Title Page

Protocol Title: An Evaluation of the 24-Hour IOP-lowering Effect of Bimatoprost SR in Participants with Open-Angle Glaucoma or Ocular Hypertension

Protocol Number: 1698-304-007

Product: Bimatoprost SR

Brief Protocol Title: 24-Hour IOP-lowering Effect of Bimatoprost SR

Study Phase: 3b

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1. Protocol Summary

1.1. Synopsis

Protocol Title: An Evaluation of the 24-Hour IOP-lowering Effect of Bimatoprost SR in Participants with Open-Angle Glaucoma or Ocular Hypertension

Protocol Number: 1698-304-007

Brief Title: 24-Hour IOP-lowering Effect of Bimatoprost SR

Study Phase: 3b

Study Rationale: Results of the completed 24-month Phase 1/2 Study 192024-041D indicated that Bimatoprost SR provides prostaglandin analog-like IOP-lowering efficacy. Additionally, the safety profile of Bimatoprost SR at dose strengths of 20 µg (2 × 10 µg) or less (15, 10, and 6 µg) in the Phase 1/2 study was acceptable, and supports additional clinical studies in humans. Four global Phase 3 studies with up to 3 administrations of Bimatoprost SR at fixed 16 week intervals, 1 global extension study, and 1 global Phase 3b study with initial scheduled and subsequent "as needed" repeat administration(s) of Bimatoprost SR [redacted] are ongoing. The current study (1698-304-007) is a multicenter, open-label Phase 3b study to evaluate the IOP-lowering effect over 24 hours of a single administration of Bimatoprost SR in participants with OAG or OHT. The purpose of this study is to obtain data on the 24-hour IOP-lowering effect at Week 8 of Bimatoprost SR treatment, with safety assessed through Month 12.

Objectives and Endpoints:

Objectives	Endpoints/Measures
Efficacy: Primary • To evaluate the 24-hour IOP-lowering effect of Bimatoprost SR in participants with OAG or OHT	• Time-matched IOP change from Baseline Sleep Lab visit at Week 8 Sleep Lab visit in Bimatoprost SR-treated eyes
Secondary • To evaluate the change in diurnal variation of IOP in eyes treated with Bimatoprost SR	• Change from baseline in range of IOP in eyes treated with Bimatoprost SR at Week 8 Sleep Lab visit
Other • To evaluate the IOP-lowering effect of Bimatoprost SR	• Hour 0 IOP change from baseline through Month 12 • Time to initial use of nonstudy IOP-lowering treatment

Objectives	Endpoints/Measures
Safety: • To evaluate the safety of Bimatoprost SR in participants with OAG or OHT	• AEs, visual fields, visual acuity, macroscopic bulbar conjunctival hyperemia, slit-lamp biomicroscopic assessments, dilated ophthalmoscopic assessments (including optic disc assessment), contact ultrasound pachymetry, gonioscopy, specular microscopy

Overall Study Design: This is a multicenter, open-label, Phase 3b study in participants with OAG or OHT.

Number of Participants: Approximately 35 participants will be enrolled: 25 to 30 in the Bimatoprost SR cohort (to achieve a minimum total of 20 evaluable participants at baseline and Week 8 to evaluate the 24-hour IOP-lowering effect of Bimatoprost SR, assuming a premature discontinuation rate of up to 33%), and 5 in the LUMIGAN® 0.01% (bimatoprost ophthalmic solution) cohort. Participants who prematurely discontinue from the study will not be replaced.

Number of Sites: Approximately 3 sites in the United States

Intervention Group and Study Duration:

Participants in the Bimatoprost SR cohort will receive a 10 µg implant in the study eye on Day 1, and the fellow eye will receive standard of care treatment (provided that there is no known crossover effect of the fellow eye's standard of care treatment to the study eye) for the duration of the study. At selected site(s) an additional cohort of participants will be enrolled and assigned to receive topical LUMIGAN 0.01% in the study eye (once daily, at 20:00 ± 1 hour, starting with the evening dose on Day 1), and standard of care treatment in the fellow eye (provided that there is no known crossover effect of the fellow eye's standard of care treatment to the study eye) for the duration of the study. Participants will be assigned to the Bimatoprost SR cohort or LUMIGAN 0.01% cohort by the investigator.

The participant and investigator will not be masked to the study treatment assignment for the duration of the study. Site staff collecting 24-hour IOP measurements at Sleep Lab visits will be masked to the study treatment and study eye.

Study Eye Treatment	Fellow Eye Treatment
Bimatoprost SR 10 µg or LUMIGAN 0.01%[a] (at selected site[s])	Standard of Care

[a] Participants will begin self-administration of LUMIGAN 0.01% in the study eye once daily in the evening (20:00 ± 1 hour) starting with the evening dose on Day 1, and will continue self-administration daily through the duration of the study.

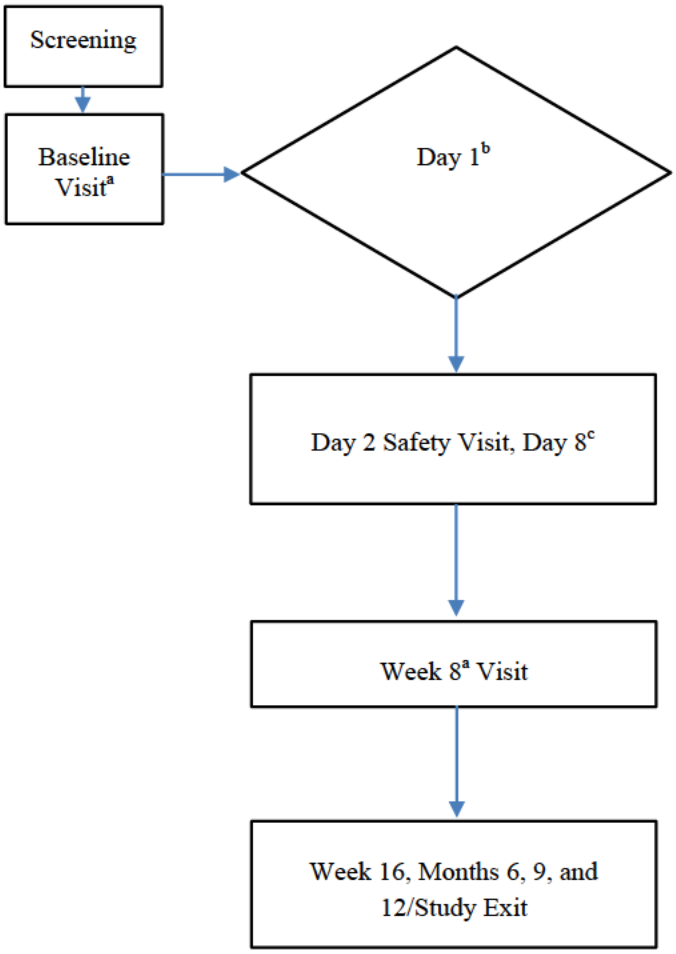
The duration of the study for each participant is approximately 15 months, consisting of a screening period of up to 60 days before washout, washout period of up to 42 days before Baseline, and 12 months of follow-up.

Data Monitoring Committee: No

1.2. Schema

The study schema is presented in Figure 1-1.

