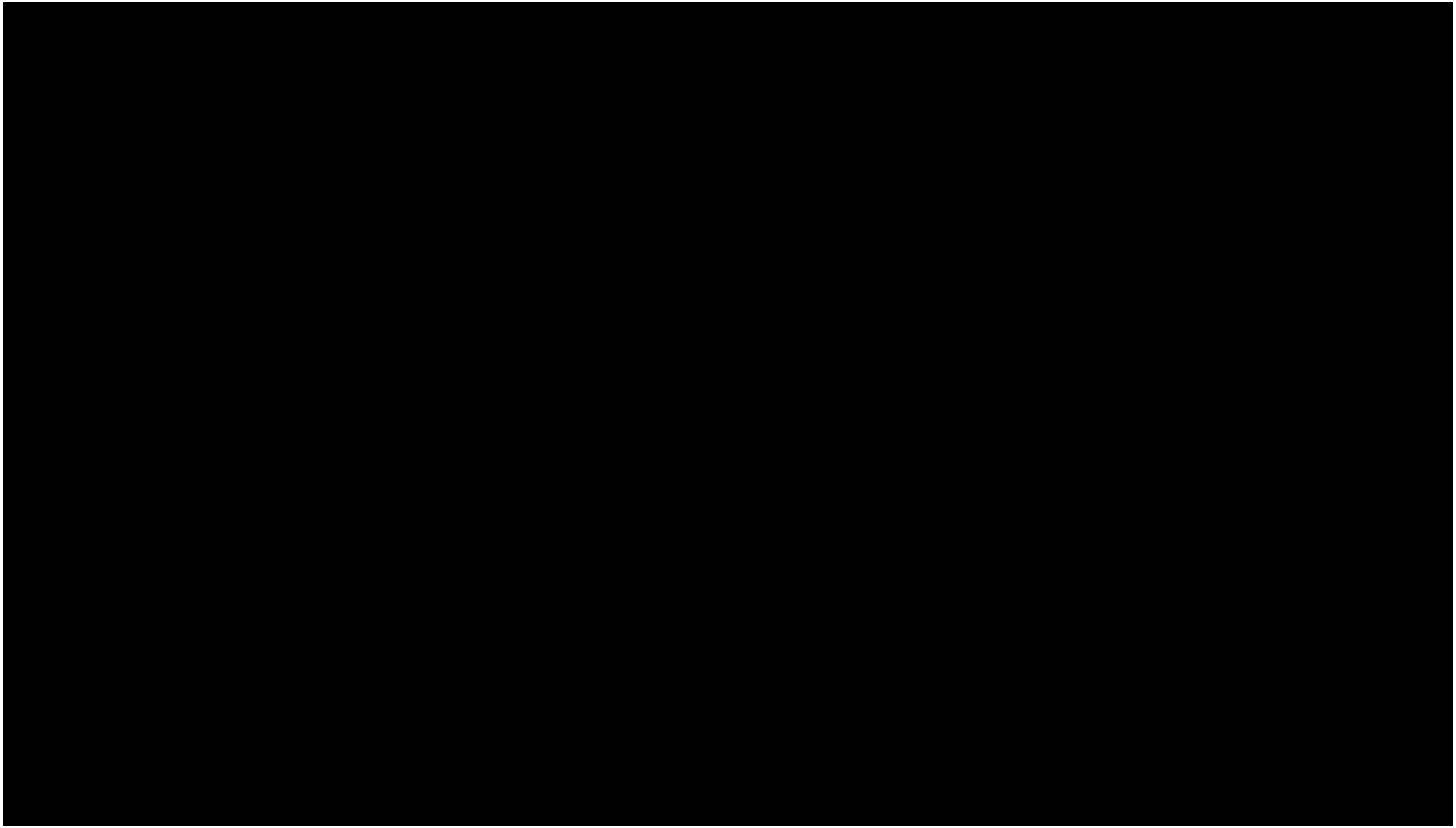


Table 6 Schedule of Visits and Procedures: Extended Follow Up Months 14, 16, 18, and 20

1. Background and Clinical Rationale

1.1 Glaucoma Overview

Glaucoma is a family of diseases commonly characterized by progressive optic neuropathy with associated visual field defects and is the leading cause of irreversible blindness in the world. Glaucoma is classified by Becker-Shaffer into 3 broad types: developmental, angle-closure, and open-angle glaucoma (OAG) (Stamper et al, 2009). Open-angle glaucoma is further categorized into primary OAG (POAG, sometimes also referred to as chronic OAG) and secondary OAG (which includes pigmentary and pseudoexfoliation glaucoma), the former being the predominant form of OAG. Primary OAG is characterized as a multi-factorial optic neuropathy with a characteristic acquired atrophy of the optic nerve and loss of ganglion cells and their axons, developing in the presence of open anterior chamber (AC) angles, and manifesting characteristic visual field abnormalities (American Academy of Ophthalmology, 2010a). It is estimated that 2.25 million people in the United States (US) over the age of 40 years have POAG, half of whom are unaware of their disease despite demonstrable visual field loss (Quigley, 1996). Globally, over 60 million people are estimated to be affected by glaucoma (the majority of whom have open angle glaucoma) and these numbers are expected to increase over time (Quigley and Broman, 2006; Varma et al, 2011; Cook and Foster, 2012).

Although many risk factors have been associated with OAG, elevated intraocular pressure (IOP) remains the most prominent factor and the only factor existing that ophthalmic intervention can reliably affect (Stamper et al, 2009). A number of controlled trials have demonstrated that lowering IOP will slow or delay the appearance or progression of glaucomatous damage. Large, randomized clinical trials such as the Ocular Hypertension Treatment Study (OHTS) (Kass et al, 2002) and the Early Manifest Glaucoma Trial (EMGT) (Heijl et al, 2002) addressed the value of early detection and lowering of elevated IOP in ocular hypertension (OHT) or POAG. The effects and parameters of various interventions in eyes with established glaucomatous damage were addressed by the Collaborative Initial Glaucoma Treatment Study (CIGTS) (Lichter et al, 2001) and the Advanced Glaucoma Intervention Study (AGIS) (AGIS, 2000). The currently available approaches to lowering IOP include pharmacological therapy, laser trabeculoplasty, incisional surgery, and cyclodestructive procedures. Each of these approaches has its own risk-benefit ratio. Because the risk-benefit ratio with drug therapy appears to be lower than that of surgical procedures, both historical and contemporary practice has been to attempt pharmacological treatment before resorting to other more invasive alternatives.

Patient nonadherence to topical therapy is one of the major challenges to preventing vision loss due to glaucoma, as consistent IOP reduction is associated with reduced risks of the development and progression of optic nerve damage (Friedman, 2009; Tsai, 2009). In patients that are nonadherent to medical therapy, guidelines are provided to clinicians for assisting patients with being adherent (Budenz, 2009). Nevertheless, frequently, patients with OAG or OHT not taking their medications will require incisional surgery to control the IOP. Some of the disadvantages of performing incisional surgery include the significant sight-threatening complications that can occur with surgery, such as the globe perforation, suprachoroidal hemorrhage, hypotony maculopathy, corneal decompensation, and cataract formation or progression that may occur with filtering surgery (Mosaed et al, 2009). Given the risks associated with incisional surgery, sustained-release formulations of ocular antihypertensive drugs are in development as an alternative to surgery for the management of elevated IOP (Knight and Lawrence, 2014).

1.2 Bimatoprost (LUMIGAN®)

Bimatoprost is a member of a series of unique prostanoid compounds that are potent and efficacious ocular antihypertensive agents (Woodward et al, 1994, 2001, and 2004). Bimatoprost appears to mimic the activity of biologically active prostamides (Study BIO-99-308; Matias et al, 2004). Chemically, prostamides differ from prostaglandin analogs by being neutral because they lack carboxylic acids (Krauss and Woodward, 2004). Prostamides can be biosynthetically derived from anandamide, an endogenous membrane lipid (Kozak et al, 2002; Weber et al, 2004; Woodward et al, 2001; Yu et al, 1997). The prostamide pathway leads to the biosynthesis of novel lipid amides that lower IOP.

The IOP-lowering efficacy of LUMIGAN (bimatoprost ophthalmic solution) 0.03% is well established. In phase 3 studies in patients with POAG or OHT, LUMIGAN administered once daily as monotherapy was superior to timolol at all timepoints (Higginbotham et al, 2002). This was further substantiated in the extension studies which followed patients in a masked manner for up to 4 years (Cohen et al, 2004; Williams et al, 2008; Study 192024-014). In clinical studies of patients with OAG or OHT with a mean baseline IOP of 26 mm Hg, the IOP-lowering effect of LUMIGAN once daily in the evening was 7 to 8 mm Hg (Cohen et al, 2004; LUMIGAN® Package Insert, 2012; Williams et al, 2008).

LUMIGAN was approved by the US Food and Drug Administration (FDA) in 2001. Worldwide, LUMIGAN 0.03% is currently licensed and marketed in more than 80 countries and LUMIGAN 0.01% is licensed and marketed in more than 40 countries. Preservative-free

bimatoprost ophthalmic solution 0.03% has been approved since November 2012 for lowering IOP, and is currently marketed in 10 countries.

1.3 Bimatoprost SR

A sustained-release formulation of bimatoprost was developed at Allergan, Inc. to evaluate ocular antihypertensive therapies that do not require patient self-administration. Bimatoprost SR refers to the biodegradable, sustained-release, preservative-free bimatoprost implant which is preloaded in an applicator for administration; together they comprise the Bimatoprost Sustained Release product (and will henceforth be referred to as Bimatoprost SR). The Bimatoprost SR implant is injected into the AC via the corneal limbus using the prefilled applicator. The biodegradable polymer matrix gradually degrades to carbon dioxide and water so that there is no need to remove the Bimatoprost SR implant once the drug has been released. The Bimatoprost SR implant used in this study contains total preservative-free bimatoprost loads of 10 µg or 15 µg, to provide average daily release (as determined by in vitro studies) of approximately 110 ng or 170 ng, respectively, over an approximate 3-month duration in the AC. In contrast, a typical 35 µL drop of LUMIGAN 0.03% contains approximately 10 µg of bimatoprost. Thus, with topical therapy, a patient would have drug exposure to the ocular surface totaling approximately 900 µg over 3 months. Substantially reducing the total daily drug exposure to the eye and delivering the drug directly to the aqueous humor may reduce the adverse effects that occur with topical therapy. The Bimatoprost SR implant is expected to release drug over approximately 3 to 4 months, and > 75% polymer matrix degradation is expected within approximately 12 months. Although the biodegradation process of the Bimatoprost SR implant exceeds the drug release duration, experience from preclinical studies, the phase 1/2 clinical study 192024-041D, and approved intravitreal implants composed of similar biodegradable polymers provide support for the anticipated safety in a phase 3 clinical trial with repeated administration.

1.3.1 Nonclinical Studies with Bimatoprost SR

Pharmacology, toxicology, and pharmacokinetic studies with multiple dose strengths, implant sizes and formulations (Generation 1 and Generation 2) of Bimatoprost SR were done in 2 species (Beagle dog, Cynomolgus monkeys) with a range of anterior chamber angle sizes in order to support the clinical program. These studies build on the already considerable amount of nonclinical and clinical information available for topical bimatoprost (see Investigator's Brochure for additional details).

Nonclinical studies with pharmacology endpoints (Reports BIO-09-803, BIO-11-920, PK09109-PK, BIO-09-785) showed dose-related reductions in IOP in normotensive Cynomolgus monkeys and Beagle dogs, as well as in laser-induced ocular hypertensive Cynomolgus monkeys following single doses. Toxicology studies, of at least 6 to 12 months duration and including single and repeat Bimatoprost SR administration, were conducted in Cynomolgus monkeys and Beagle dogs (TX09051-TX, TX09066-TX, TX10016-TX, TX11076-TX, TX12012-TX, TX12018-TX, and TX12102-TX). Monkeys, which have a characteristically small anterior chamber angle compared to both dogs and humans, did not tolerate Bimatoprost SR dose strengths tested (≥ 10 µg Bimatoprost SR) due to chronic contact of the implant with corneal endothelium. Single and repeat ocular toxicity studies with Generation 2 Bimatoprost SR in dogs with varying AC angle sizes demonstrated acceptable safety and ocular tolerability with single doses ≤ 20 µg (TX11076-TX, TX12012-TX, TX12018-TX) and with repeat doses of ≤ 15 µg (TX12012-TX, TX12018-TX). Furthermore, no adverse drug- or implant-related ocular findings have been seen following three intracameral injections of up to 20 µg (two 10 µg implants) Bimatoprost SR in the 18-month repeat dose Good Laboratory Practice (GLP) study in dogs (Report TX12102-TX).

Pharmacokinetic studies (PK09109-PK, PK11086-PK) in Beagle dogs demonstrated that systemic exposure of bimatoprost and bimatoprost acid was below the limit of quantitation (BLQ) with doses ≤ 60 µg. Aqueous humor concentrations generally peaked by 10 weeks postdose for doses ≤ 30 µg (Generation 1 and Generation 2), then declined to low levels suggestive of near-complete drug release from the device at 3 months for doses ≤ 20 µg. By 14 weeks following a 20 µg (Generation 2) dose, ocular tissues samples were collected for analysis, which demonstrated that drug and metabolite concentrations were BLQ in aqueous humor, vitreous humor, retina, and the remnant implants, but detected in cornea, choroid, and iris-ciliary body. A pharmacokinetic study (PK14025-PK) was conducted in Beagle dogs comparing the ocular distribution of topical bimatoprost 0.03% solution or a single Generation 2 Bimatoprost SR implant (15 µg). Following topical administration, bimatoprost and bimatoprost acid distributed into the iris-ciliary body as well as other (off target) tissues with concentrations in the bulbar conjunctiva, eyelid margin, and periorbital fat significantly higher than those observed in the iris-ciliary body. In contrast, following administration of a single Generation 2 Bimatoprost SR implant at 15 µg, bimatoprost and bimatoprost acid concentrations were either below the limit of quantitation (BLQ) or near the detection limit in bulbar conjunctiva, eyelid margin, and periorbital fat while the highest bimatoprost and bimatoprost acid concentrations were observed in the target tissue, the iris ciliary body. Retinal concentrations were BLQ following both topical and Bimatoprost SR administration.

1.3.2 Other Biodegradable Ocular Implants

A number of sustained-release drug delivery implants using the Allergan biodegradable polylactic acid (PLA) and/or polylactic-*co*-glycolic acid (PLGA) NOVADUR® drug delivery system preceded the development of the Bimatoprost SR implant. The extensive clinical experience with previous intraocular implants demonstrates the safety and tolerability of an intraocular biodegradable implant administered into the eye via an applicator system. For example, late phase clinical trials of sustained-release implants have been completed for the OZURDEX® dexamethasone intravitreal implant using the NOVADUR drug delivery system for intraocular injections. Because Bimatoprost SR is similar to OZURDEX in a number of aspects and uses the NOVADUR drug delivery system for intraocular injections, these data may be supportive of the safety and tolerability of Bimatoprost SR in humans.

1.3.3 Clinical Study with Bimatoprost SR

Study 192024-041D was a Phase 1/2, paired-eye comparison evaluating the safety and efficacy of 4 dose strengths of Bimatoprost SR (6 µg, 10 µg, 15 µg, or 20 µg [2 × 10 µg implants]), as single or repeat administration in one eye (study eye), versus the use of topical LUMIGAN® 0.03% in the fellow eye (nonstudy eye). The objective of this study was to evaluate the safety and IOP-lowering efficacy of Bimatoprost SR in patients with OAG.

A total of 109 patients received a single administration and 24 patients received a repeat administration of Bimatoprost SR. A trend in dose-response was observed across the 4 dose strengths that were tested. Data suggest that the implant may provide topical prostaglandin analog-like efficacy up to 3 to 4 months post-implantation in the majority of patients. Data following the second administration in the redosed patients showed similar IOP lowering to that observed following the first administration of Bimatoprost SR.

Bimatoprost SR showed an acceptable safety profile with single and repeat administrations in Study 192024-041D. Most adverse events were ocular, mild or moderate in severity, occurred within the first 2 days after Bimatoprost SR administration, and were considered related to the study drug administration procedure. There were no reports of serious study drug-related adverse events, and no new safety concerns were observed after the second treatment. Please refer to the Investigator's Brochure for details on reported safety findings.

1.4 Study Rationale

In the 192024-041D Phase 1/2 clinical study, results suggest that Bimatoprost SR provides IOP-lowering efficacy similar to topical prostaglandin analogs in the dose strengths proposed

for this Phase 3 investigation. Additionally, the safety profile of Bimatoprost SR at dose strengths of 20 µg (2 × 10 µg) or less in the Phase 1/2 study was acceptable, and supports additional clinical study in man. Study 192024-092 is a randomized, patient and efficacy evaluator-masked, parallel-group comparison to evaluate the safety and IOP-lowering effects of repeated administrations of 10 µg or 15 µg Bimatoprost SR in patients with OAG or OHT and open iridocorneal angles inferiorly in the study eye by clinical gonioscopy.

The 2 dose strengths of Bimatoprost SR will be compared versus a control group treated with the active comparator, topically applied timolol 0.5%. Timolol is a well-established treatment for IOP lowering in glaucoma and OHT, and has been used as a comparator in other IOP-lowering studies (Weinreb and Kaufman, 2009).

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

- To 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

2.2 Clinical Hypotheses

- At least 1 dose strength (10 µg or 15 µg) of Bimatoprost SR will have an IOP-lowering effect that is noninferior to that of topically administered timolol maleate 0.5% (hereafter referred to as timolol) eye drops in patients with OAG or OHT following single and repeat administrations.
- Bimatoprost SR administered intracamerally in dose strengths of 10 µg or 15 µg will have an acceptable safety profile in patients with OAG or OHT, following single and repeat administrations.

3. Study Design

This study is a multicenter, dose-ranging, randomized, parallel-group, patient and efficacy-evaluator masked 52-week evaluation (52-week treatment period with 8 months extended follow-up) of the safety and efficacy of Bimatoprost SR compared to timolol twice daily (BID) in patients with OAG or OHT. The patients and the evaluators of the primary endpoint (IOP) will be masked to the treatment received. The site coordinator and designated staff will not be masked to whether the patient received 1 of the two dose strengths of Bimatoprost SR or the Sham administration, but will be masked to the specific dose strength that the patient receives. Vehicle eye drops will be used BID to mask the treatment of

patients receiving Bimatoprost SR in the study eye. The fellow eye will receive a Sham administration plus topical timolol eye drops BID. Control group patients will receive a Sham administration plus timolol in both eyes (see Table 7). The study will be conducted at approximately 180 sites globally.

Two Bimatoprost SR dose strengths (10 µg or 15 µg) will be tested in this study. Patients will receive a scheduled second administration of Bimatoprost SR at 16 weeks following the first administration and a third scheduled administration at 16 weeks following the second administration (ie, 32 weeks after the initial administration). Control group patients will receive Sham administrations at all administration visits.

Table 7 Treatment Groups

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 Eyedrops: Timolol BID	Sham administration procedure Eyedrops: Timolol BID

BID = twice daily

Patients will begin self-administration of the study-provided eye drops in both eyes starting with the evening dose on the first administration (Day 1) visit (at which they will receive Bimatoprost SR administration or Sham administration). Patients will continue self-administration of study-provided eye drops in the morning (at 08:00 ± 1 hour) and in the evening (at 20:00 ± 1 hour), which is approximately 12 hours apart. Patients will be instructed not to administer their drops on the morning of a study visit. Drops will be administered immediately after the Hour 0 IOP measurement.

The duration of the study for each patient is approximately 22 months (screening duration of up to 28 days before washout, plus washout of up to 42 days before the first administration, plus the 52-week treatment period, plus 8 months extended follow-up). Patients will be followed for at least 12 months after their last Bimatoprost SR (or Sham) administration, and may exit early at or after the twelfth month following the last administration if there are no safety concerns in the opinion of the investigator.

4. Study Population and Entry Criteria

4.1 Number of Patients

Enrollment of approximately 510 patients in total at approximately 180 sites, with approximately 170 patients per group, is planned to ensure 162 completed patients per group, assuming a premature discontinuation rate of 5%.

4.2 Study Population Characteristics

The study population consists of patients with OAG or OHT and an open iridocorneal angle inferiorly by clinical gonioscopy in the study eye, and OAG or OHT in the fellow eye, where both eyes require IOP-lowering medication. The eye that meets the entry criteria (Sections 4.3 and 4.4) will be selected as the study eye. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 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.

Angle qualification will be independently confirmed as being qualified by 2 ophthalmologists, and endothelial cell density qualification for study entry will be determined by the Reading Center based on specular microscopy assessment (see Protocol Procedure Manual for details).

4.2.1 Patients With Sickle Cell Trait or Disease

Patients with sickle cell trait or disease (or other hemoglobinopathies) may be enrolled at the discretion of the investigator based on an individual risk-benefit assessment. Because of a slightly higher risk of IOP elevation and intraocular complications in the setting of a microhyphema, patients with these disorders may undergo optional additional biomicroscopy and IOP measurements after injection/Sham injection at the investigator's discretion (see Section 8.4). Additional information about the Bimatoprost SR experience in patients with sickle trait is provided in the Investigator's Brochure.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, ≥ 18 years of age

2. Written informed consent has been obtained

3. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent [EU sites])

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

[redacted]

5. Patient has the ability to understand and willingness to follow study instructions and is likely to complete all required visits and procedures

6. A negative pregnancy test result for females of childbearing potential at Baseline

7. Diagnosis of either OAG (ie, primary, pseudoexfoliation, or pigmentary glaucoma) or OHT in each eye and both eyes require IOP-lowering treatment (Note: diagnosis does not have to be the same in both eyes)

8. In the investigator's opinion, either eye can be treated adequately with topical ophthalmic beta-blocker (eg, timolol) eye drops as the sole therapy

9. In the investigator's opinion, either eye can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy

10. The iridocorneal angle in the study eye 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, patient has been appropriately washed out of all IOP-lowering medications

12. At the Baseline visit:

    a. Hour 0 IOP in the study eye of ≥ 22 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≤ 32 mm Hg

    b. Hour 2 IOP in the study eye of ≥ 19 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≤ 32 mm Hg

13. Central corneal endothelial cell density by specular microscopy:

[redacted]

    b. By Baseline: final central endothelial cell density in both eyes must be confirmed as being qualified by Reading Center assessment, with at least one eye qualified for inclusion as the study eye

[redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

Non-ocular Criteria for Exclusion

1. Uncontrolled systemic disease

2. Female patients 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 (see Section 4.5.3)

3. Known allergy or sensitivity to any study medication or its components, any component of the delivery vehicle, procedure-related materials, or diagnostic agents used during the study (eg, topical anesthetic, dilating drops, fluorescein)

4. Contraindications to beta-blocker therapy[redacted]

[redacted]

[redacted]

5. Any condition which would preclude the patient's ability to comply with study requirements, including completion of the study

6. Patients who have a condition or are in a situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

7. Anticipated use of oral, intramuscular, or intravenous corticosteroids from 2 months prior to the Baseline visit through Week 52

8. Concurrent or anticipated enrollment in an investigational drug or device study or participation in such a study within 2 months prior to the Baseline visit through the final study visit

9. Previous enrollment in another Allergan Bimatoprost SR study

[redacted]

Ocular Criteria for Exclusion

11. In the investigator's opinion, patient is nonresponsive to topical ophthalmic beta-blockers and/or topical prostamides, prostaglandins, or prostaglandin analogs (eg, LUMIGAN, Xalatan, Travatan)

12. History or evidence of clinically relevant, substantial ocular trauma (eg, a traumatic cataract, traumatic angle recession, etc) in the study eye

13. The following surgical history:

    a. History or evidence of complicated cataract surgery in the study eye: 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 in the study eye

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

[redacted]

16. Incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions in the study eye

[redacted]

25. Anticipated need for any incisional or laser ocular surgery in either eye within the first 52 weeks of the study duration

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

The fellow eyes of patients randomized to the Bimatoprost SR or Control groups will receive timolol BID for IOP lowering.

Intermittent use of artificial tear products is allowed if they are not taken ≤ 15 minutes before any study procedure or ≤ 15 minutes before or after topical administration of study medication. Intermittent use of ocular decongestants or antihistamines is allowed if not taken within 2 days prior to a scheduled visit and/or ≤ 15 minutes before or after topical administration of study medication. Use of artificial tear products and ocular decongestants or antihistamines may be restarted 3 days after any Bimatoprost SR (or Sham) administration procedure.

Use of postoperative topical ocular antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs) from the Administration Day (on Day 1, Week 16, and Week 32) to Day 7 following administration is allowed.

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.

Required surgical procedures may be performed in the fellow eye only after completion of Week 52.

In addition, therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, these medications should be administered in dosages that remain constant throughout the entire duration of the study. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

The use of systemic NSAIDs is also permitted.

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 (see Protocol Procedure Manual for details).

Note that in the event that the investigator performs an unanticipated incisional surgical procedure on the study eye during which ocular fluid is to be removed, ocular fluid/implant samples may be collected for analysis (see Protocol Procedure Manual for further details) at the investigator's discretion.

4.5.2 Prohibited Medications/Treatments

The decision to administer a prohibited medication and/or treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

During the study, patients should not participate in other investigational drug or device studies.

Nonstudy IOP-lowering Medications

Use of any topical ophthalmic medication containing an ocular antihypertensive, other than use of study medication (timolol) in Control group or fellow eyes, is 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 should be confirmed at a subsequent visit (scheduled or unscheduled visit). Prior to Week 52, the investigator will be expected to attest to the need for additional nonstudy IOP- lowering medication for safety reasons. After the Week 52 visit, nonstudy topical IOP-lowering medications will be permitted if in the investigator's clinical judgment the IOP is not adequately controlled at two consecutive visits. Initiation of medication in one eye should not automatically lead to initiation of medication in the other eye. Each eye should be evaluated on an individual basis when determining the need for additional nonstudy IOP-lowering medications. If nonstudy IOP-lowering medication is initiated prior to Week 52, the investigator will be expected to attest to the need for additional nonstudy IOP-lowering medication for safety reasons for each eye individually.

Contact Lenses

Use of soft contact lenses within 3 days and use of rigid gas permeable or hard contact lenses within 1 week prior to a scheduled study visit or Administration Day, or use of contact lenses of any kind within 1 week following any Bimatoprost SR (or Sham) administration in either eye is prohibited.

Contact lenses should be removed prior to instilling any study-provided eye drops and patients should wait at least 15 minutes before putting contact lenses back in the eyes after instilling topical drops.

Other Medications

The following medications (or classes of medications) and treatment procedures are not permitted as concurrent therapy during the study through 12 months after the last Bimatoprost SR or Sham administration unless the patient has already been treated with nonstudy IOP-lowering medication in both eyes:

- Subconjunctival, sub-Tenon's, intravitreal, or other ophthalmic injections of any medications in either eye
- Surgical procedures that are not related to Bimatoprost SR (or sham) administration procedures in the study eye (surgical procedures are allowed in the fellow eye after Week 52 as described in Section 4.5.1)

- Use of any topical ophthalmic medications (except as described above and in Section 4.5.1) in either eye.
- Use of any ophthalmic (including topical, intravitreal, sub-Tenon's, subconjunctival) corticosteroids in either eye from 2 months prior to the baseline visit through 12 months after the last administration, except for use of postoperative topical ocular coritcosteroids after administration as described in Section 4.5.1.
- Oral, intramuscular, or intravenous corticosteroids from 2 months prior to the baseline visit through the twelfth month after the last injection.
- Use of LATISSE® (bimatoprost for hypotrichosis) during the study period in either eye
- Systemic use of carbonic anhydrase inhibitors (eg, Diamox®)
- Any initiation of or alterations in systemic regimen of beta-blocker containing medications from 2 months prior to Screening through the final study visit

4.5.3 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For purposes of this study, women will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, hysterectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause. For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or true sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject).

The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

[redacted]

[redacted]

5. Study Treatments

5.1 Study Treatments and Formulations

[redacted]

5.2 Control Treatments

For Sham administration, a needleless applicator is provided.