Figure 1-1 Study Schema



[a] 24-Hour IOP monitoring
[b] Bimatoprost SR administration or, at selected sites, participants assigned to LUMIGAN will begin self-administration of LUMIGAN once daily in the evening in the study eye starting at 20:00 ± 1 hour.
[c] Phone call

1.3. Schedule of Activities (SoA)

Table 1-1 Schedule of Activities – Screening through Week 8

Visit	Screen-ing		Baseline		Day 1	Day 2 Safety Visit	Day 8 Phone Call	Week 8	
			Office Visit	Sleep Lab Visit[d]				Office Visit	Sleep Lab Visit[d]
Visit Windows	Up to 60 days[a]		-7 days from Sleep Lab Visit[c]				+14 days	-7 days from Sleep Lab Visit[c]	± 7 days
Informed Consent/Authorization	X	Washout[b] up to 42 days							
Demographic Data	X								
Medical/Ophthalmic History	X		X						
Adverse Events	X		X	X	X	X	X	X	X
Concomitant Medications/ Procedures	X		X	X	X	X	X	X	X
Alcohol/Caffeine/Smoking/Sleep	X			X					X
Physical Examination	X								
Vital Signs (at rest ≥ 5 minutes)	X		X	X	X	X		X	X
Pregnancy Test[e]			X						
Blood and Urine Sample Collection[f]	X								
Ocular Examinations in bold should be performed in the order shown									
Pre-Hour 0 Exam (perform before Hour 0 IOP):									
Macroscopic Conjunctival Hyperemia Assessment	OU	Washout[b] up to 42 days	OU			OU		OU	
Manifest Refraction[g]	OU		OU						
Best-Corrected Visual Acuity	OU		OU			OU		OU	
Intraocular Pressure Measurement Hour 0	OU		OU			OU		OU	
Anterior Segment Imaging[h] (may perform any time after Hour 0 IOP)	OU		OU					OU	
Non-contact Exams (may perform in any order at any time before gonioscopy, including prior to H0 IOP)									
Visual Field[i]	OU		OU						
Specular Microscopy[j]	OU		OU						

Visit	Screening		Baseline		Day 1	Day 2 Safety Visit	Day 8 Phone Call	Week 8	
			Office Visit	Sleep Lab Visit[d]				Office Visit	Sleep Lab Visit[d]
Visit Windows	Up to 60 days[a]		-7 days from Sleep Lab Visit[c]				+14 days	-7 days from Sleep Lab Visit[c]	± 7 days
Biomicroscopy	OU	Washout[b] up to 42 days	OU			OU		OU	
Gonioscopy/Angle Assessment	OU		OU					OU	
Pachymetry: (may be performed any time after non-contact exams)	OU		OU						
Pupil Dilation (may perform exams in any order)	OU		OU						
Dilated Ophthalmoscopy	OU		OU						
Optic Disc Examination	OU		OU						
Determination of Eligibility	X		X						
Contact IWRS[k]	X		X		X				
24-Hour IOP Measurements[l]				OU					OU
Study Treatment[m]					SE				

Hour 0 = 08:00 ± 1 hour assessed with a Goldmann applanation tonometer

[a] Eligibility criteria may be rechecked at any time prior to and during washout, at the discretion of the investigator.

[b] Washout in both eyes may begin after all screening procedures have been completed.

[c] Office visit procedures may be performed up to 7 days prior to Sleep Lab visit.

[d] Perform 24-hour Sleep Lab visit on a different day from all other Office visit study procedures.

[e] At sites where required by local institution or health authority, a serum test may be done, with negative results for all tests confirmed prior to the time of Bimatoprost SR administration. Pregnancy testing at Baseline is required regardless.

[f] Blood and urine samples are collected only at Screening unless a retest is necessary.

[g] Manifest refraction will be used to provide a correction for best-corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.

[h] At selected sites/selected participants only, anterior segment imaging may be performed in both eyes of consenting participants using Allergan-approved instruments.

[i] For a given participant, the same test methodology must be used for all visual fields performed at Screening, Baseline, and throughout the study.

[j] For a given participant, the same specular microscope model and analysis methodology must be used at Screening, Baseline, and throughout the study.

[k] Screening: participant number; Baseline: Hour 0 IOP; Day 1: enrollment after eligibility confirmation (may be done at end of Baseline visit if needed)

[l] All 24-hour Sleep Lab visit IOP exams will be performed with an Allergan-specified tonometer. Diurnal IOP measurements will be taken supine ≥ 5 minutes at rest then sitting ≥ 5 minutes at rest at 8:00 ± 30 min, 10:00 ± 30 min, 12:00 ± 30 min, 14:00 ± 30 min, 16:00 ± 30 min, 18:00 ± 30 min, 20:00 ± 30 min, and 22:00 ± 30 min. Nocturnal IOP measurements will be taken supine only ≥ 5 minutes at rest 00:00 ± 30 min, 02:00 ± 30 min, 04:00 ± 30 min, and 06:00 ± 30 min. Please see Procedure Manual for details.

[m] Bimatoprost SR is administered on Day 1. At selected sites, participants assigned to LUMIGAN 0.01% will begin self-administration of LUMIGAN 0.01% once daily in the evening in the study eye starting with the evening dose on Day 1. Those participants will continue self-administration of LUMIGAN 0.01% once daily in the evening (20:00 ± 1 hour) throughout the study.

Table 1-2 Schedule of Activities – Week 16 through Month 12/Study Exit

Visit	Week 16	Month 6	Month 9	Month 12/ Study Exit
Visit Windows	± 4 days	± 14 days	± 14 days	± 14 days
Adverse Events	X	X	X	X
Concomitant Medications/ Procedures	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X	X
Pregnancy Test				X
Ocular Examinations in bold should be performed in the order shown				
Pre-Hour 0 Exams (perform before Hour 0 IOP):				
Macroscopic Conjunctival Hyperemia Assessment	OU	OU	OU	OU
Best-Corrected Visual Acuity	OU	OU	OU	OU
Intraocular Pressure Measurement Hour 0	OU	OU	OU	OU
Anterior Segment Imaging[a] (may perform any time after Hour 0 IOP)		OU		OU
Non-contact Exams (may perform in any order at any time before gonioscopy, including prior to H0 IOP)				
Visual Field[b]		OU		OU
Manifest Refraction[c]				OU
Specular Microscopy[d]	OU	OU	OU	OU
Biomicroscopy	OU	OU	OU	OU
Gonioscopy/Angle Assessment	OU	OU	OU	OU
Pachymetry: (may be performed any time after non-contact exams)	OU	OU	OU	OU
Pupil Dilation (may perform exams in any order)				OU
Dilated Ophthalmoscopy				OU
Optic Disc Examination				OU
Contact IWRS[e]				X

Hour 0 = 08:00 ± 1 hour assessed with a Goldmann applanation tonometer

[a] At selected sites/selected participants only, anterior segment imaging may be performed in both eyes of consenting participants using Allergan-approved instruments.

[b] For a given participant, the same test methodology must be used for all visual fields performed at Screening, Baseline, and throughout the study.

[c] Manifest refraction will be used to provide a correction for best-corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.

[d] For a given participant, the same specular microscope model and analysis methodology must be used at Screening, Baseline, and throughout the study.

[e] Contact IWRS for study completion or participant discontinuation/withdrawal.