The following topical eye drops are also used as controls:

- Timolol 0.5% ophthalmic solution [redacted]
- Timolol vehicle [redacted] is identical in appearance to the timolol 0.5% ophthalmic solution [redacted]

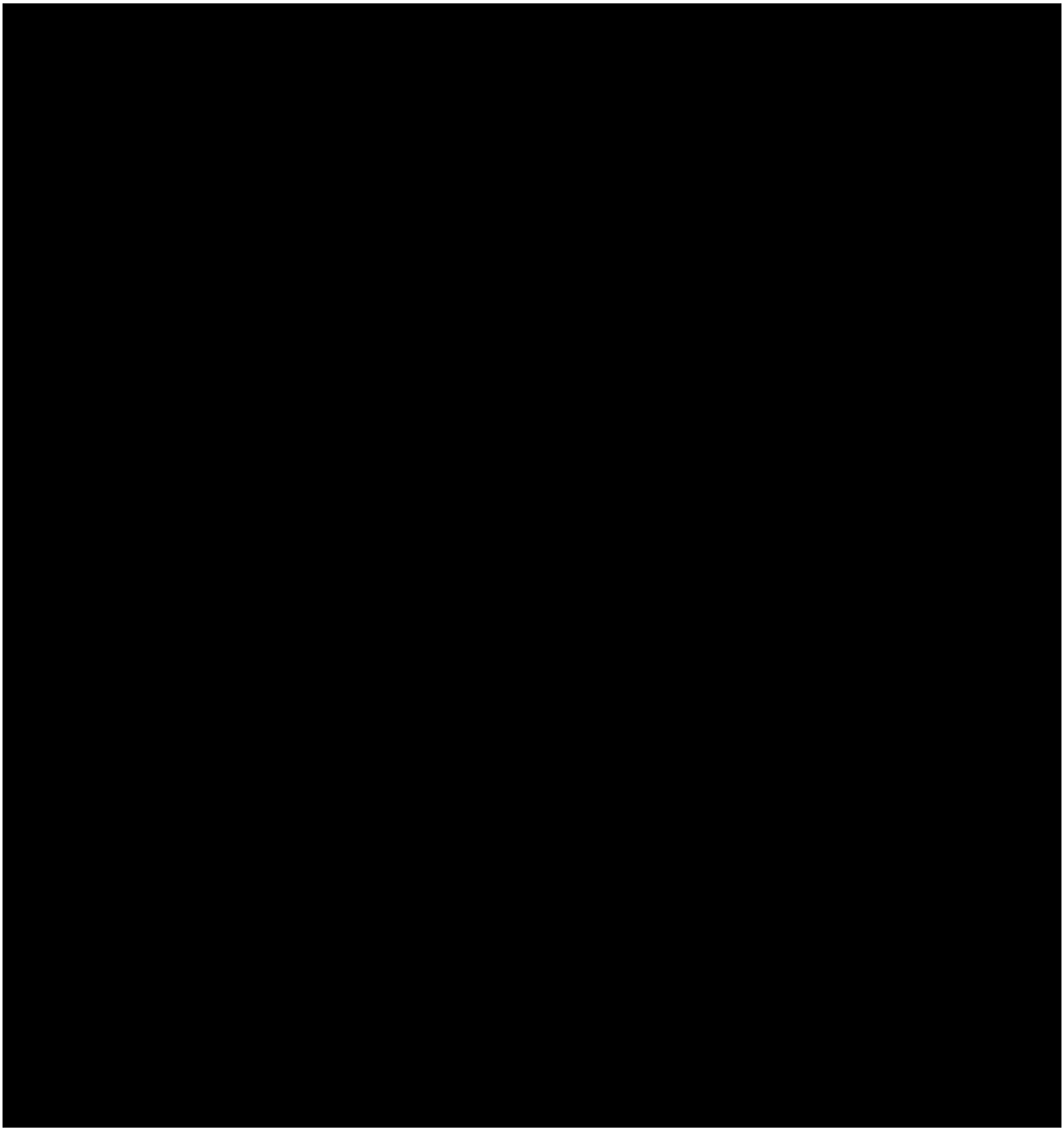
5.3 Methods for Masking

Patients in the Control group will receive timolol eye drops BID plus Sham administration in both eyes. Vehicle eye drops will 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 will be a Sham administration procedure + timolol eye drops BID.

The site coordinator and designated staff will not be masked to whether the patient received 1 of the 2 dose strengths of Bimatoprost SR or the Sham administration procedure, but will be masked to the specific implant dose strength. The patient and the remaining staff will be masked to the patient's treatment assignment. Efficacy IOP measurements will be masked by using a 2-person reading method as described in Section 6.1.1 (for optional postoperative

IOP measurements for patients with sickle cell disease or trait [or other hemoglobinopathies], see Section 8.4).

The site staff who perform IOP readings will be 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 will be instructed and reminded throughout the study not to discuss study medication assignments to ensure maintenance of the masking.



[redacted]

5.4 Treatment Allocation Ratio and Stratification

Randomization to treatment groups will use a 1:1:1 ratio. Patients will be randomized to receive Bimatoprost SR (either 10 µg or 15 µg) plus vehicle eye drops, or a Sham administration procedure plus timolol eye drops, in the study eye. Randomization will be stratified by Baseline study eye Hour 0 IOP (≤ 25 mm Hg or > 25 mm Hg).

5.5 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of any study procedures, each patient who provides informed consent will be assigned a subject number that will serve as the patient's identification number on all study documents.

Eligible patients will be 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. The randomization will be stratified by Baseline Hour 0 IOP (baseline study eye IOP ≤ 25 mm Hg or > 25 mm Hg).

[redacted]

[redacted]

5.6 Treatment Regimen and Dosing

The treatment groups are shown in Table 7. Patients randomized to 1 of the Bimatoprost SR dose groups will receive an intracameral administration of Bimatoprost SR in the study eye on Day 1, Week 16, and Week 32, in addition to using topical vehicle eye drops (1 drop BID). They will receive timolol eye drops (1 drop BID) plus Sham administration in the fellow eye. Patients randomized to the Control group will receive a Sham administration in both eyes on Day 1, Week 16, and Week 32, in addition to timolol eye drops (1 drop BID) in both eyes.

[redacted]

5.6.1 Treatment Regimen/Dosage Adjustments

Patients who have received nonstudy topical IOP-lowering medication (prohibited before Week 52 unless required for safety reasons due to inadequate IOP control and attested to by the investigator) in a Bimatoprost SR study eye will receive Sham administration in that eye on the Bimatoprost SR repeat administration day(s). Patients who have received nonstudy topical IOP-lowering medication in a fellow eye or a Control Group study eye will continue to receive Sham administration in that eye on the administration day(s).

Patients who have received nonstudy IOP-lowering medication in both eyes will not undergo Bimatoprost SR administration or Sham administration in either eye.

Patients who use nonstudy IOP-lowering medication (prohibited before Week 52 unless required for safety reasons due to inadequate IOP control and attested to by the investigator) in only one eye will be followed for the duration of the study. If used in both eyes, patients will be followed at minimum for 12 months after the last administration of Bimatoprost SR or Sham. Patients using nonstudy IOP-lowering medications in both eyes prior to the Week 16 or Week 32 Administration Day will not attend the administration visit(s), nor will they attend the Day 2, Days 4 and 8 (phone call), or 2-week visits (ie, Weeks 2, 18, and 34) following an administration. They would continue the schedule at Week 22 or Week 38, as appropriate for the administration cycle.

[redacted]

5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol. Only assigned study personnel, authorized by the investigator, may have access to study medication. [redacted]

[redacted]

5.8 Preparation of Study Medications/Treatments

Bimatoprost SR is loaded into the single use applicator during manufacturing and is provided within the applicator as a sterile, finished product. Study site personnel should notify Allergan or its designee immediately to advise of any situation in which the study medication is defective.

5.9 Treatment Administration

Study medication must only be administered to patients who meet the eligibility criteria in accordance with the conditions specified in this protocol. [redacted]

5.9.1 Patient Preparation

[redacted]

5.9.2 Study Treatment Location

At the discretion of the investigator, Bimatoprost SR (or Sham) administration may be performed at an Ambulatory Surgical Center (ASC; free standing or hospital based) or in the office setting (eg, in a procedure room with an operating microscope). [redacted] A separate standard consent to have the procedure at an Ambulatory Surgical Center may be required per the standard operating procedures at the facility.

Sterile technique will be practiced at all times.

5.9.3 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 principal investigator at a site may designate a subinvestigator to perform the procedure, subject to Allergan approval and training. The study medication kit should be readily available during the procedure.

[redacted]

5.9.4 Immediate Posttreatment Observation

Following study treatment administration, the patient is allowed to sit upright and is kept for a minimum of 1 hour of observation. The surgeon will examine each of the patient's eyes to ensure that the anterior chamber is formed prior to the patient being released.

[redacted]

Prior to leaving the site, patients should be instructed to contact the study site immediately if they experience any adverse events after treatment. If the patient reports having experienced adverse events, these should be recorded on the appropriate eCRF.

The same posttreatment observation requirements apply after the second and third administrations of Bimatoprost SR or Sham administration.

Note: Patients with sickle cell disease or trait (or other hemoglobinopathies) may undergo optional biomicroscopy and IOP examination in both eyes 4 hours after each Bimatoprost SR administration (or Sham administration). This optional IOP examination is for postoperative purposes only, and as such does not require a masked, 2-person reading method. The IOP should be taken only once to avoid excessive postadministration (or Sham administration) manipulation of the eye, and should be taken by the investigator (or other unmasked, qualified personnel). This postadministration (or Sham administration) examination may be performed using a Goldmann applanation tonometer or a hand-held tonometer. (See the Study Procedure Manual for details.)

5.10 Retreatment

Administration of Bimatoprost SR will occur at fixed intervals of 16 weeks, up to a total of 3 administrations. Patients will be readministered the Bimatoprost SR dose strength to which they were randomized unless in the investigator's opinion it would not be in the best interest of the patient to readminister Bimatoprost SR based on previous adverse events or safety concerns. [redacted]

6. Response Measures and Summary of Data Collection Methods

[redacted]

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

The primary efficacy measure, IOP, will be 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 will 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. The right eye is to be measured first and the left eye measured second. Two consecutive measurements will be taken of each eye. If the first 2 measurements differ by > 1 mm Hg, a third measurement will be taken. If the first 2 measurements differ by 1 mm Hg or less, the IOP for the given eye will be the average of the 2 readings. If the difference between the first 2 measurements is > 1 mm Hg, the IOP for the given eye will be the median of the 3 readings.

All Hour 0 IOP examinations should be scheduled at 08:00 ± 1 hour. As scheduling permits, the patient should have approximately the same Hour 0 time of day throughout the study. Hour 2 IOP examinations should occur 2 hours after the Hour 0 IOP exam. The acceptable window for the Hour 2 IOP examination is ± 30 minutes.

6.2 Safety Measures

The following will be collected and recorded on the appropriate eCRF page(s):

A**dverse Events:** All adverse events, from the moment the patient signs the informed consent form, will be monitored and recorded in the patient's source documents. All events will be reported to Allergan on an adverse event eCRF, including seriousness, severity, action taken and relationship to study drug. If adverse events occur, the first concern will be the safety of the study patient.

Weight and Height: Weight will be measured in pounds (lb) or kilograms (kg) using a scale. Height will be measured in inches (in) or centimeters (cm). Height and weight will be measured at screening as part of the demographic data; historical patient information and/or patient reports should not be used for either measurement.

Vital signs: Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes. Body temperature will be measured orally (or with an infrared forehead thermometer) and recorded as °F or °C.

Hematology, blood chemistry, and urinalysis: Blood and urine samples will be collected for blood chemistry and hematology panels and urinalysis.

Pregnancy: Females of childbearing potential will have pregnancy tests performed. Pregnancy test kits will be provided by Covance Central Laboratory Services or a designated regional laboratory and will be administered according to the instructions provided with the tests.

Measures of ocular safety include:

Visual Acuity: Visual acuity tests will be performed at all scheduled visits except on any of the 3 administration days. Manifest refraction using Snellen equivalent with a logMar chart (see Protocol Procedure Manual) will be performed at Screening, Baseline, Weeks 12 and 52, and Month 20/Exit. At all other visits, the visual acuity technician will use the last manifest refraction performed and determine the Snellen equivalent visual acuity using the logMar chart. If there is a 2-line or more reduction in visual acuity from the last BCVA performed, a repeat manifest refraction in both eyes and BCVA will be performed.

Macroscopic Iris Color Assessment: Iris color will be assessed visually at each designated visit using the appropriate assessment guide (see the Protocol Procedure Manual for further details). Macroscopic, binocular color photography will be performed at baseline to document iris color. The baseline photograph printout from each patient will be used as a comparator to assess any change in iris color at subsequent visits. A suspected change in iris color will be documented with a binocular color photograph at that visit. A binocular color photograph will also be obtained at Week 52 and a final binocular color photograph will be obtained during the Month 20/Exit visit in all patients.

Progressive changes in iris color will be photographed and compared to the last photograph taken.

Macroscopic Conjunctival Hyperemia Assessment: Macroscopic conjunctival hyperemia will be assessed using the appropriate Assessment Guide (see the Protocol Procedure Manual for further details).

Bimatoprost SR Implant Assessment: Using gonioscopy, the investigator will evaluate the Bimatoprost SR implant and the inferior iridocorneal angle.

Biomicroscopic Examination: Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, cornea, AC, iris/pupil, and lens.

Lens Assessment: Biomicroscopic findings will be evaluated for the presence and severity of nuclear, cortical, and posterior subcapsular lens opacities. See the Protocol Procedure Manual for further details.

Gonioscopy: Gonioscopic examination for eligibility at Screening (only) will be independently performed by 2 ophthalmologists as described in the Protocol Procedure Manual. The independent eligibility assessors should not share their assessments with each other until the assessment is recorded. The 2 ophthalmologists' independent eligibility assessments must confirm patient eligibility for participation in the study. Subsequent gonioscopic examinations will be performed by the study investigator.