2. Introduction

In an effort to develop ocular antihypertensive therapies that do not require patient self-administration, an SR formulation of bimatoprost was developed at Allergan, Inc. Bimatoprost SR refers to a biodegradable, sustained-release, preservative-free bimatoprost implant that is preloaded in an applicator for administration; together they comprise the Bimatoprost SR product. The Bimatoprost SR implant is injected into the AC through clear cornea adjacent to the corneoscleral limbus using the 28-gauge needle of the prefilled applicator. The biodegradable polymer matrix of the implant gradually degrades to carbon dioxide and water so that there is no need to remove the implant once the drug has been released. The Bimatoprost SR implant used in this study contains a total preservative-free bimatoprost load of 10 µg. Intracameral administration of the 10 µg implant is expected to reduce the total daily drug exposure to the eye by approximately 120-fold compared with daily topical LUMIGAN® 0.03% (bimatoprost ophthalmic solution) application over 4 to 6 months, as well as possibly reduce the adverse effects observed with topical glaucoma medications. To date, 24-hour (diurnal and nocturnal) IOP data collection in participants administered with Bimatoprost SR has not been performed.

2.1. Study Rationale

Results of the completed 24-month Phase 1/2 Study 192024-041D indicated that Bimatoprost SR provides prostaglandin analog-like IOP-lowering efficacy. Additionally, the safety profile of Bimatoprost SR at dose strengths of 20 µg (2 × 10 µg) or less (15, 10, and 6 µg) in the Phase 1/2 study was acceptable, and supports additional clinical studies in humans. Four global Phase 3 studies with up to 3 administrations of Bimatoprost SR at fixed 16 week intervals, 1 global extension study, and 1 global Phase 3b study with initial scheduled and subsequent "as needed" repeat administration(s) of Bimatoprost SR [redacted] are all ongoing. The current study (1698-304-007) is a multicenter, open-label Phase 3b study to evaluate the IOP-lowering effect over 24 hours of a single administration of Bimatoprost SR in participants with OAG or OHT. The purpose of this study is to obtain data on the 24-hour IOP lowering effect at Week 8 of Bimatoprost SR treatment, with safety assessed until Month 12.

2.2. Background

2.2.1. Glaucoma and Treatment

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 (Stamper 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), with POAG being the predominant form of OAG. POAG is characterized as a multifactorial 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

AC angles, and manifesting characteristic visual field abnormalities (American Academy of Ophthalmology 2010a, Skuta 2008). Globally, over 60 million people are estimated to be affected by glaucoma (the majority of whom have OAG) and these numbers are expected to increase over time (Quigley 2006, Varma 2011, Cook 2012). Approximately 10% of eyes with elevated IOP will progress to OAG over the course of a decade (Quigley 1994).

Although many risk factors have been associated with OAG, elevated IOP remains the most prominent factor and the only factor existing that ophthalmic intervention can reliably affect (Stamper 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 (Kass 2002) and the Early Manifest Glaucoma Trial (Heijl 2002) addressed the value of early detection and lowering of elevated IOP in ocular hypertension or POAG. The effects and parameters of various interventions in eyes with established glaucomatous damage were addressed by the Collaborative Initial Glaucoma Treatment Study (Lichter 2001) and the Advanced Glaucoma Intervention Study (AGIS 2000).

2.2.2. Bimatoprost (LUMIGAN)

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

The IOP-lowering efficacy of LUMIGAN 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 through 12 months (Higginbotham 2002). This was further substantiated in the extension studies which followed patients in a masked manner for up to 4 years (Cohen 2004, Williams 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 administered once daily in the evening was 7 to 8 mm Hg (Cohen 2004, LUMIGAN Package Insert 2017, Williams 2008). LUMIGAN 0.03% was approved by the US 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.

2.2.3. Other Biodegradable Ocular Implants

Formulation of a number of SR drug delivery implants using the Allergan PLA and/or PLGA biodegradable platform preceded the development of the Bimatoprost SR implant. The extensive clinical experience with the OZURDEX® implant (first approved in 2009 and is registered globally in over 70 countries), which also uses the NOVADUR® drug delivery system for

intraocular administration, demonstrates the safety and tolerability of an intraocular biodegradable implant administered into the eye via an applicator system. Because Bimatoprost SR is similar to OZURDEX in a number of aspects and uses the NOVADUR drug delivery system for intraocular injections, these data are considered supportive of the safety and tolerability of Bimatoprost SR in humans.

2.2.4. Clinical Studies with Bimatoprost SR

Study 192024-041D was a Phase 1/2 paired-eye comparison study evaluating the safety and efficacy of 4 dose strengths of Bimatoprost SR (6, 10, 15, or 20 µg [2 x10 µg implants]), as single or repeat administrations in 1 eye (study eye), versus the use of topical LUMIGAN 0.03% once daily in the contralateral eye (nonstudy eye). The objective of the study was to evaluate the safety and IOP-lowering efficacy of Bimatoprost SR in participants with OAG.

A total of 109 participants received at least a single administration of Bimatoprost SR, and 24 participants received a repeat administration of their initial Bimatoprost SR dose strength. A trend in dose response was observed across the 4 dose strengths that were tested. Data collected in this study suggested that the implant would provide topical prostaglandin analog-like efficacy up to 3 to 4 months after implantation in the majority of participants. Data following the second administration in the retreated participants showed similar IOP-lowering efficacy to that observed following the first administration of Bimatoprost SR.

There have been 2 generations of the Bimatoprost SR implant: the original Generation 1 formulation, and Generation 2, which is the formulation currently used in the Phase 3 studies. Among all Generation 2 dose strengths, most participants (> 66%) were still maintained on monotherapy with the initial Bimatoprost SR implant by Month 6. Additionally, at least 33% of participants had not received rescue topical IOP-lowering medication or a second Bimatoprost SR administration by Month 12. At Month 24, at least 23% of participants had not received rescue IOP-lowering treatment or a second administration of Bimatoprost SR.

Bimatoprost SR showed an acceptable safety profile with single and repeat administrations in Study 192024-041D. Most AEs 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 AEs, and no new safety concerns were observed after the second treatment that were not already known from the initial administration of Bimatoprost SR. Please refer to the investigator's brochure for details on reported safety findings.

The implant is being investigated in Phase 3 studies to evaluate efficacy and safety following a fixed administration schedule of every 16 weeks for up to 3 administrations. Two identical global Phase 3 studies (Studies 192024-091 [NCT02247804] and 192024-092 [NCT02250651]) were initiated in late 2014. These studies are assessing the safety and efficacy of Bimatoprost SR in multicenter, randomized, masked, parallel-group comparisons of 2 dose strengths of Bimatoprost SR (10 and 15 µg) to an active control (topical ophthalmic timolol maleate 0.5%). Two additional global Phase 3 studies (Studies 192024-093 [NCT02507687] and 192024-095 [NCT02636946]) were initiated in late 2015. These studies are assessing the safety and efficacy

of Bimatoprost SR in multicenter, randomized, masked, paired eye comparisons of 2 dose strengths of Bimatoprost SR (10 µg or 15 µg) to an active control (360° SLT). Participants from all 4 Phase 3 studies will have the opportunity to participate in a long-term safety and efficacy extension study (Study 1698-302-007 [NCT03891446]), with potential repeat "as needed" administration(s) of Bimatoprost SR 10 or 15 µg if they qualify; this extension study was initiated in early 2019. Additionally, the implant is also being investigated in a global Phase 3b study (1698-301-007 [NCT03850782]) initiated in early 2019 to evaluate the duration of effect and safety of up to 3 "as needed" administrations of Bimatoprost SR.

2.3. Benefit/Risk Assessment

Although a variety of effective topical ocular antihypertensive medications (including bimatoprost) are available, 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). One literature review found that up to 80% of patients deviated from their prescribed medication regimen (Olthoff 2005). In addition, most patients with OAG or OHT are elderly, and many have inherent difficulties applying daily antihypertensive eye drops due to physical and/or cognitive disabilities such as arthritis and poor memory (European Glaucoma Society Guidelines 2014, Tsai 2009). Guidelines for clinicians to assist patients with being adherent have been developed and are available (Budenz 2009). In addition, surgical interventions, both laser-based (eg, LT) and incisional, are recommended as treatment options for patients with OAG and OHT who have challenges with topical medication adherence or tolerance (European Glaucoma Society Guidelines 2014). Laser trabeculoplasty is a safe and noninvasive procedure; however, repeatability of LT is inconsistent (Realini 2008). Repeat ALT procedures are limited due to tissue fibrosis and scarring of the trabecular meshwork (Kramer 2001). While the SLT procedure is repeatable, mean IOP reductions following repeat SLT appears to be smaller (Garg 2018). Patients will often require adjunctive therapy after LT, and may eventually require incisional surgery to control their IOP (Francis 2005, Koucheki 2012). Incisional surgery presents the risk of significant sight-threatening complications, such as the globe perforation, suprachoroidal hemorrhage, hypotony maculopathy, corneal decompensation, and cataract formation or progression that may occur with filtering surgery (Mosaed 2009). Allergan has developed the Bimatoprost SR implant as an additional therapeutic option for lowering IOP in patients with OAG and OHT.

IOP is a dynamic parameter that has circadian and postural variations, with IOP typically elevated at night when an individual is in a supine position (Liu 1999). The magnitude and timing of peak IOP values may be an independent contributor to glaucoma progression (Konstas 2012). Due to the fluctuating nature of IOP, affected by physiological and environmental conditions, uniform reduction throughout a 24 hour period is a desired therapeutic target (Liu 2005). Patients typically visit the physician's office during the day, which are usually limited to typical "business hours." Measuring a single IOP value at a single timepoint in this limited window may fail to capture the breadth of variation of an individual's IOP over the full 24 hours in a day. For patients with OAG and/or OHT, Bimatoprost SR offers ocular antihypertensive therapy that is not dependent on daily patient self-administration, potentially

improving both treatment adherence and continuous IOP control. Based on data from a completed Phase 1/2 study, plus the ongoing monitoring of 4 long-duration masked Phase 3 studies, continued development and understanding of the 24-hour IOP-lowering effect of Bimatoprost SR is warranted.

More detailed information about the known and expected benefits and risks, and the reasonably expected AEs of Bimatoprost SR, may be found in the investigator's brochure.

3. Objectives and Endpoints

Objectives	Endpoints/Measures
Efficacy: Primary • To evaluate the 24-hour IOP-lowering effect of Bimatoprost SR in participants with OAG or OHT	• Time-matched IOP change from Baseline Sleep Lab visit at Week 8 Sleep Lab visit in Bimatoprost SR-treated eyes
Secondary • To evaluate the change in diurnal variation of IOP in eyes treated with Bimatoprost SR	• Change from baseline in range of IOP in eyes treated with Bimatoprost SR at Week 8 Sleep Lab visit
Other • To evaluate the IOP-lowering effect of Bimatoprost SR	• Hour 0 IOP change from baseline through Month 12 • Time to initial use of nonstudy IOP-lowering treatment
Safety: • To evaluate the safety of Bimatoprost SR in participants with OAG or OHT	• AEs, visual fields, visual acuity, macroscopic bulbar conjunctival hyperemia, slit-lamp biomicroscopic assessments, dilated ophthalmoscopic assessments (including optic disc assessment), contact ultrasound pachymetry, gonioscopy, specular microscopy

4. Study Design

4.1. Overall Design

This is a multicenter, open-label, Phase 3b study in participants with OAG or OHT. Approximately 35 participants will be enrolled: 25 to 30 in the Bimatoprost SR cohort (to achieve a minimum total of 20 evaluable participants at baseline and Week 8 to evaluate the 24-hour IOP-lowering effect of Bimatoprost SR, assuming a premature discontinuation rate of up to 33%), and 5 in the LUMIGAN 0.01% cohort. Participants who prematurely discontinue from the study will not be replaced.

Participants in the Bimatoprost SR cohort will receive a 10 µg implant in the study eye on Day 1, and the fellow eye will receive standard of care treatment (provided that there is no known crossover effect of the fellow eye's standard of care treatment to the study eye) for the duration of the study (see Sections 6.5.2 and 6.5.4 for additional details). At selected site(s) an additional cohort of participants will be enrolled and assigned to receive topical LUMIGAN 0.01% in the study eye (once daily, at 20:00 ± 1 hour, starting with the evening dose on Day 1), and standard of care treatment in the fellow eye (provided that there is no known crossover effect of the fellow eye's standard of care treatment to the study eye) for the duration of the study. Participants will be assigned to the Bimatoprost SR cohort or LUMIGAN 0.01% cohort [redacted].

The participant and investigator will not be masked to the study treatment assignment for the duration of the study. Site staff collecting 24-hour IOP measurements at Sleep Lab visits will be masked to the study treatment and study eye.

Study Eye Treatment	Fellow Eye Treatment
Bimatoprost SR 10 µg or LUMIGAN 0.01%[a] (at selected site[s])	Standard of Care

[a] Participants will begin self-administration of LUMIGAN 0.01% in the study eye once daily in the evening (20:00 ± 1 hour) starting with the evening dose on Day 1, and will continue self-administration daily through the duration of the study.

The duration of the study for each participant is approximately 15 months, consisting of a screening period of up to 60 days before washout; washout period of up to 42 days before Baseline; and 12 months of follow-up.

4.2. Scientific Rationale for Study Design

With IOP being a dynamic measure subject to fluctuations over the course of a 24-hour period, this Phase 3b study is designed to collect information on the 24-hour (diurnal and nocturnal) IOP profile after a single administration of Bimatoprost SR.

4.3. Justification for Dose

The 10 µg dose strength of Bimatoprost SR is 1 of 2 dose strengths currently being evaluated in ongoing Phase 3 studies. Based on data from the completed Phase 1/2 Study 192024-041D, the

10 µg dose strength has an acceptable safety and efficacy profile and was selected for this Phase 3b study to provide information on the 24-hour IOP lowering effect of Bimatoprost SR.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study.

A participant assigned and treated with Bimatoprost SR is considered to have completed the study if he/she has completed all visits of the study to Month 12. At the Month 12/Study Exit visit, if the investigator determines that any safety concerns warrant participant follow-up, the participant may be followed post exit until safety concerns are resolved based on the investigator's discretion. Participants assigned and treated with LUMIGAN 0.01% may early exit the study after completion of the Week 8 Sleep Lab visit, if there are no safety concerns in the opinion of the investigator, and at which time all assessments performed at the Month 12/Study Exit visit should be performed.