Optic Disc Examination: The cup/disc ratio and presence of optic disc pathology will be determined using stereoscopic evaluation.

Dilated Ophthalmoscopic Examination: The stereoscopic fundus assessments should be conducted through a dilated pupil. The examinations will include evaluation of the macula, vitreous, and retina.

Optical Coherence Tomography (OCT): OCT of the macula will be performed to assess macular edema. The same instrument should be used throughout the study for a given patient. See the Protocol Procedure Manual for further details.

Specular Microscopy: Endothelial cell density will be assessed using specular microscopy performed on the central cornea at all sites. The final qualification of central endothelial cell density for study entry will be determined by the Reading Center. Qualification will remain valid for 1 year after Screening in patients who are not enrolled at the time of Screening, if in the investigator's opinion there have been no clinically significant changes occurring in the eye (eg, ocular surgery) during that time. All additional specular microscopy images taken during the study will be assessed by the Reading Center. See the Protocol Procedure Manual for further details. The same instrument should be used throughout the study for a given patient.

Pachymetry: Corneal thickness using ultrasound (contact) pachymetry will be performed on the central cornea. The same instrument should be used throughout the study for a given patient. Contact pachymetry may be performed any time after the Hour 2 IOP measurement. See the Protocol Procedure Manual for further details.

Anterior Segment Optical Coherence Tomography (AS-OCT): AS-OCT measurements will be performed at all sites and a Reading Center will be used to examine angle size for

investigational purposes. See the OCT Image Acquisition manuals from the Reading Center for further details on the use of OCT. In the event that the AS-OCT type as specified in the manuals is not available, a suitable alternative may be approved by Allergan and the designated Reading Center for use. The same instrument should be used throughout the study for a given patient.

Visual Field Examination: Visual field examinations will be assessed using automated perimetry ([redacted]). The same test methodology must be used throughout the entire study for a given patient.

6.3 Other Measures (Optional)

[redacted]

6.4 Examination Procedures, Tests, Equipment, and Techniques

Study evaluations should be performed by the same investigator/subinvestigator throughout the study whenever possible. If it is not possible to use the same individual to follow the patient, then an attempt should be made to have investigators overlap (examine the patient together and discuss findings) for at least 1 visit.

6.4.1 Medical History, Physical Examination, and Vital Signs

6.4.1.1 Medical History

A standard medical history (including all relevant conditions that the patient has had in the past or currently has) will be captured in the patient source documents. All surgical procedures should have an associated medical history entry. Current medications as well as those stopped within 60 days prior to the screening visit and procedures within 90 days prior to the screening visit will be recorded. In addition, all previous medications taken for OAG

or OHT for at least 3 months prior to study entry will be recorded on the appropriate source document page.

6.4.1.2 Physical Examination

The patient will be examined by qualified medical personnel for any physical abnormality of the following systems: general appearance; head, eyes, ears, nose, and throat; heart/cardiovascular; lungs; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; and skin. The patient's height and weight will be recorded at the Screening visit only.

6.4.1.3 Vital Signs

The below vital signs will be measured at all patient visits and should be recorded prior to any invasive procedures.

- Pulse rate (beats per minute [bpm]): the patient should be resting in a seated position for a minimum of 5 minutes prior to measurement. Pulse rate is then counted over 30 seconds (and multiplied by 2 to obtain bpm).
- Blood pressure (mm Hg): the patient should be resting in a seated position for a minimum of 5 minutes prior to measurement. Systolic/diastolic blood pressure will be measured with a sphygmomanometer (manual sphygmomanometer or automated blood pressure measuring device).
- Temperature (°C/°F): patients should be seated and the body temperature taken orally (or with an infrared forehead thermometer).

6.4.2 Pregnancy Testing

Urine will be collected from females of childbearing potential for pregnancy testing (urine pregnancy test). The urine test for pregnancy will be performed at the site utilizing the dipstick method at all specified timepoints. Serum testing may be performed instead of urine testing if required by the local institution.

6.4.3 Laboratory Procedures

A central laboratory ([redacted]) will analyze blood and urine specimens for this study; including any repeat laboratory tests. Blood and urine samples will be obtained for the analysis of blood chemistry, hematology, and urinalysis.

Refer to the Central Laboratory Manual for further details regarding central laboratory collection and shipment procedures.

Laboratory test results will be forwarded from the central laboratory to the study site and to Allergan or its designee. The investigator or qualified site personnel must review all laboratory results for any adverse events. Laboratory test results that represent adverse events should be reflected on an adverse event eCRF page.

Evaluation and management of abnormal laboratory results should be conducted according to local site practice.

6.4.3.1 Hematology

Hematology will be measured and includes hematocrit, hemoglobin, glycated hemoglobin, (HbA1c), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets, red blood cell (RBC) count, RBC morphology, total white blood cell (WBC) count and differential (neutrophils, bands, lymphocytes, monocytes, basophils, and eosinophils).

6.4.3.2 Serum Chemistry

Serum chemistry will include albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), bicarbonate, calcium, chloride, creatinine, creatine kinase, direct bilirubin, glucose, indirect bilirubin, magnesium, phosphorous, potassium, sodium, total bilirubin, total cholesterol, total protein, urea nitrogen, and uric acid.

6.4.3.3 Urinalysis

Urine will be analyzed for clarity, color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic sediment (WBCs, RBCs, casts, bacteria, crystals, and epithelial cells).

6.5 Other Study Supplies

[redacted]

[redacted]

6.6 Summary of Methods of Data Collection

[redacted]

7. Statistical Procedures

Three database locks are planned. The first database lock will take place after all patients have completed or prematurely discontinued before the Week 12 visit. Similarly, the database will be locked after all patients have completed or prematurely discontinued before Week 52 and Month 20/Exit. Analyses will be performed after each lock. Prior to the first database lock a detailed analysis plan will be finalized. To maintain the integrity of the ongoing study, Allergan study personnel who are directly involved in data handling and supporting the trial (such as the clinical study team) will remain masked to treatment assignment of individual patients during the study. To avoid potential data unmasking between locks and to protect trial integrity, study statistical personnel who have been unmasked after each lock will no longer be involved directly in any ongoing masked study conduct. Another statistician, who is still masked to study treatment, will assume these

responsibilities until the next lock. Unmasked data handling and appropriate data and results access will be specified prior to each lock.

Efficacy analyses specific for the US FDA (Division of Transplant and Ophthalmology Products) review are described in Section 7.6.

The details of all analyses will be provided in the analysis plan.

7.1 Analysis Populations

The intent-to-treat population (ITT) is defined as all randomized patients and will be used for demographic and efficacy analyses. The per protocol (PP) population will consist of the subset of the ITT population with no protocol deviations affecting the primary efficacy analysis and will be used to confirm the primary efficacy analysis. A list of patients excluded from the PP population will be finalized prior to database lock. The safety population is defined as all patients who received study drug treatment and will be used for safety analyses. Analyses in the ITT population will be based on the treatment to which a patient was randomized, and analyses in both PP and safety populations will be based on the actual treatment a patient received.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

The primary efficacy measurement is IOP, which will be measured in each eye using the Goldmann applanation tonometer. Two consecutive measurements will be taken for each eye. If these 2 measurements differ by > 1 mm Hg then a third measurement will be performed. If the first 2 measurements differ by 1 mm Hg or less, or a third measurement is required but only 2 measurements are obtained, then the IOP value for a given eye is the average of the 2 measurements. If 3 measurements are required (ie, the first 2 measurements differ by > 1 mm Hg) and obtained, then the IOP value for the given eye is the median of the 3 measurements. If, for any reason, only a single measurement is obtained, then this measurement will be used as the IOP value.

To avoid confounding of efficacy data, IOP measurements obtained after initiating the use of nonstudy IOP-lowering medication in an eye will be excluded from the calculation of the summary statistics and the statistical analyses for that eye but raw values will be presented in the listings.

7.2.1 Primary Efficacy Variable

The primary efficacy variable is the study eye time-matched IOP change from baseline (follow-up minus time-matched baseline) at each hour evaluated (Hours 0 and 2).

7.2.2 Secondary Efficacy Variable

The secondary efficacy variable is time-matched IOP.

7.3 Hypothesis and Methods of Analysis

In general, continuous variables will be summarized by descriptive statistics including sample size, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency and percentage.

7.3.1 Primary Efficacy Analyses

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

The null and alternative hypotheses for the comparison between a given Bimatoprost SR dose strength and timolol at each hour of Week 12 are:

- 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 will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The model will include 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 effects. Unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance matrix fails to converge, multiple imputation (MI) will be implemented before MMRM. The details of the model specifications will be provided in the analysis plan.

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 will be provided for each hour (Hours 0 and 2) at each visit. The formal noninferiority test will be performed at Week 12 for each Bimatoprost SR dose strength versus timolol using a noninferiority margin of 1.5 mm Hg. A gatekeeping procedure will be 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 for a given hour at Week 12 is valid only if the noninferiority of Bimatoprost SR 15 µg to timolol is demonstrated for the same timepoint. Bimatoprost SR 15 µg (or 10 µg) will be declared noninferior to timolol if the upper limit of the 95% confidence interval is ≤ 1.5 mm Hg for both Hours 0 and 2 at Week 12.

Sensitivity analyses of handling missing data will be performed using multiple imputation.

7.3.2 Secondary Efficacy Analyses

Secondary efficacy analyses comparing each Bimatoprost SR dose strength and timolol to test the no-difference null hypothesis will be performed at scheduled visits (Weeks 2, 6, and 12) and hours for (1) IOP and (2) time-matched IOP change from baseline.

The analysis of time-matched IOP change from baseline utilizes the identical model as that described for the primary analysis in Section 7.3.1 with the same 2-sided 95% confidence intervals constructed at each hour and each visit for the mean difference between each Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol). An upper 95% confidence limit of the mean difference that is less than zero corresponds to a significant difference in favor of the given Bimatoprost SR dose strength for the given timepoint.

Each Bimatoprost SR dose strength that demonstrates the following at all scheduled timepoints within the 12-week period (at Hours 0 and 2 at Weeks 2, 6, and 12) will be considered superior to timolol:

- The upper 95% confidence limit of the mean difference is less than zero (ie, a significant difference in favor of the given Bimatoprost SR dose strength)

The analysis of IOP will be similarly performed as described above with IOP replacing time-matched IOP change from baseline in the analysis model.

7.3.3 Other Efficacy Analyses

[redacted]

7.3.4 Safety Analyses

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Adverse events will be coded from the verbatim text into preferred term and system organ class (SOC). The number and percent of patients reporting treatment emergent adverse events will be tabulated based on the primary SOC and preferred terms. Summary tables will be generated for all adverse events regardless of causality as well as treatment-related adverse events for the entire study and by treatment cycle.

Other safety variables include vital signs (blood pressure, pulse rate, and temperature) and pregnancy test results. Ocular safety will be evaluated through assessment of visual acuity and visual field; evaluation of macroscopic bulbar conjunctival hyperemia and iris color; assessment of endothelial cell density and corneal thickness; IOP measurement, biomicroscopic and ophthalmoscopic examinations (including gonioscopy with Bimatoprost SR implant assessment, optic disc examination and dilated fundus examination); and OCT of the macula.

Ocular adverse events and safety variables will be tabulated by study eye and fellow eye within each treatment dose strength, and nonocular safety variables will be summarized by patient. A separate summary will be provided for safety events occurring after nonstudy IOP-lowering medication has been initiated.

7.4 Subgroup Analyses

Subgroup analyses for the primary variable will be performed

7.5 Interim Analyses

No interim analysis is planned for this study. Each database lock will correspond to a milestone and statistical analysis when all randomized patients have either completed or exited from the targeted visit.

7.6 Analyses for US FDA

Primary Efficacy Analyses

For the US FDA review, the primary efficacy variable will be the study eye IOP. The primary analysis will be based on Weeks 2, 6, and 12 using the ITT population. Mean IOP will be compared between each Bimatoprost SR dose strength and timolol for each hour (Hours 0 and 2) at Weeks 2, 6, and 12.

The null and alternative hypotheses for the comparison between a given Bimatoprost SR dose strength and timolol for each hour at each visit are:

- The null hypothesis is that the difference in mean IOP between the given Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) is > 1.5 mm Hg.
- The alternative hypothesis is that the difference (Bimatoprost SR minus timolol) in mean IOP between the given Bimatoprost SR dose strength and timolol is ≤ 1.5 mm Hg.

IOP will be analyzed using an MMRM approach based on the same model as described in Section 7.3.1. Within the framework of this model, the mean difference between each Bimatoprost SR dose strength and timolol and the corresponding 2-sided 95% confidence interval will be provided for each hour (Hours 0 and 2) and each visit (Weeks 2, 6, and 12). A gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level at each timepoint, testing Bimatoprost SR 15 µg against timolol first and followed by the comparison between Bimatoprost SR 10 µg and timolol. The test for Bimatoprost SR 10 µg versus timolol for a given hour at a visit is valid only if the noninferiority of Bimatoprost SR 15 µg to timolol has been demonstrated for the given timepoint.

Each Bimatoprost SR dose strength that shows noninferiority to timolol at all 6 timepoints with a 1.5 mm Hg margin (ie, the upper limit of the 95% confidence interval is ≤ 1.5 mm Hg) will be declared clinically noninferior to timolol if the upper limit of the 95% confidence interval is ≤ 1.0 mm Hg for 3 or more timepoints.

Sensitivity analyses of handling missing data will be performed using multiple imputation.

Secondary Efficacy Analyses

For each Bimatoprost SR dose strength which demonstrates efficacy (clinical noninferiority) as described in the primary efficacy analyses, secondary efficacy analyses comparing the Bimatoprost SR dose strength and timolol to test the no-difference null hypothesis will be

performed at scheduled visits (Weeks 2, 6, and 12) and hours for IOP. A gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level within each dose strength; the specific sequence of the tests will be provided in the analysis plan.

Other Efficacy Analyses

[redacted]

7.7 Sample Size Calculation

The sample size calculation is based on the primary efficacy analysis of the IOP for US FDA review since the sample size based on the primary efficacy analysis for other regions is expected to be smaller.

The initial 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 (ie, 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 standard deviation 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 made at the study design phase based on the data obtained from the ongoing clinical study 192024-041D. Based on simulations, a sample size of 540 patients (180 per group) would provide approximately 95% and 81% power to show noninferiority (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. 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.

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) is 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) would 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) are to be enrolled into this study.

8. Study Visit Schedule and Procedures

Patients who complete the entire study without receiving nonstudy IOP-lowering medication will have a minimum of 25 visits and 6 phone calls. The schedule begins with Screening, followed by a Washout period of up to 42 days for both eyes, and then Baseline. These visits are followed by 3 cycles of Bimatoprost SR or Sham administration. Each administration cycle includes Bimatoprost SR or Sham administration (Day 1), visit on Day 2, phone calls on Days 4 and 8, and visits on Weeks 2, 6, 12, and 15 (which is the visit prior to the next administration day). Additional treatment period visits occur through Week 52 and extended follow-up continues into Months 14, 16, 18, and 20/exit.

The study visits should adhere as closely as possible to the schedule shown in Table 2 through Table 6. See Figure 1 for a flowchart of patient participation.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization (US only), data protection consent (Europe only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each patient who provides informed consent will be assigned a subject number that will be used on patient documentation throughout the study.

8.2 Washout Intervals

All patients must provide informed consent prior to beginning any drug washout for the purposes of inclusion in this study. Patients currently being treated with IOP-lowering medication(s) in either eye will begin washout of these medication(s) following completion of the screening procedures. The Screening and Washout periods may not be concurrent. The Washout period will be up to 42 days depending on the minimum washout period schedule below.

If, after initial washout, the IOP does not meet entry criteria and the investigator believes this is due to inadequate washout, if time remains in the Washout period, he/she may perform additional washout, as long as the total Washout period does not exceed 42 days.

For patients undergoing a washout, interim safety evaluation(s) of IOP at some time during the washout period may be performed at the discretion of the investigator.

Note: Medications should only be discontinued (washed out) if the investigator feels that it is safe and appropriate, and if the patient is willing to discontinue the medication for the duration of the study. If the medication cannot be discontinued, then the patient will not be eligible for study entry.

8.3 Procedures for Final Study Entry

The results from the screening ocular and physical examinations, and laboratory tests (hematology/blood chemistry/urinalysis) must be evaluated and determined to be acceptable to the investigator prior to the patient's entry into the study. If repeat laboratory tests are done, the results must be reviewed prior to study treatment initiation on Day 1. Reading Center qualification of endothelial cell density must be confirmed by the Baseline visit. After confirmation of eligibility on Day 1, IV/WRS is contacted for randomization. However, this contact for randomization may take place at the end of the Baseline visit if needed. See Section 5.5 for the method for assignment to treatment groups/randomization.

A patient is considered to have enrolled in the study at the time of the first study treatment administration (or Sham).

8.4 Visits and Associated Procedures

The following sections provide a list of procedures for each scheduled visit. [redacted]

[redacted]

8.4.1 Screening Visit

After informed consent and other documentation have been obtained (as described in Section 8.1.2), the procedures listed below are done. Intraocular pressure measurements must be performed in one day; however, other procedures (eg, postdilation and imaging procedures) may be performed on a different day as long as the screening procedures are completed within a 28-day period. Perform pupil dilation/diagnostic procedures after the completion of the final IOP measurement of the day or on a different day.

- Collection of demographic data
- Collection of medical and ophthalmic history
- Collection of adverse events
- Collection of concomitant medications and procedures
- Physical examination
- Vital signs
- Collection of blood and urine samples

Washout may begin after screening procedures have been completed.

8.4.2 Baseline Visit

The Baseline visit occurs after the Washout period has been completed. Final Reading Center confirmation of central endothelial cell density should be received by the site by the Baseline visit. Baseline visit procedures, excluding IOP measurements (which must be performed in 1 day), can be performed over a 3-day period; all must be completed by the day before the Administration Day. Perform pupil dilation/diagnostic procedures after the completion of the final IOP measurement of the day or on a different day.

- Collection of medical and ophthalmic history (changes since the Screening visit)
- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs
- Pregnancy test for females of childbearing potential (as defined in Section 4.5.3)

[redacted]

8.4.3 Treatment Period

8.4.3.1 Cycle 1: Day 1 Administration Day

The following procedures are performed on the day of study treatment administration:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs
- Confirm eligibility

[redacted]

- Administer assigned study treatment

[redacted]

[redacted]

8.4.3.2 Cycle 1: Day 2

On Day 2 after study treatment administration, the following procedures are performed:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.5 Cycle 1: Week 6

The following procedures are performed at Week 6 (±4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

8.4.3.6 Cycle 1: Week 12

The following procedures are performed at Week 12 (± 4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.7 Cycle 1: Week 15

The following procedures are performed at Week 15 (± 4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.8 Cycle 2: Week 16 Administration Day

The following procedures are performed at Week 16 (-2 to +4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

- Administer assigned study treatment

[redacted]

8.4.3.9 Cycle 2: Day 2

On Day 2 after the second study treatment administration, the following procedures are performed:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.10 Cycle 2: Day 4 and Day 8 (Phone Calls)

On Day 4 and Day 8 after the second cycle administration procedure, the patient will be contacted by telephone to collect the following:

- Collection of adverse events
- Collection of concomitant medications and procedures

8.4.3.11 Cycle 2: Week 18

The following procedures are performed at Week 18 (±4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

[redacted]

8.4.3.12 Cycle 2: Week 22

The following procedures are performed at Week 22 (±4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.13 Cycle 2: Week 28

The following procedures are performed at Week 28 (±4 days):

- Collection of adverse events

- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.14 Cycle 2: Week 31

The following procedures are performed at Week 31 (± 4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.15 Cycle 3: Week 32 Administration Day

The following procedures are performed at Week 32 (-2 to + 4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

- Administer assigned study treatment

[redacted]

8.4.3.16 Cycle 3: Day 2

On Day 2 after the third study treatment administration, the following procedures are performed:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.17 Cycle 3: Day 4 and Day 8 (Phone Calls)

On Day 4 and Day 8 after the third cycle administration procedure, the patient will be contacted by telephone to collect the following:

- Collection of adverse events
- Collection of concomitant medications and procedures

8.4.3.18 Cycle 3: Week 34

The following procedures are performed at Week 34 (± 4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.19 Cycle 3: Week 38

The following procedures are performed at Week 38 (±4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

8.4.3.20 Cycle 3: Week 44

The following procedures are performed at Week 44 (± 4 days):

- Collection of adverse events

- Collection of concomitant medications and procedures
- Vital signs

8.4.3.21 Cycle 3: Week 48

The following procedures are performed at Week 48 (± 4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.3.22 Cycle 3: Week 52

The following procedures are performed at Week 52 (± 7 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

[redacted]

8.4.4 Extended Follow Up

8.4.4.1 Month 14

The following procedures are performed at the Month 14 (± 14 days) visit:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.4.2 Month 16

The following procedures are performed at the Month 16 (± 14 days) visit:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

[redacted]

8.4.4.3 Month 18

The following procedures are performed at the Month 18 (± 14 days) visit:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs

8.4.4.4 Month 20/Exit

The following procedures are performed at the Month 20 (± 14 days) visit or at early exit:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs
- Pregnancy test for females of childbearing potential

[redacted]

8.5 Instructions for the Patients

Patients should be instructed to strictly follow the study visit schedule and to report all changes in their condition to the investigative site.

Instruction should be given to the patient to maintain a stable dose of any concomitant medication used chronically, or any new medications initiated during the study whenever possible. Patients should be instructed to communicate any changes to their medication at their next study visit. Patients should also be reminded to contact the study site if they are experiencing any difficulties during their study participation.

Patients should keep the study medication bottles in the original kit that was provided and return the bottles to the designated (unmasked) site staff. Patients should be instructed that bottles of provided medications should only be used for 28 days each.

8.6 Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study period. Unscheduled visit eCRFs should be completed for each unscheduled visit. An assessment of any adverse event should be completed.

8.7 Compliance with Protocol

Patients must be able to adhere to the study visit schedule; appropriate inclusion, exclusion, and treatment criteria; permitted and prohibited medication criteria; and testing parameters as described in the protocol. At each study visit, patients will be asked if they have used their study-provided eye drops as instructed and whether they have used any concomitant medications/therapies or had any concurrent procedures since the previous visit.

Patients should be scheduled for study visits as closely to the day specified in the visit schedule as possible.

8.8 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time.

Patients who have received nonstudy IOP-lowering medication in only one eye will be followed for the duration of the study through the Month 20 visit.

Patients who have received nonstudy IOP-lowering medication in both eyes, or who do not complete an Administration Day visit, may discontinue the study 12 months after the last Bimatoprost SR or Sham administration at which time they should complete the Month 20/Exit visit procedures.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

When patients exit before Month 20, the site should complete all procedures for the Month 20/Exit visit at the patient's last visit.

8.9 Withdrawal Criteria

After the first administration (or Sham), failure to undergo an Administration Day visit does not indicate total withdrawal from the study. Patients who have received nonstudy IOP-lowering medication in only one eye will continue through the duration of the study. Patients who have received nonstudy IOP-lowering medication in both eyes, or patients who do not undergo Cycle 2 or 3 (or both) Administration Visits, will still be followed for 12 months after the last Bimatoprost SR or Sham administration for safety reasons. These patients are eligible for Early Discontinuation (Early Exit) as described in Section 8.8, above.

The investigator should consider withdrawing a patient from the study early if any of the following criteria are met:

- Patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, compromises the patient's ability to participate in the study
- Patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, compromises the patient's ability to participate in the study
- Patient is unwilling or unable to continue to comply with study procedures
- Patient is unwilling or unable to continue in the study

If a patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk by continuing study participation, the patient will be withdrawn from the study.

Whenever possible, the decision to withdraw a patient from the study or study treatment should be discussed with Allergan.

8.10 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the CRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by

querying for adverse events by asking each patient a general, nondirected question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Preplanned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

If an adverse event is deemed related to study treatment, the investigator will be asked to further delineate whether the adverse event was related to the administration procedure (versus the study medication).

Note: A study procedure occurring during the Screening/Baseline period can include a washout of medication or introduction of a run-in medication or study required diagnostic procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate case report form.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked "ongoing" at the exit visit must be followed up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 4 months after the last dose of study drug must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan (or Agent of Allergan) [redacted] All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately [redacted]

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unmasking of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. [redacted]

[redacted]

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Human Subjects

10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

There are special situations in which oral informed consent may be taken. Approval to utilize oral consent procedures and instructions on how to properly obtain oral informed consent must be obtained from Allergan personnel.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and reapproval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization (US sites only), data protection consent (European sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ["EU Directive"]).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

10.4 Documentation

10.4.1 Source Documents

[redacted]

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's case report forms and related documents. [redacted]

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file.

[redacted]

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

Packaged and labeled study medication will be supplied by Allergan.

[redacted]

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction. [redacted]

Any malfunctioning applicators should be returned to Allergan or designee. Written instructions provided by Allergan should be followed when returning a malfunctioning applicator to Allergan or its representative.

10.6 Monitoring by the Sponsor

A representative of the sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Laboratory specimens for blood chemistry panel, hematology including complete blood count with differential, and urinalysis will be sent to a centralized clinical laboratory ( ) with certification from a recognized accreditation agency) to be assayed using validated methods.

10.8 Publications

Allergan, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

[redacted]

11. References

AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130:429-440.

American Academy of Ophthalmology Glaucoma Panel. Preferred Practice Pattern® Guidelines. Primary open-angle glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2010a. 27 p.

Budenz DL. A clinician's guide to the assessment and management of nonadherence in glaucoma. Ophthalmology. 2009;116:S43-S47.

Cohen JS, Gross RL, Cheetham JK, VanDenburgh AM, Bernstein P, Whitcup SM. Two-year double-masked comparison of bimatoprost with timolol in patients with glaucoma or ocular hypertension. Surv Ophthalmol. 2004;49 (Suppl 1):S45-S52.

Cook C, Foster P. Epidemiology of glaucoma: What's new? Can J Ophthalmol. 2012;47:223-226.

Friedman DS. Introduction: new insights on enhancing adherence to topical glaucoma medications. Ophthalmology. 2009;116:S29.

Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268-1279.

Higginbotham EJ, Schuman JS, Goldberg I, Gross RL, VanDenburgh AM, Chen K, et al. One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. Arch Ophthalmol. 2002;120:1286-1293.

Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701-713.

Knight O'RJ, Lawrence SD. Sustained drug delivery in glaucoma. Current Opinion in Ophthalmology 2014;25(2):112-117.

Kozak KR, Crews BC, Morrow JD, Wang L-H, Ma YH, Weinander R, et al. Metabolism of the endocannabinoids, 2-arachidonylglycerol and anandamide, into prostaglandin, thromboxane, and prostacyclin glycerol esters and ethanolamides. J Biol Chem. 2002;277:44877-44885.

Krauss AH, Woodward DF. Update on the mechanism of action of bimatoprost: a review and discussion of new evidence. Surv Ophthalmol. 2004;49(Suppl 1):S5-11.

Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108:1943-1953.

LUMIGAN® [Package Insert]. Irvine, CA: Allergan, Inc. 2012.

Matias I, Chen J, De Petrocellis L, Bisogno T, Ligresti A, Fezza F, et al. Prostaglandin ethanolamides (prostamides): in vitro pharmacology and metabolism. J Pharmacol Exp Ther. 2004;309:745-757.

Mosaed S, Dustin L, Minckler DS. Comparative outcomes between newer and older surgeries for glaucoma. Trans Am Ophthalmol Soc. 2009;107:127-33.

Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol. 1996;80:389-393.

Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90:262-267. Doi: 10.1136/bjo.2005.081224. Downloaded from bjo.bm.com, April 9, 2014.

Stamper RL, Lieberman MF, Drake MV, eds. Introduction and Classification of the Glaucomas. In: Stamper RL, Lieberman MF, Drake MV, editors. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas, 8th ed. Amsterdam, Netherlands: Mosby Elsevier; 2009;Chap 1:1-7.

Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. Ophthalmology. 2009;116:S30-S36.

Varma R, Lee PP, Goldberg I, Kotak S. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol. 2011;152:515-522.