5. Study Population

The study population consists of participants with OAG or OHT in at least 1 eye that requires IOP lowering treatment and has an open iridocorneal angle inferiorly by clinical gonioscopy. The eye that meets the entry criteria (Sections 5.1 and 5.2) 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.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be at least 18 years of age at the time of signing the informed consent
2.	**Sex**
2.01	Male or female
3.	**Informed Consent**
3.01	Written informed consent and authorization for use and release of personal health information are 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.	**Contraceptives**
4.01	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period
4.02	A female participant is eligible to participate if she is not pregnant (ie, has a negative urine pregnancy result at Baseline; see Appendix 7), not breastfeeding, and at least 1 of the following conditions applies: a. Not a WOCBP as defined in Appendix 7 OR b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 7 during the study period

5.	**Other General Criteria**
5.01	Participant is willing to withhold his/her IOP treatments in both eyes according to the study requirements, and in the opinion of the investigator, can do so without significant risk Note: If participants cannot discontinue their currently prescribed therapy in both eyes for up to 6 weeks to meet the Washout period for study entry, the investigator may switch the participant's medication to one that requires a shorter washout interval during the washout of the original medication.
5.02	Participant has the ability to understand and willingness to follow study instructions and is likely to complete all required visits and procedures
5.03	Participant is currently a nonsmoker and has not smoked any nicotine-containing products within the previous 6 months
6.	**Ocular Inclusion Criteria**
6.01	Diagnosis of either OAG (ie, primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in the **study eye**, requiring IOP-lowering treatment
6.02	In the investigator's opinion, the **study eye** could be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy
6.03	The iridocorneal angle in the **study eye** must be, in the opinion of the investigator, able to safely receive the Bimatoprost SR implant using the following criteria: a. Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle b. Peripheral anterior chamber depth by Van Herick examination ≥ 1/2 corneal thickness
6.04	At the Baseline visit, participant has been appropriately washed out of all IOP-lowering medications
6.05	At the Baseline visit (08:00 ± 1 hour), IOP of ≥ 22 and ≤ 34 mm Hg in the **study eye** using a Goldmann applanation tonometer
6.06	Central corneal endothelial cell density by specular microscopy deemed acceptable, in the opinion of the investigator (at Screening, and a minimum endothelial cell density of 1800 cells/mm^2 in the **study eye** by automated analysis)
6.07	At the Baseline visit: best-corrected visual acuity (Snellen equivalent, by manifest refraction) of 20/50 or better in the **study eye** and 20/100 or better in the **fellow eye**

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Uncontrolled systemic disease
1.02	Females who are pregnant, nursing, or planning a pregnancy during the study OR who are WOCBP and will not follow contraceptive guidance (see Appendix 7)
1.03	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, povidone-iodine)
1.04	Participants who have a condition or are in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study
1.05	Participants who have a history of a clinically significant sleep disorder (eg, insomnia, obstructive sleep apnea, etc.) or irregular sleep schedule which, in the investigator's opinion, may confound the study results, or may interfere significantly with the participant's participation in the study
1.06	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
1.07	Known history of bleeding disorder or prolonged bleeding after surgery (in the opinion of the investigator) Note: Participants receiving pharmacologic blood thinners (eg, aspirin, Coumadin) may be enrolled at the investigator's discretion
1.08	Current use of systemic beta-blockers or systemic beta-blocker containing medications
2.	**Ocular Exclusion Criteria**
2.01	Previous administration of Bimatoprost SR in the **study eye** [redacted]
2.02	History of previous laser trabeculoplasty in the **study eye**
2.03	History or evidence of clinically relevant, substantial ocular trauma (eg, a traumatic cataract, traumatic angle recession, etc.) in the **study eye**

2.04	The following surgical history in the **study eye**: a. History or evidence of complicated cataract/lens surgery: eg, surgery resulting in complicated lens placement (such as anterior chamber 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
2.05	Intraocular surgery (including cataract surgery) in the **study eye** within the 6 months prior to Bimatoprost SR administration
2.06	Any history of corneal graft, including partial grafts (eg, Descemet's Stripping Endothelial Keratoplasty [DSEK], Descemet's Membrane Endothelial Keratoplasty [DMEK]); or incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions in the **study eye**
2.07	Corneal or other ocular abnormalities that would preclude accurate readings with an applanation tonometer, specular microscope, and/or a contact pachymeter, or could confound study results in **either eye**, eg, moderate to severe corneal dystrophy, including Anterior Basement Membrane Disease (ABMD; ie, Map-Dot-Fingerprint) and guttata. Mild ABMD or mild guttata are not exclusionary by clinical examination if, in the opinion of the investigator, the condition is stable and not likely to cause corneal changes during the course of the study
2.08	Active or recurrent ocular disease in the **study eye** (eg, uveitis, ocular infection, chronic moderate to severe blepharitis or severe dry eye, ocular seasonal allergies) or sight threatening diseases (eg, neovascular age-related macular degeneration [AMD], diabetic macular edema) that, in the opinion of the investigator, would put the participant at a significant risk or would interfere with the interpretation of the study data Note: Participants with slowly progressive eye diseases (ie, mild cataracts, non-neovascular AMD) can be enrolled at the discretion of the investigator. If a participant has a potentially exclusionary condition or disease in one eye that tends to be bilateral or is likely to affect both eyes, the investigator should consider excluding that participant
2.09	Any history of external ocular or intraocular malignancy, and/or any history of benign ocular neoplasia in the **study eye** that in the investigator's opinion resulted in clinically significant ocular morbidity
2.10	History of herpetic ocular diseases in the **study eye** (including herpes simplex virus and varicella zoster virus)
2.11	Active ocular surface findings other than bulbar conjunctival hyperemia, on either macroscopic or slit-lamp examination, > +1 (mild) at Baseline in the **study eye**

2.12	The anticipated wearing of contact lenses in the **study eye** during the study that deviates from the following (contact lens wear is allowed during the study, but is to be temporarily discontinued before study visits, and before and after Bimatoprost SR administration according to the following): a. Use of soft lenses should be discontinued at least 3 days prior to Baseline, and use of rigid gas permeable or hard contact lenses should be discontinued at least 1 week prior to Baseline b. Use of soft lenses should be discontinued at least 3 days and use of rigid gas permeable or hard contact lenses should be discontinued at least 1 week prior to a scheduled study visit or Bimatoprost SR administration visit c. Use of contact lenses of any kind should be discontinued for 1 week following any Bimatoprost SR administration d. Use of contact lenses of any kind from 08:00 ± 30 minutes through completion of last IOP measurement of Sleep Lab visits ending at 06:00 ± 30 minutes
2.13	Central corneal thickness of < 480 or > 620 micrometers in the **study eye**
2.14	Anticipated need for any incisional or laser ocular surgery in the **study eye** during the study
2.15	History of anatomically narrow angle resulting in evidence of angle changes, and/or any history of acute angle closure glaucoma, in the **study eye** Note: historically narrow-angled participants who have not experienced an acute attack of angle closure and whose angle has been opened by cataract surgery or peripheral iridotomy may be eligible for enrollment if they have no evidence of angle abnormalities
2.16	History or evidence of a peripheral iridotomy/iridectomy in the inferior iris in the **study eye**
2.17	Any history of trabeculectomy or other types of glaucoma surgery, including a glaucoma seton or aqueous bypass stents (including MIGS) in the **study eye**
2.18	Any history of intracameral implants or intracameral device administration in the **study eye**
2.19	Peripheral anterior synechiae in the inferior iridocorneal angle on gonioscopic examination at Screening in the **study eye**
2.20	Visual field loss in **either eye** that, in the opinion of the investigator, is functionally significant (eg, split fixation, field defect within the central 10 degrees that is visually significant or likely to cause central visual impairment upon progression) or shows evidence of progressive visual field loss within the year prior to Baseline Note: The same test methodology should be used for all study-related examinations for a given participant
2.21	Evidence of macular edema in **either eye** during screening or in participant's medical

	history
2.22	Anticipated use of corticosteroids in **either eye** (except as described in Section 6.5.2) or systemically during the study, or historical use prior to Baseline within: a. 3 years: intraocular fluocinolone acetonide b. 6 months: intraocular corticosteroid(s) other than fluocinolone; any injectable periocular or sub-Tenon's/subconjunctival corticosteroid c. 2 months: systemic (eg, oral, intramuscular, intravenous) or topical ocular corticosteroids d. 2 weeks: dermal corticosteroids applied to skin of the eyelid(s), around the eye, or adnexa
2.23	Anticipated use of other topical ocular medications in **either eye** except as described in Section 6.5.2.