Weber A, Ni J, Ling KH, Acheampong A, Tang-Liu DD, Burk R, et al. Formation of prostamides from anandamide in FAAH knockout mice analyzed by HPLC with tandem mass spectrometry. J Lipid Res. 2004;45:757-763.

Weinreb RN, Kaufman PL. The Glaucoma Research Community and FDA look to the future: a report from the NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium. Inv Ophthalomol & Vis Sci. 2009;50(4):1497-1505.

Williams RD, Cohen JS, Gross RL, Liu CC, Safyan E, Batoosingh AL. Long-term efficacy and safety of bimatoprost for intraocular pressure lowering in glaucoma and ocular hypertension: year 4. Br J Ophthalmol. 2008;92:1387-1392.

Woodward DF, Chan MF, Burke JA, Cheng-Bennett A, Chen G, Fairbairn CE, et al. Studies on the ocular hypotensive effects of prostaglandin F2 alpha ester prodrugs and receptor selective prostaglandin analogs. J Ocul Pharmacol. 1994;10:177-193.

Woodward DF, Krauss AH, Chen J, Lai RK, Spada CS, Burk RM. The pharmacology of bimatoprost (Lumigan). Surv Ophthalmol. 2001;45(Suppl 4):S337-S345.

Woodward DF, Phelps RL, Krauss AH, Weber A, Short B, Chen J, et al. Bimatoprost: A novel antiglaucoma agent. Cardiovasc Drug Rev. 2004;22:103-120.

Yu M, Ives D, Ramesha CS. Synthesis of prostaglandin E2 ethanolamide from anandamide by cyclooxygenase-2. J Biol Chem. 1997;272:21181-21186.

12. Attachments

12.1 Package Insert

The appropriate package insert or Summary of Product Characteristics will be supplied to investigators in countries where timolol (study-provided eye drops) is marketed.

12.2 Glossary of Abbreviations

Term/Abbreviation	Definition
ABMD	Anterior Basement Membrane Disease
AC	Anterior chamber
ARMD	Age-related Macular Degeneration
ASC	Ambulatory Surgical Center
AS-OCT	Anterior segment optical coherence tomography
BCVA	Best-corrected visual acuity
BID	Twice daily
BLQ	Below the limit of quantitation
CRF	Case report form
DMEK	Descemet's Membrane Endothelial Keratoplasty
DSEK	Descemet's Stripping Endothelial Keratoplasty
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOL	Intraocular lens implant
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IV/WRS	Interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model repeated measures
NI	Noninferiority
NSAID	Non-steroidal anti-inflammatory drug
OAG	Open-angle glaucoma
OCT	Optical coherence tomography
OHT	Ocular hypertension
OU	Both eyes

Term/Abbreviation	Definition
PAS	Peripheral anterior synechiae
PLA	Polylactic acid
PLGA	Polylactic-*co*-glycolic acid
POAG	Primary open-angle glaucoma
PP	Per protocol
RBC	Red blood cell
SC/T	Patients with sickle cell disease or trait or other hemoglobinopathies
SOC	System Organ Class (MedDRA)
SR	Sustained release
US	United States
WBC	White blood cell

12.3 Protocol Amendment Summary

12.3.1 Amendment 1

Title: The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

Protocol 192024-092 Amendment 1

Date of Amendment: August 2015

Amendment Summary

This summary includes changes made to Protocol 192024-092 (approved September 2014). This protocol was amended to clarify some sections and to modify the inclusion/exclusion criteria.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Title Page	Updated Allergan Medical Safety Physician and Allergan Signatory information.	
Protocol Summary	Updated and reordered the following key inclusion criteria as follows: • Diagnosis of either OAG (ie, primary ~~OAG~~, pseudoexfoliation ~~glaucoma~~, or pigmentary glaucoma) or OHT in each eye, and both eyes require IOP-lowering treatment (Note: diagnosis does not have to be the same in both eyes) • In the investigator's opinion, either eye can be treated adequately with ~~timolol~~ topical ophthalmic beta-blocker (eg, timolol) eye drops as the sole therapy • In the ~~opinion of the~~ investigator's opinion, ~~based on prior use or on IOP rebound (elevation) during the washout period, patient is a responder to IOP lowering by topical prostamides, prostaglandins, or prostaglandin analogs~~ either eye can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy • The iridocorneal angle ~~inferiorly~~ in the study eye must be confirmed as being qualified by Reading Center AS-OCT assessment • ~~In both eyes, a~~At the Baseline visit: Hour 0 IOP in the study eye of ≥ 22 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≥ 17 mm Hg and ≤ 32 mm Hg, with difference between eyes of ≤ 5 mm Hg • ~~In both eyes~~ At ~~Hour 2 at~~ the Baseline visit: Hour 2 IOP in the study eye of ≥ 19 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≥ 14 mm Hg and ≤ 32 mm Hg Updated the following key exclusion criterion: • In the investigator's opinion, patient is nonresponsive to topical ophthalmic beta-blockers and/or topical prostamides, prostaglandins, or prostaglandin analogs (eg, LUMIGAN, Xalatan, Travatan)	Revised key entry criteria based on the updated inclusion and exclusion criteria in the body of the protocol.

[redacted]

Section	Revision	Rationale
[redacted]		
Section 1.3.3	The objective of this ~~stage of the~~ study is to evaluate the safety and ~~intraocular pressure (~~IOP~~)~~-lowering efficacy of Bimatoprost SR in patients with OAG. As of March 2015~~April, 2014~~, a total of ~~87~~ 109 patients had received a single administration; and ~~of those~~ as of June 2015, ~~12~~ 24 had received a repeat administration of Bimatoprost SR. Based on a review of the efficacy data as of March 2015, a trend in dose-response has been observed across the 4 dose strengths that were tested. Available data suggest that the implant may provide topical prostaglandin analog-like efficacy up to 3 to 4 months post-implantation in the majority of patients. ~~from the 10 µg and 15 µg single administrations show comparable IOP pressure lowering between the study eye and the nonstudy eye during the first 12 to 16 weeks after dosing. Of the 67 patients across all dose groups who had reached the Week 16 visit, 62 (92.5%) had not required the use of additional intraocular pressure-lowering topical medication by that visit. A total of 12 patients had received a repeat administration of Bimatoprost SR (2 at 6 µg, 5 at 10 µg, and 5 at 15 µg), providing up to 20 weeks of data following the second administration. The timing of the second administration ranged from 20 weeks after the first dose in the 6 µg group, 14 to 33 weeks (14, 16, 19, 24, and 33 weeks) in the 10 µg group, and 17 to 37 weeks (17, 19, 19, 26, and 37 weeks) in the 15 µg group.~~ Data ~~for up to 16 weeks of follow up after~~following the second administration in the redosed patients showed similar IOP lowering to that observed following the first administration of Bimatoprost SR. As of ~~April~~March, ~~2014~~2015, Bimatoprost SR has shown an acceptable safety profile with single and repeat	Updated the summary of data from Study 192024-041D with more current results.

Section	Revision	Rationale
	administrations in ongoing study 192024-041D. ~~The most frequently reported adverse events (> 10% of patients) for the study eye have been conjunctival hyperaemia, conjunctival haemorrhage, eye pain, foreign body sensation, and lacrimation increased.~~ Most ~~of these~~ adverse events were ocular, mild in severity, occurred within the first 8 days after Bimatoprost SR administration, and were considered related to the study drug administration procedure. There have been no reports of serious study drug-related adverse events, and no new safety concerns have been observed after the second treatment. Please refer to the Investigator's Brochure for details on reported safety findings.	
Sections 3 and 4.1	Updated the number of study sites from 170 to 180.	Updated the number of study sites based on a revised estimate of global participating sites.
Section 4.3	Updated the following inclusion criteria: 4. Patient is willing to withhold his/her IOP-lowering treatments according to the study requirements, and in the opinion of the investigator can do so without significant risk. [redacted] 7. Diagnosis of either OAG (ie, primary pseudoexfoliation, or pigmentary glaucoma) or OHT in each eye and both eyes require IOP-lowering treatment~~.~~ (Note: diagnosis does not have to be the same in both eyes) 8. In the investigator's opinion, either eye can be treated adequately with topical ophthalmic beta-blocker (eg, timolol) eye drops as the sole therapy.	Updated inclusion criteria 4, 7, and 8 for better clarity.
	Added the following inclusion criterion: 9. In the investigator's opinion, either eye can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy. Removed the following original inclusion criterion: ~~11. In the opinion of the investigator based on prior use or on IOP rebound (elevation) during the Washout period, patient is a responder to IOP lowering by topical prostamides, prostaglandins, or prostaglandin analogs (eg, LUMIGAN, Xalatan, Travatan)~~	Replaced original inclusion criterion 11 with new inclusion criterion 9 for consistency in requirements related to the study medication and the control treatment groups of the study, avoiding potential bias, which is consistent with previous bimatoprost studies. Data from the ongoing 192024-041D study support this change. There have been no safety concerns for the patients who have been re-implanted based on the "investigator's opinion" for getting the injection.

Section	Revision	Rationale
	Updated the following inclusion criteria: 13. At the Baseline visit: a. Hour 0 IOP <u>in the study eye of</u> ≥ 22 mm Hg and ≤ 32 mm Hg, <u>and in the fellow eye of ≥ 17 mm Hg and ≤ 32 mm Hg</u>, with difference between eyes of ≤ 5 mm Hg b. Hour 2 <u>IOP in the study eye of</u> ≥ 19 mm Hg and ≤ 32 mm Hg<u>, and in the fellow eye of ≥ 14 mm Hg and ≤ 32 mm Hg</u> 14. Central Corneal Endothelial Cell Density by specular microscopy: [redacted]	Updated criteria 13 and 15 because the study design is not paired eye comparison and to ease entry criteria related to nonstudy eye. Updated criterion 14 to make the automated specular microscopy count consistent with the Reading Center manual count.
Section 4.4	Updated the following exclusion criterion: 3. Known allergy or sensitivity to ~~the~~<u>any</u> study medication or its components, any component of the delivery vehicle, <u>procedure-related materials</u>, or diagnostic agents used during the study (eg, topical anesthetic, dilating drops, fluorescein) Removed the following original exclusion criterion: ~~6. Patients who plan for an extended absence away from the area of the study center that would preclude them from returning for all protocol-specified study visits~~ Updated the following inclusion criteria: 7. Anticipated use of oral, intramuscular, or intravenous ~~(IV)~~ corticosteroids from 2 months prior to the Baseline visit through ~~the 12th month after the last Bimatroprost SR or Sham administration~~ <u>Week 52</u> 11. In the investigator's opinion, patient is nonresponsive to topical ophthalmic beta-blockers <u>and/or topical prostamides, prostaglandins, or prostaglandin analogs (eg, LUMIGAN, Xalatan, Travatan)</u> 12. History of traumatic cataract and/or <u>traumatic</u> angle recession in ~~either~~ <u>the study</u> eye [redacted]	Revised exclusion criterion 3 for clarity. Exclusion criterion 6 was deleted to allow flexibility when possible. For exclusion criterion 7, decreased the time to 52 weeks because it is difficult to predict more than 1 year in advance. Revised exclusion criterion 11 for consistency with inclusion criteria. Revised exclusion criteria12, [redacted] and 16 because this is not a paired eye comparison design; therefore, history only needs to be from the study eye.

Section	Revision	Rationale
[redacted]		

Section	Revision	Rationale
[redacted]		
Section 4.5.1	Revised the following: Intermittent use of ocular decongestants or antihistamines is allowed if not taken within 2 ~~weeks~~days prior to a scheduled visit and/or ≤ 15 minutes before or after topical administration of study medication. Added the following: Required surgical procedures may be performed in the fellow eye only after completion of Week 52. Updated as follows: Note that in the event that the investigator performs an unanticipated incisional surgical procedure on the study eye during which ocular fluid is to be removed, ocular fluid/implant samples may be collected for analysis (see Protocol Procedure Manual for further details~~).~~) at the investigator's discretion.	Decreased to 2 days in order to reduce limitations on patients in a 2-year study. Because this is not a paired eye comparison, the fellow eye may have required surgery after the treatment period has been completed. Revised the description of ocular fluid collection for clarity.
Section 4.5.2	Nonstudy IOP-lowering Medications Use of any topical ophthalmic medication containing an ocular antihypertensive, other than use of study medication (timolol) in Control group or fellow eyes, is prohibited as concurrent therapy in either eye ~~during the study through Week 52~~, unless necessary for the safety of the patient due to inadequate control of IOP as determined by the investigator. ~~Nonstudy~~Inadequate control of IOP should be confirmed at a subsequent visit (scheduled or unscheduled visit). Prior to Week 52 the investigator will be expected to attest to the need for additional nonstudy IOP -lowering medication for safety reasons. After the Week 52 visit, nonstudy topical IOP-lowering medications will be permitted ~~after the Week 52 visit~~, if in the investigator's clinical judgment the IOP is not adequately controlled at two consecutive visits ~~at least 1 week apart~~. Initiation of medication in one eye should not automatically lead to initiation of medication in the other eye. Each eye should be evaluated on an individual basis when determining the need for additional non-study IOP-lowering medications. If nonstudy IOP lowering medication is initiated prior to Week 52, the investigator will be expected to attest to the need for additional non-study IOP- lowering medication for safety reasons for each eye individually. Contact Lenses Use of soft contact lenses within 3 days and use of rigid gas permeable or hard contact lenses within 1 week prior to a scheduled study visit or Administration Day, or use of contact lenses of any kind within 1 week following any Bimatoprost SR (or Sham) administration in either eye is prohibited. Contact lenses should be removed prior to instilling any study-provided eye drops and patients should wait at least 15 minutes before putting contact lenses back in the eyes	Updated text for clarity. Updated text for clarity and to reduce limitations for patients who use contact lenses.

Section	Revision	Rationale
	after instilling topical drops. Other Medications • Surgical procedures that are not related to Bimatoprost SR (or sham) administration procedures in ~~either eye~~ the study eye. (Surgical procedures are allowed in the fellow eye after Week 52 as described in Section 4.5.1) • Use of any ~~nonstudy~~ topical ophthalmic medications (except as described above and in Section 4.5.1) in either eye • ~~Use of soft contact lenses within 1 week and use of rigid gase permeable or hard contact lenses within 2 weeks prior to a scheduled study visit, or use of contact lenses of any kind within 2 weeks following any Bimatroprost SR (or Sham) administration in either eye~~	
Section 4.5.3	For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject. [redacted]	Updated text for clarity.

Section	Revision	Rationale
[redacted]		
Section 5.6.1	Patients who have received nonstudy topical IOP- lowering medication (prohibited before Week 52 unless required for safety reasons due to inadequate IOP control and attested to by the investigator) in a Bimatoprost SR study eye will receive Sham administration in that eye on the Bimatoprost SR repeat administration day(s). Patients who use nonstudy IOP-lowering medication (prohibited before Week 52 unless required for safety reasons due to inadequate IOP control and attested to by the investigator) in only one eye will be followed for the duration of the study.	Updated text for clarity.
[redacted]		

Section	Revision	Rationale
[redacted]		
Section 6.2	**Biomicroscopic Examination:** Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, cornea, AC, iris/pupil, and lens ~~(through a dilated pupil)~~. **Lens Assessment ~~(Phakic Eyes Only)~~:** Biomicroscopic findings will be evaluated for the presence and severity of nuclear, cortical, and posterior subcapsular lens opacities. See the Protocol Procedure Manual for further details. **Specular Microscopy:** Endothelial cell density will be assessed using specular microscopy performed on the central cornea at all sites. The final qualification of central endothelial cell density for study entry will be determined by the Reading Center ~~based on manual specular microscopy analysis.~~. Qualification will remain valid for 1 year after Screening in patients who are not enrolled at the time of Screening, if in the investigator's opinion there have been no clinically significant changes occurring in the eye (eg, ocular surgery) during that time. All additional specular microscopy images taken during the study will be assessed by the Reading Center. See the Protocol Procedure Manual for further details. The same instrument should be used throughout the study for a given patient. **Anterior Segment Optical Coherence Tomography (AS-OCT):** AS-OCT measurements will be performed at all sites as a criterion for inclusion and a Reading Center will be used to confirm patient iridocorneal angle size and determine eligibility. Each patient's iridocorneal angle eligibility is valid for the duration of the study; however, if in the investigator's opinion the patient's angle size may have changed, an unscheduled AS-OCT may be performed prior to retreatment. Qualification will remain valid for 1 year after Screening in patients who are not enrolled at the	Updated text for clarity. Defined a time frame and requirements for the validity of the qualifications provided by the Reading Center.

Section	Revision	Rationale
	time of Screening, if in the investigator's opinion there have been no clinically significant changes occurring in the eye). See the OCT Image Acquisition manuals from the Reading Center for further details on the use of OCT. In the event that the AS-OCT type as specified in the manuals is not available, a suitable alternative may be approved by Allergan and the designated Reading Center for use. The same instrument should be used throughout the study for a given patient.	
[redacted]		
Section 8.3	Reading Center qualification of angle must be confirmed by the completion of Screening and endothelial cell density must be confirmed by the Baseline visit.	Updated text for clarity.
Section 8.4	Ocular examination procedures should be performed in the order listed at each visit. Some flexibility in procedure order is allowed. However, the general flow of examinations set forth in the schedule starting with noncontact examinations, followed by IOP, followed by contact examinations, and followed by dilation and post-dilation activities should be maintained. Intraocular pressure should be measured at approximately the same time of day at each visit. Hour 0 ~~(H0)~~ is 8 AM ± 1 hour and Hour 2 ~~(H2)~~ is 2 hours after Hour 0 (± 30 minutes). Study-provided eye drop medications should be administered immediately after performing the Hour 0 IOP measurements. All IOP measurements for a given visit day must be completed prior to performing any examination procedures that require pupil dilation.	Updated text for clarity.
[redacted]		

Section	Revision	Rationale
[redacted]		
Section 8.8	Patients who have received nonstudy IOP-lowering medication in both eyes, or who do not complete an Administration Day visit, may discontinue the study 12 months after the last Bimatoprost SR or Sham administration~~.~~ at which time they should complete the Month 20/Exit visit procedures.	Updated text for clarity.
Section 8.9	After the first administration (or Sham), failure to undergo an Administration visit does not indicate total withdrawal from the study. Patients who have received nonstudy IOP-lowering medication in only one eye will be followed for the duration of the study. Patients who have received nonstudy IOP-lowering medication in both eyes, or patients who do not undergo Cycle 2 or 3 (or both) administrations (or Sham administrations), will still be followed for 12 months after the last Bimatoprost SR or Sham administration for safety reasons. These patients are eligible for Early Discontinuation (Early Exit) as described in Section 8.8, above. •Patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, ~~would put~~compromises the ~~patient at an unacceptable medical risk by continuing~~patient's ability to participate in the study ~~participation~~ If a patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk by continuing study participation, the patient will be withdrawn from the study.	Updated text for clarity, as in this study design, patients are followed for 12 months after their last injection (or Sham) for safety purposes, and cessation of injection does not constitute study withdrawal.

12.3.2 Amendment 2

Title: The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

Protocol 192024-092 Amendment 2

Date of Amendment: March 2017

Amendment Summary

This summary includes changes made to Protocol 192024-092 Amendment 1 (approved August 2015). This protocol was amended to change the screening requirement for angle eligibility confirmation in the study eye, modify/clarify the inclusion/exclusion criteria, clarify the statistical analyses, and change additional procedures for patients with sickle cell disease from required to optional.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Summary	Removed text from the visit schedule section referring to reading center confirmation of iridocorneal angle: • Screening (up to 28 days); Washout period of up to 42 days for both eyes (which may begin once screening procedures have been completed ~~and the site has obtained confirmation of anterior segment optical coherence tomography [AS-OCT] iridocorneal angle qualification from the Reading Center~~); Baseline (~~Days -3 to -1~~ up to 3 days) Updated the following key inclusion criteria: • The iridocorneal angle in the study eye must be independently confirmed as being qualified by ~~Reading Center AS-OCT assessment~~ 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. • At the Baseline visit: Hour 0 IOP in the study eye of ≥ 22 mm Hg and ≤ 32 mm Hg, and in the fellow eye of	Updated to reflect changes in the body of the protocol.

Section	Revision	Rationale
	~~≥ 17 mm Hg and~~ ≤ 32 mm Hg~~, with difference between eyes of ≤ 5 mm Hg~~ • At the Baseline visit: Hour 2 IOP in the study eye of ≥ 19 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ~~≥ 14 mm Hg and~~ ≤ 32 mm Hg • By the Baseline visit, the final central endothelial cell density in both eyes must be confirmed as being qualified by Reading Center assessment, with at least one eye qualified for inclusion as the study eye Updated the following key exclusion criterion: • The following surgical history: a. History or evidence of complicated cataract surgery in the study eye: eg, surgery resulting in complicated lens placement (such as anterior chamber intraocular lens implant (IOL)~~; phakic IOL;~~ sulcus IOL; aphakia, etc) or intraoperative complications (~~eg~~ 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 in the study eye Updated the statistical analyses as follows: • Intraocular pressure change from baseline will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The model will include ~~the fixed effects of treatment;~~ IOP time-matched change from baseline ~~IOP stratification; visit (~~ as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12)~~, hour; the two-way interaction between treatment and each of hour and visit; and the three-way~~ treatment-by-timepoint interaction~~ between treatment, hour, and visit~~ and baseline IOP stratification as fixed effects. Unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance matrix fails to converge, multiple imputation (MI) will be implemented before MMRM. • For the United States Food and Drug Administration (US FDA), the primary efficacy variable will be the study eye ~~time-matched~~ IOP. The primary analysis will be based on Weeks 2, 6, and 12 using the ITT population. Specifically, the following analysis will be performed: ~~time-matched~~ IOP will be analyzed using an MMRM approach based on the same model as described for the primary efficacy analysis of time-matched IOP change from baseline. • Sample Size Calculation: The sample size calculation is based on the primary efficacy analysis of the	

Section	Revision	Rationale
	~~time-matched~~ IOP for US FDA review because the sample size based on the primary efficacy analysis for other regions is expected to be smaller.	
[redacted]		
Section 1.3.1	Nonclinical studies with pharmacology endpoints (Reports BIO-09-803, BIO-11-920, PK09109-PK, BIO-09-785) showed dose-related reductions in IOP in normotensive Cynomolgus monkeys and Beagle dogs, as well as in laser-induced ocular hypertensive Cynomolgus monkeys following single doses. Toxicology studies, of at least 6 to 12 months duration and including single and repeat Bimatoprost SR administration, were conducted in Cynomolgus monkeys and Beagle dogs (TX09051-TX, TX09066-TX, TX10016-TX, TX11076-TX, TX12012-TX, TX12018-TX, and TX12102-TX~~-I1 [ongoing]~~). Monkeys, which have a characteristically small anterior chamber angle compared to both dogs and humans, did not tolerate Bimatoprost SR dose strengths tested (≥ 10 µg Bimatoprost SR) due to chronic contact of the implant with corneal endothelium. Single and repeat ocular toxicity studies with Generation 2 Bimatoprost SR in dogs with varying AC angle sizes demonstrated acceptable safety and ocular	Updated information from completed studies

Section	Revision	Rationale
	tolerability with single doses ≤ 20 µg (TX11076 TX, TX12012-TX, TX12018-TX) and with repeat doses of ≤ 15 µg (TX12012 TX, TX12018-TX). Furthermore, no adverse drug- or implant-related ocular findings have been seen following three intracameral injections of up to 20 µg (two 10 µg implants) Bimatoprost SR ~~(9 month timepoint including histopathology)~~ in the ~~ongoing~~ 18-month repeat dose Good Laboratory Practice (GLP) study in dogs (Report TX12102-TX). Pharmacokinetic studies (PK09109 PK, PK11086-PK) in Beagle dogs demonstrated that systemic exposure of bimatoprost and bimatoprost acid was below the limit of quantitation (BLQ) with doses ≤ 60 µg. Aqueous humor concentrations generally peaked by 10 weeks postdose for doses ≤ 30 µg (Generation 1 and Generation 2), then declined to low levels suggestive of near-complete drug release from the device at 3 months for doses ≤ 20 µg. By 14 weeks following a 20 µg (Generation 2) dose, ocular tissues samples were collected for analysis, which demonstrated that drug and metabolite concentrations were BLQ in aqueous humor, vitreous humor, retina, and the remnant implants, but detected in cornea, choroid, and iris-ciliary body. A pharmacokinetic study (PK14025-PK) was conducted in Beagle dogs comparing the ocular distribution of topical bimatoprost 0.03% solution or a single Generation 2 Bimatoprost SR implant (15 µg). Following topical administration, bimatoprost and bimatoprost acid distributed into the iris-ciliary body as well as other (off target) tissues with concentrations in the bulbar conjunctiva, eyelid margin, and periorbital fat significantly higher than those observed in the iris-ciliary body. In contrast, following administration of a single Generation 2 Bimatoprost SR implant at 15 µg, bimatoprost and bimatoprost acid concentrations were either below the limit of quantitation (BLQ) or near the detection limit in bulbar conjunctiva, eyelid margin, and periorbital fat while the highest bimatoprost and bimatoprost acid concentrations were observed in the target tissue, the iris ciliary body. Retinal concentrations were BLQ following both topical and Bimatoprost SR administration.	
Section 1.3.3	Study 192024-041D ~~is an ongoing~~ was a Phase 1/2, paired-eye comparison evaluating the safety and efficacy of 4 dose strengths of Bimatoprost SR (6 µg, 10 µg, 15 µg, or 20 µg [2 × 10 µg implants]), as single or repeat administration in one eye (study eye), versus the use of topical LUMIGAN® 0.03% in the fellow eye (nonstudy eye). The objective of this study ~~is~~ was to evaluate the safety and IOP-lowering efficacy of Bimatoprost SR in patients with OAG. A~~s of March 2015, a~~ total of 109 patients ~~had~~ received a single administration~~;~~ and ~~as of June 2015,~~ 24 patients ~~had~~ received a repeat administration of Bimatoprost SR. ~~Based on a review of the efficacy data as of March 2015, a~~ A trend in dose response ~~has been~~ was observed across the 4	Updated information from recently completed study

Section	Revision	Rationale
	dose strengths that were tested. ~~Available d~~ Data suggest that the implant may provide topical prostaglandin analog-like efficacy up to 3 to 4 months post-implantation in the majority of patients. Data following the second administration in the redosed patients showed similar IOP lowering to that observed following the first administration of Bimatoprost SR. ~~As of March 2015,~~ Bimatoprost SR ~~has shown~~ showed an acceptable safety profile with single and repeat administrations in ~~ongoing s~~ Study 192024-041D. Most adverse events were ocular, mild or moderate in severity, occurred within the first ~~8~~ 2 days after Bimatoprost SR administration, and were considered related to the study drug administration procedure. There ~~have been~~ were no reports of serious study drug-related adverse events, and no new safety concerns ~~have been~~ were observed after the second treatment. Please refer to the Investigator's Brochure for details on reported safety findings.	
Section 4.2	The study population consists of patients with OAG or OHT and an open iridocorneal angle inferiorly by clinical gonioscopy in the study eye, and OAG or OHT in the fellow eye, where both eyes require IOP-lowering medication. The eye that meets the entry criteria (Sections 4.3 and 4.4) will be selected as the study eye. If both eyes meet the entry criteria ~~(including iridocorneal angles that have been confirmed as qualified by the Reading Center anterior segment optical coherence tomography [AS-OCT assessment])~~, the eye with the higher IOP at Baseline Hour 0 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. Angle qualification will be independently confirmed as being qualified by 2 ophthalmologists, and endothelial cell density qualification for study entry will be determined by the Reading Center based on ~~AS-OCT and~~ specular microscopy assessment ~~respectively~~ (see Protocol Procedure Manual for details).	Revised for consistency with updated inclusion criteria
Section 4.2.1	4.2.1 Patients With Sickle Cell Trait or Disease ~~At screening all patients will be tested for sickle cell trait or disease.~~ Patients with sickle cell trait or disease (or other hemoglobinopathies) may be enrolled at the discretion of the investigator based on an individual risk-benefit assessment. Because of a slightly higher risk of IOP elevation and intraocular complications in the setting of a microhyphema, patients with these disorders ~~must~~ may undergo optional additional ~~safety monitoring~~ ~~(~~biomicroscopy and IOP measurements~~)~~ after injection/Sham injection at the investigator's discretion (~~as outlined in~~ see Section 8.4). Additional information about the Bimatoprost SR experience in patients with sickle trait is provided in the Investigator's Brochure.	Based on the ongoing safety monitoring of the 192024-091 and 192024-092 studies, no increased risk of hyphema or microhyphema with sickle cell traits or sickle cell disease is confirmed. There are 400+ patients had at least one Bimatoprost SR injection in the 2 studies (estimated based on 1:1:1 ratio), there is only one report of microhyphema in a NON-sickle cell patient. No anterior chamber safety concerns reported in the 14 sickle cell or traits patients.
Section	10. The iridocorneal angle in the study eye ~~inferiorly in~~	Inclusion criterion for angle