5.3. Lifestyle Considerations

5.3.1. Caffeine, Alcohol, Tobacco, and Sleep

1. Though not required, participants should be encouraged to maintain a consistent 8-hour sleep schedule for 7 days prior to Sleep Lab visits. Participants' sleep schedules in the 7 days prior to each Sleep Lab will be recorded at the corresponding Sleep Lab visit.
2. Though not required, participants should be encouraged to abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours prior to first IOP measurement of Sleep Lab visit beginning at 08:00 ± 30 min. From 08:00 ± 30 minutes through completion of last IOP measurement of Sleep Lab visit ending at 06:00 ± 30 minutes, participants will not have access to caffeine or xanthine-containing products.
3. Though not required, participants should be encouraged to abstain from drinking alcohol from 72 hours prior to first IOP measurement of Sleep Lab visit beginning at 08:00 ± 30 minutes. From 08:00 ± 30 minutes through completion of last IOP measurement of Sleep Lab visit ending at 06:00 ± 30 minutes, participants will not have access to alcohol.
4. Participants must currently be nonsmokers and have not smoked any nicotine-containing products within the previous 6 months.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened unless the participant's condition has changed, in the investigator's opinion.

6. Study Treatment

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Treatment Administered

Details regarding the study treatment administered is summarized in Table 6-1.

Table 6-1 Study Treatment Administered

Study Treatment Name	Bimatoprost SR	At Selected Site(s) LUMIGAN 0.01% (Bimatoprost Ophthalmic Solution)
Dosage Formulation	Bimatoprost SR is an intraocular implant that contains preservative-free bimatoprost dispersed in a biodegradable polymer matrix (including PLA and/or PLGA). Implants are preloaded into an applicator to facilitate insertion of the implant into the AC of the eye.	LUMIGAN 0.01% contains bimatoprost 0.01%, benzalkonium chloride, sodium chloride, sodium phosphate, dibasic, citric acid, and purified water.
Unit Dose Strength/ Dosage Level	A dose strength of 10 µg (formula number 11047X) bimatoprost will be administered.	A dose strength of 0.01% bimatoprost ophthalmic solution will be administered.
Route of Administration	Intracameral	Topical
Administration Instructions	Bimatoprost SR is administered directly into the AC of the study eye using the prefilled applicator.	LUMIGAN 0.01% is instilled topically to the study eye once daily in the evening (20:00 ± 1 hour).
Packaging and Labeling	Study treatment will be provided in a sterile, laminated foil pouch in an individual carton. Each package will be labeled as required per country requirement.	Licensed and approved LUMIGAN 0.01% will be acquired by the site in a multidose bottle.
Manufacturer	Allergan	Allergan

Study Treatment Name	Bimatoprost SR	At Selected Site(s) LUMIGAN 0.01% (Bimatoprost Ophthalmic Solution)
Number and Timing of Treatments	This study consists of 1 Bimatoprost SR administration in the study eye: On Day 1, participants will receive an intracameral administration of Bimatoprost SR 10 µg in the study eye and begin standard of care treatment in the fellow eye (provided that there is no known potential crossover effect of the fellow eye's standard of care treatment to the study eye).	On Day 1, the participant will begin treatment with LUMIGAN 0.01%. The drop will be instilled once daily in the evening (20:00 ± 1 hour) to the study eye throughout the duration of the study. Standard of care treatment will be used in the fellow eye (provided that there is no known potential crossover effect of the fellow eye's standard of care treatment to the study eye).

6.1.1. Instructions for Use and Administration of Bimatoprost SR

Study treatment must only be administered to participants who meet the eligibility criteria in accordance with conditions specified in this protocol.

6.1.1.1. Participant Preparation

Administration day assessments (including vital signs and query for concomitant medications and adverse events) should be completed. At least 3 administrations of a broad-spectrum topical ophthalmic antibiotic drop and topical anesthetic drop will be administered to the study eye approximately every 5 minutes beginning approximately 15 minutes prior to the procedure. With the participant in a supine position, the eye and conjunctival fornices should be irrigated with 5% ophthalmic povidone-iodine solution and the lids and surrounding orbital area should be prepped and draped according to the standard protocol detailed in the Procedure Manual.

6.1.1.2. Study Treatment Location

At the discretion of the investigator, Bimatoprost SR 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). As a standard ASC technique, an intravenous catheter may be placed and intravenous sedatives may be used at the discretion of the investigator and/or anesthesiologist. The ASC may have SOPs that require an electrocardiogram and/or a chest radiograph performed prior to the procedure. A separate standard consent to have the procedure at an ASC may be required per the SOPs at the facility.

Sterile technique should be practiced at all times.

6.1.1.3. 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 an ophthalmologist subinvestigator to perform the

procedure, subject to Allergan approval and training. The study medication kit should be readily available during the procedure.

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

6.1.1.4. Immediate Posttreatment Observation

Following Bimatoprost SR administration, the participant is expected to sit upright and is kept for a minimum of 1 hour of observation. The surgeon will examine the Bimatoprost SR treated eye to ensure that the AC is formed prior to the participant being released.

The participant will be supplied a bottle of topical ophthalmic antibiotic drops and instructions to use them for the next 3 days (including the day of the administration) in the Bimatoprost SR treated eye and to follow up as per protocol.

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

6.2. Preparation/Handling/Storage/Accountability

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 immediately to advise or any situation in which the Bimatoprost SR applicator is defective.

At selected site(s), licensed and marketed LUMIGAN 0.01% will be acquired in a multidose bottle by the site and be stored per manufacturer's instructions prior to dispensing to the participant.

The study medications must be stored in a secure area and administered/dispensed only to participants entered into the clinical study, at no cost to the participant, in accordance with the conditions specified in this protocol. Only assigned study personnel authorized by the investigator may have access to medications. Bimatoprost SR must be stored in the original sealed foil pouch.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medications received and any discrepancies are reported and resolved before use of the study medications.

Only participants enrolled in the study may receive study medications, and only authorized site staff may supply or administer study medications. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. More details regarding storage conditions of study medications are available in the Procedure Manual.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All used Bimatoprost SR applicators should be properly disposed of into a sharps container following the site's standard procedure and not physically returned to the depot. Malfunctioning applicators may be returned to the sponsor at the sponsor's request. All unused Bimatoprost SR kits must be returned to the sponsor at the termination of the study. Unit counts will be performed when Bimatoprost SR kits are returned, and all Bimatoprost SR kits must be accounted for.

At selected site(s) for participants assigned to LUMIGAN 0.01%, sites must ensure appropriate dispensing and documentation in source for the duration of the study.

6.3. Measures to Minimize Bias: Randomization and Blinding

Prior to initiation of study treatment, each participant who provides informed consent will be assigned a participant number that will serve as the participant identification number on all study documents.

This is an open-label study, and neither the investigator nor the participant will be masked to the assigned study treatment.

The IWRS will dispense the appropriate Bimatoprost SR medication kit(s) on Day 1. Study medication kits for Bimatoprost SR will be labeled with medication kit numbers. Sites will receive IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

The participant and the investigator will not be masked to the study treatment assignment for the duration of the study. However, delegated site staff collecting 24-hour IOP measurements will be masked to the study treatment and study eye. Participants and unmasked site staff should be discouraged from discussing treatment assignments with 24-hour IOP assessors. Hour 0 IOP measurements will be performed using a 2-person reading method.

The study site will keep an accurate drug disposition record that specifies the kit number of the IP administered to each participant, the eye receiving the treatment, and the date of administration.

At selected site(s), participants will be assigned to either Bimatoprost SR or LUMIGAN 0.01% in the study eye on Day 1 [redacted]. Sites will provide LUMIGAN 0.01% to assigned participants on Day 1 and keep an accurate drug disposition record that specifies the eye receiving treatment, and the start date of treatment.

6.4. Study Treatment Compliance

On Day 1, participants assigned to Bimatoprost SR will receive an intracameral administration of Bimatoprost SR 10 µg in the study eye. Study treatment compliance will be assumed to be 100% when administration has been recorded in the eCRF.

The study center will keep an accurate drug disposition record that specifies the amount of study treatment administered to each participant and the date of administration.

Participants assigned to LUMIGAN 0.01% will begin self-administration of LUMIGAN 0.01% once daily in the evening (at 20:00 ± 1 hour) starting with the evening dose on Day 1 and will continue self-administration through the duration of the study. Study treatment compliance will be discussed with these participant at scheduled study visits and documented in source. At the Week 8 Sleep Lab visit, these participants must use their evening dose of LUMIGAN 0.01% at 20:00 ± 1 hour, which will be documented in source. Please see the Procedure Manual for details.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter and/or prescription medicines; vitamins; herbal supplements, and/or cannabis or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.5.1. Prohibited Interventions and Washout Before the Study

All participants must provide informed consent prior to beginning any drug washout for the purposes of inclusion in this study. Participants currently being treated with IOP-lowering medication(s) in either eye will begin washout of these medication(s) following completion of 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 participants cannot discontinue their prescribed therapy for up to 6 weeks to meet the washout period for study entry, the investigator may switch the participant's medication to one that requires a shorter washout interval during the washout of the original medication (Table 6–2). Nonetheless, the investigator should adhere to the minimum washout period for all IOP-lowering medications used, as indicated in Table 6–2.

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.

Table 6–2 Minimum Washout Period by Ophthalmic Medication Class

Ophthalmic Medications	Minimum Washout Period
Parasympathomimetics (eg, PILAGAN®, Carbachol, Pilocar®)	4 days
Carbonic Anhydrase Inhibitors (topical or systemic) (eg, Diamox®, Trusopt®, Azopt®)	4 days
Sympathomimetics (eg, PROPINE®, Epifrin®)	14 days
Alpha-agonists (eg, ALPHAGAN P, Iopidine®)	14 days
Beta-adrenergic blocking agents (eg, Timoptic®, BETAGAN®, Betoptic®, Betoptic-S®, Opti-Pranolol®, Ocupress®, Timoptic XE®)	28 days
Rho-kinase inhibitors (eg, Rhopressa®, Glanatec®)	28 days
Prostamides, prostaglandins and prostaglandin analogs, as well as combination products that include these medications (eg, LUMIGAN, Xalatan, Travatan, Rescula®, GANFORT®)	28 days
Combination therapy (for example, COMBIGAN® [28 days], Cosopt® [28 days], GANFORT® [28 days], Simbrinza® [14 days], Azarga® [28 days], Roclatan® [28 days], etc)	Longest minimum duration of any component based on medication class

For participants undergoing a washout, interim safety evaluation(s) of IOP at any 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 participant is willing to discontinue the medication for the duration of the study. If the medication cannot be discontinued, then the participant will not be eligible for study entry.

6.5.2. Permitted Treatments

Ophthalmic Treatments

The fellow eye will receive standard of care for IOP lowering, provided there is no known potential crossover effect to the study eye (eg, prostaglandin analogues, carbonic anhydrase inhibitors, laser or surgical procedures, etc) (see Section 6.5.4 for details on prohibited treatments). If the fellow eye requires laser or surgical treatment, it must be performed not less than 3 days after Bimatoprost SR administration in the study eye.

Intermittent use of artificial tear products is allowed if they are not taken ≤ 15 minutes before any study procedure or examination in either eye. Use of cyclosporine ophthalmic solution, lifitegrast ophthalmic solution, and intermittent use of ocular decongestants or antihistamines is allowed if not taken:

- Within 2 days prior to the Baseline visit, through 3 days after Bimatoprost SR administration procedure
- Within 2 days prior to the Week 8 visit, through the completion of the 24-hour lab assessments

Use of artificial tear products, cyclosporine ophthalmic solution, lifitegrast ophthalmic solution, and ocular decongestants or antihistamines may be restarted in the study eye 3 days after the Bimatoprost SR administration procedure.

For participants assigned to LUMIGAN 0.01%, if the participant uses any other additional, permitted, topical ophthalmic medications, the topical ophthalmic medication(s) must be administered at least 5 minutes apart from the LUMIGAN 0.01% in the study eye.

Use of postinjection topical ocular antibiotics is expected following the Bimatoprost SR administration procedure (see Procedure Manual). Use of topical ophthalmic corticosteroids and NSAIDs from Day 1 through Day 7 following administration is allowed at the investigator's discretion.

Implant Removal

In the event that the Bimatoprost SR implant requires removal for significant safety reasons, this may be performed at the discretion of the investigator (see Procedure Manual for details). The investigator may contact the medical safety physician at Allergan for further discussion as needed.

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

Systemic Medications

The use of systemic NSAIDs is permitted.

In addition, therapy considered necessary for the participant'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.

6.5.3. Rescue Medicine

In the event that the study eye IOP does not meet or does not maintain IOP-lowering expectations, rescue IOP-lowering treatment (medication[s] or procedure[s] or both) can be initiated at the investigator's discretion. Inadequate control of IOP should be confirmed at a subsequent visit (scheduled or unscheduled visit) not on the same day. Rescue treatment can be initiated at the investigator's discretion at any time during the study if it is in the best interest of the participant. Prior to completion of the Month 12/Study Exit visit, the investigator will be expected to attest to the need for additional nonstudy IOP-lowering (rescue) treatment in the study eye for safety reasons.

6.5.4. Prohibited Interventions During the Study

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, participants should not participate in other investigational drug or device studies.

Nonstudy IOP-lowering Treatments

The fellow eyes of participants will receive standard of care for IOP lowering, provided there is no crossover effect on the study eye. Use of any concurrent nonstudy IOP-lowering treatment in the fellow eye with a known potential effect on outcomes (ie, alpha agonists and beta-adrenergic blocking agents) in the study eye is prohibited during the study.