Section	Revision	Rationale
4.3	~~both eyes~~ must be ~~open based on clinical gonioscopic examination~~ 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. Iridocorneal angle in the study eye must be confirmed as being qualified by Reading Center AS-OCT assessment~~ ~~13~~ 12a. Hour 0 IOP in the study eye of ≥ 22 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ~~≥ 17 mm Hg and~~ ≤ 32 mm Hg~~, with difference between eyes of ≤ 5 mm Hg~~ ~~13~~ 12b. Hour 2 IOP in the study eye of ≥ 19 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ~~≥ 14 mm Hg and~~ ≤ 32 mm Hg ~~14~~ 13b. By Baseline: final central endothelial cell density in both eyes must be confirmed as being qualified by Reading Center assessment, with at least one eye qualified for inclusion as the study eye	assessment revised to use clinical measures in order to develop a more "real-life" measure of angle openness. Lower limit of IOP in fellow eye removed to allow for flexibility in enrollment. Fellow eye IOP upper limit is required for safety purposes, but lower limit is not included in analysis. Revised for clarity; at least one eye needs to be qualified as study eye for patient to be included in the study.
Section 4.4	9. Previous enrollment in another Allergan Bimatoprost SR Study ~~192024-041D~~ 12. History or evidence of ~~a~~ clinically relevant, substantial ocular trauma (eg, a traumatic cataract, ~~and/or~~ traumatic angle recession, etc) in the study eye 13. The following surgical history: a. History or evidence of complicated cataract surgery in the study eye: eg, surgery resulting in complicated lens placement (such as anterior chamber intraocular lens implant ([IOL])~~;~~, ~~phakic IOL;~~, sulcus IOL~~;~~, aphakia~~;~~, etc) or intraoperative complications (~~eg,~~ such as a posterior capsular tear [with or without vitreous loss], iris trauma, etc). Note: history of uncomplicated cataract surgery is not an exclusion. b. History of phakic IOL insertion for refractive error correction in the study eye	Revised because multiple studies are ongoing. Revised for clarity. Revised for clarity

[redacted]

Section	Revision	Rationale
[redacted]		
Section 5.3	The site coordinator and designated staff will not be masked to whether the patient received 1 of the 2 dose strengths of Bimatoprost SR or the Sham administration procedure, but will be masked to the specific implant dose strength. The patient and the remaining staff will be masked to the patient's treatment assignment. Efficacy IOP measurements will be masked by using a 2-person reading method as described in Section 6.1.1 (for optional postoperative IOP measurements for patients with sickle cell disease or trait [or other hemoglobinopathies], see Section 8.4).	Based on the ongoing safety monitoring of the 192024-091 and 192024-092 studies, no increased risk of hyphema or microhyphema with sickle cell traits or sickle cell disease is confirmed. There are 400+ patients had at least one Bimatoprost SR injection in the 2 studies (estimated based on 1:1:1 ratio), there is only one report of microhyphema in a NON-sickle cell patient. No anterior chamber safety concerns reported in the 14 sickle cell or traits patients.
[redacted]		
Section 5.9.4	Note: Patients with sickle cell disease or trait (or other hemoglobinopathies) ~~will be expected to~~ may undergo optional biomicroscopy and IOP examination in both eyes 4 hours after each Bimatoprost SR administration (or Sham administration). This optional IOP examination is for postoperative purposes only, and as such does not require a masked, 2-person reading method. The IOP should be taken only once to avoid excessive postadministration (or Sham administration) manipulation of the eye, and should be taken by the investigator (or other unmasked, qualified personnel). This postadministration (or Sham administration) examination may be performed using a Goldmann applanation tonometer or a hand-held tonometer. (See the Study Procedure Manual for details.)	Based on the ongoing safety monitoring of the 192024-091 and 192024-092 studies, no increased risk of hyphema or microhyphema with sickle cell traits or sickle cell disease is confirmed. There are 400+ patients had at least one Bimatoprost SR injection in the 2 studies (estimated based on 1:1:1 ratio), there is only one report of microhyphema in a NON-sickle cell patient. No anterior chamber safety concerns reported in the 14 sickle cell or traits patients.
Section 6.2	Hematology, blood chemistry, and urinalysis: Blood and urine samples will be collected for blood chemistry and hematology panels ~~(including sickle cell testing by local laboratories)~~ and urinalysis.	Based on the ongoing safety monitoring of the 192024-091 and 192024-092 studies, no increased risk of hyphema or microhyphema with sickle cell traits or sickle cell disease is confirmed. There are 400+ patients had at least one Bimatoprost SR injection in the 2 studies (estimated based on 1:1:1 ratio), there is only one report of microhyphema in a NON-sickle cell patient. No anterior chamber safety concerns reported in the 14 sickle cell or traits patients.
	Visual Acuity: Visual acuity tests will be performed at all scheduled visits except on any of the 3 administration days. Manifest refraction using Snellen equivalent with a logMar	Revised for consistency with updated visit schedule

Section	Revision	Rationale
	chart (see Protocol Procedure Manual) will be performed at Screening~~;~~, Baseline~~;~~, Weeks 12~~, 28, 44,~~ and 52~~;~~, and Month 20/Exit.	
	Gonioscopy: Gonioscopic examination for eligibility at Screening (only) will be independently performed by 2 ophthalmologists as described in the Protocol Procedure Manual. The independent eligibility assessors should not share their assessments with each other until the assessment is recorded. The 2 ophthalmologists' independent eligibility assessments must confirm patient eligibility for participation in the study. Subsequent gonioscopic examinations will be performed by the study investigator.	Revised for consistency with revised eligibility criteria
	Pachymetry: Corneal thickness using ultrasound (contact) pachymetry will be performed on the central cornea ~~at all sites.~~. The same instrument should be used throughout the study for a given patient. Contact pachymetry ~~will~~may be performed any time after the Hour 2 IOP ~~Measurement and before gonioscopy~~measurement. See the Protocol Procedure Manual for further details.	Revised for consistency with visit schedule
	Anterior Segment Optical Coherence Tomography (AS-OCT): AS-OCT measurements will be performed at all sites ~~as a criterion for inclusion and a Reading Center will be used to confirm patient iridocorneal angle size and determine eligibility. Each patient's iridocorneal angle eligibility is valid for the duration of the study; however, if in the investigator's opinion the patient's angle size may have changed, an unscheduled AS-OCT may be performed prior to retreatment. Qualification will remain valid for 1 year after Screening in patients who are not enrolled at the time of Screening, if in the investigator's opinion there have been no clinically significant changes occurring in the eye)~~ and a Reading Center will be used to examine angle size for investigational purposes. See the OCT Image Acquisition manuals from the Reading Center for further details on the use of OCT. In the event that the AS-OCT type as specified in the manuals is not available, a suitable alternative may be approved by Allergan and the designated Reading Center for use. The same instrument should be used throughout the study for a given patient.	Revised for consistency with updated eligibility criteria
Section 6.4.3.1	~~The blood tests performed at the screening visit will include testing for sickle cell disease or trait by a site-selected and qualified local laboratory, as outlined in the Protocol Procedure Manual.~~	Based on the ongoing safety monitoring of the 192024-091 and 192024-092 studies, no increased risk of hyphema or microhyphema with sickle cell traits or sickle cell disease is confirmed. There are 400+ patients had at least one Bimatoprost SR injection in the 2 studies (estimated based on 1:1:1 ratio), there is only one report of microhyphema in a NON-sickle cell patient. No anterior chamber safety concerns reported in the 14 sickle cell or traits patients.

Section	Revision	Rationale
Section 7	Three database locks are planned. The first database lock will take place after all patients have completed or prematurely discontinued before the Week 12 visit. Similarly, the database will be locked after all patients have completed or prematurely discontinued before Week 52 and Month 20/Exit. Analyses will be performed after each lock. Prior to the first database lock a detailed analysis plan will be finalized. To maintain the integrity of the ongoing study, Allergan study personnel who are directly involved in data handling and supporting the trial (such as the clinical study team) will remain masked to treatment assignment of individual patients ~~until~~ during the study ~~completion~~. To avoid potential data unmasking between locks and to protect trial integrity, study statistical personnel who have been unmasked after each lock will no longer be involved directly in any ongoing masked study conduct. Another statistician, who is still masked to study treatment, will assume these responsibilities until the next lock. Unmasked data handling and appropriate data and results access will be specified prior to each lock.	Updated text for clarity.
Section 7.2	To avoid confounding of efficacy data, IOP measurements obtained after initiating the use of nonstudy IOP-lowering medication in an eye will be ~~treated as missing for that eye~~ excluded from the calculation of the summary statistics and the statistical analyses for that eye but raw values will be presented in the listings.	Updated text for clarity.
Section 7.3.1	Intraocular pressure change from baseline will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The model will include ~~the fixed effects of treatment;~~ IOP time-matched change from baseline ~~IOP stratification; visit (~~as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12)~~; hour; the two-way~~, treatment-by-timepoint interaction, ~~between treatment~~ and ~~each of hour and visit; and the three-way interaction between treatment, hour, and visit~~ baseline IOP stratification as fixed effects. Unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance matrix fails to converge, multiple imputation (MI) will be implemented before MMRM. The details of the model specifications will be provided in the analysis plan.	Updated text for clarity.
Section 7.3.2	Secondary efficacy analyses comparing each Bimatoprost SR dose strength and timolol to test the no-difference null hypothesis will be performed at scheduled visits (Weeks 2, 6, and 12) and hours for (1) ~~time-matched~~ IOP and (2) time-matched IOP change from baseline. The analysis of ~~time-matched~~ IOP will be similarly performed as described above with ~~time-matched~~ IOP replacing time-matched IOP change from baseline in the analysis model.	Updated text for clarity.

Section	Revision	Rationale
Section 7.6	For the US FDA review, the primary efficacy variable will be the study eye ~~time-matched~~ IOP. For each Bimatoprost SR dose strength which demonstrates efficacy (clinical noninferiority) as described in the primary efficacy analyses, secondary efficacy analyses comparing the Bimatoprost SR dose strength and timolol to test the no-difference null hypothesis will be performed at scheduled visits (Weeks 2, 6, and 12) and hours for ~~time-matched~~ IOP.	Updated text for clarity.
Section 7.7	The sample size calculation is based on the primary efficacy analysis of the ~~time-matched~~ IOP for US FDA review since the sample size based on the primary efficacy analysis for other regions is expected to be smaller.	Updated text for clarity.
Section 8.2	Patients currently being treated with IOP-lowering medication(s) in either eye will begin washout of these medication(s) following completion of the screening procedures ~~and Reading Center confirmation of AS-OCT iridocorneal angle qualification~~.	Revised for consistency with revised inclusion criterion
[redacted]		
Section 8.3	Reading Center qualification of ~~angle must be confirmed by the completion of Screening and~~ endothelial cell density must be confirmed by the Baseline visit.	Revised for consistency with revised inclusion criterion
[redacted]		

Section	Revision	Rationale
[redacted]		

12.3.3 Amendment 3

Title: The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

Protocol 192024-092 Amendment 3

Date of Amendment: June 2018

Amendment Summary

This summary includes changes made to Protocol 192024-092 Amendment 2 (approved March 2017). This protocol was amended to reduce the sample size.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Title Page	Change in Allergan signatory	Personnel change
Protocol Summary	Number of Patients: Approximately ~~600~~ 510 patients will be enrolled in the study. Sample Size Calculation: The sample size calculation is based on the primary efficacy analysis of the IOP for US FDA review because the sample size based on the primary efficacy analysis for other regions is expected to be smaller. Based on simulations, a sample size of ~~540~~ 486 patients (~~180~~ 162 per group) will provide approximately ~~95~~ 95.1% and ~~81~~ 83.5% power to show noninferiority (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. Assuming a premature discontinuation rate of ~~10~~ 5% within 12 weeks (before the primary database lock), approximately ~~600~~ 510 patients (~~200~~ 170 per group) are to be enrolled into this study.	Updated to reflect changes in the body of the protocol.
Section 4.1	Enrollment of approximately ~~600~~ 510 patients in total at approximately 180 sites, with approximately ~~200~~ 170 patients per group, is planned to ensure ~~180~~ 162 completed patients per group, assuming a premature discontinuation rate of ~~10~~ 5%.	Revised based on new sample size calculation

Section	Revision	Rationale
Section 7.7	The initial sample size ~~is~~ 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 (ie, 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 standard deviation of 4.0 mm Hg and a common within-subject correlation of 0.6. It ~~is~~ 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 ~~are~~ were made at the study design phase based on the data obtained from the ongoing clinical study 192024-041D. Based on simulations, a sample size of 540 patients (180 per group) ~~will~~ would provide approximately 95% and 81% power to show noninferiority (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. Assuming a premature discontinuation rate of 10% within 12 weeks (before primary database lock), approximately 600 patients (200 per group) ~~are~~ were to be enrolled into this study. 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) is 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) would 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) are to be enrolled into this study.	Revised because the observed discontinuation rate and IOP variability are lower than initially assumed

ALLERGAN

Protocol 192024-092 Amd 3

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
05-Jun-2018 11:22 GMT-070	[redacted]	Clinical Development Approval