Contact Lenses

Use of soft contact lenses within 3 days and/or use of rigid gas permeable or hard contact lenses within 1 week prior to a scheduled study visit or Day 1, and/or use of contact lenses of any kind within 1 week following Bimatoprost SR administration in the study eye, is prohibited. From 08:00 ± 30 minutes through completion of last IOP measurement of Sleep Lab visits ending at 06:00 ± 30 minutes, participants will not be permitted to wear contact lenses. For participants assigned to LUMIGAN 0.01%, contact lenses must be removed prior to instillation and may be reinserted 15 minutes following administration of LUMIGAN 0.01%.

Other Treatments

The following medications (or classes of medications) and treatment procedures are not permitted as concurrent therapy during the study through completion of the Month 12/Study Exit visit, unless the participant has already been treated with rescue IOP-lowering medication in the study eye:

- Subconjunctival, sub-Tenon's, intravitreal, or other ophthalmic injections of any medications in either eye
- Use of any topical ophthalmic medications (except as described in Section 6.5.2) in the study eye
- Surgical procedures in the study eye that are not related to the Bimatoprost SR administration procedure
- Use of bimatoprost for hypotrichosis during the study period in the study eye
- Systemic use of carbonic anhydrase inhibitors
- Any systemic regimen of beta-blocker containing medications

- Use of corticosteroids in the study eye (except as described in Section 6.5.2 for postinjection use) or systemically during the study or historical use prior to Baseline within:
    - 3 years: intraocular fluocinolone acetonide
    - 6 months: intraocular corticosteroid(s) other than fluocinolone; any injectable periocular or sub-Tenon's/subconjunctival corticosteroid
    - 2 months: systemic (eg, oral, intramuscular, intravenous) or topical ocular corticosteroids
    - 2 weeks: dermal corticosteroid applied to skin of the eyelid(s), around the eye, or adnexa

6.6. Dose Modification

Dose modification is not applicable.

6.7. Treatment after the End of the Study

No interventions after the end of the study are planned; participants will be treated per standard of care by their health care provider.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation from study treatment will occur if a participant who signs the ICF and receives study treatment ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

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

Reasons for discontinuation from the study treatment and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Completed	Failure to meet enrollment criteria
Lack of efficacy	Progressive disease
Lost to follow-up	Technical problems
Noncompliance with study drug	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1. Discontinuation of Study Intervention

The Bimatoprost SR implant is designed to bioerode in the AC of the eye and is not meant to be removed. In the event that the Bimatoprost SR implant requires removal for significant safety reasons, please see Section 6.5.2 for guidance on implant removal and Section 7.2 for follow up requirements for participant discontinuation in the event the implant is removed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If a participant develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, would put the participant at an unacceptable medical risk by continuing study participation, the participant will be withdrawn from the study.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- Participants assigned to and treated with Bimatoprost SR who have received nonstudy IOP-lowering treatment (rescue) in the study eye, will be followed for the duration of the study through the Month 12/Exit visit. If the implant has been removed, the participant may discontinue the study if based on investigator assessment the eye is in stable condition, at which time they should complete the Month 12/Exit visit procedures. Notification of early participant discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate case report form. If participants discontinue before Month 12/Exit, the site should complete all procedures for the Month 12/Exit visit at the participant's last visit.

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

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

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

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- A detailed listing of study assessments by day is provided in Appendix 8.
- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants who complete all regularly scheduled study visits should have 9 study office visits, 2 sleep lab visits, and 1 phone call. The schedule includes the following:

- Screening (up to 60 days); Washout Period of up to 42 days; and Baseline (Office visit and Sleep Lab visit)
- Day 1; Day 2 Safety visit
- Day 8 phone call
- Weeks 8 (Office and Sleep Lab visit) and 16; and Months 6, 9, and 12/Study Exit visits

8.1. Efficacy Assessments

Efficacy assessments are to be completed as outlined in the SoA (Section 1.3).

The primary and secondary efficacy measures of IOP collected over 24 hours at the Baseline Sleep Lab visit and Week 8 Sleep Lab visit will be measured using an Allergan-specified tonometer. The right eye is to be measured first and the left eye measured second. Two consecutive IOP 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, 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. The 24-hour IOP values collected at the Baseline Sleep Lab visit and Week 8 Sleep Lab visit will be performed at 08:00 ± 30 minutes, 10:00 ± 30 minutes, 12:00 ± 30 minutes, 14:00 ± 30 minutes, 16:00 ± 30 minutes, 18:00 ± 30 minutes, 20:00 ± 30 minutes, 22:00 ± 30 minutes, 00:00 ± 30 minutes, 02:00 ± 30 minutes, 04:00 ± 30 minutes, and 06:00 ± 30 minutes. Diurnal IOP measurements are defined as the IOP values collected between 08:00 ± 30 minutes to 22:00 ± 30 minutes and nocturnal IOP measurements are defined as the

IOP values collected between 00:00 ± 30 minutes to 06:00 ± 30 minutes. For all 24-hour IOP measurements collected at the Sleep Lab visits, sites should attempt to collect IOP at least 90 minutes after the previous time point. Diurnal IOP measurements performed at Baseline Sleep Lab visit and Week 8 Sleep Lab visit will be performed with the participants in a supine position ≥ 5 minutes at rest then sitting ≥ 5 minutes at rest. Nocturnal IOP measurements will be collected with the participants ≥ 5 minutes at rest in a supine position only. Lights in individual sleep rooms will be turned off at 23:00 and nocturnal IOP measurements will be performed under dim lighting with monitoring of the participant's sleep status. At least 2 individuals, one being of the same sex as the participant, will be present in individual participant rooms for nocturnal assessments. At the Week 8 Sleep Lab visit, participants assigned to LUMIGAN 0.01% must continue their evening dose of LUMIGAN 0.01% at 20:00 ± 1 hour. Caution must be taken not to unmask the IOP assessor. Please see Procedure Manual for additional details.

Other efficacy measures assess Hour 0 IOP and time to initial use of nonstudy IOP-lowering treatment. All Hour 0 IOP examinations will be scheduled at 08:00 ± 1 hour and will be measured using a Goldmann applanation tonometer. As scheduling permits, the participant should have approximately the same Hour 0 time of day throughout the study. The right eye is to be measured first and the left eye measured second. Two consecutive IOP 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, the IOP for the given eye will be the average of the 2 readings, corresponding to the median. 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 will be performed with the participants in a sitting position.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1. Physical Examinations

The participant will be examined by qualified medical personnel performing a modified physical examination, which may include assessments of: general appearance; head, eyes, ears, nose, and throat; heart/cardiovascular; lungs; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; and skin. Height and weight will also be measured and recorded.

8.2.2. Vital Signs

Vital signs will be assessed as follows:

- Temperature, pulse rate, and BP will be assessed.
- BP and pulse measurements will be assessed with participants in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a seated position.

8.2.3. Pregnancy Testing

Pregnancy testing will be conducted at the Baseline Office visit. Urine pregnancy tests will be used unless the study site requires the use of serum testing, in which case serum testing will be used. WOCBP must have a negative test result before receiving study treatment. This test may also be performed at any other visit, at the investigator's discretion. At each visit, the investigator should discuss contraceptive use compliance with WOCBP females of childbearing potential (see Appendix 7 for more details).

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the Schedule of Activities (Section 1.3) for the timing and frequency.

At Screening, the investigator or qualified subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.

8.2.5. Ocular Safety Assessments

8.2.5.1. Macroscopic Conjunctival Hyperemia Assessment

Macroscopic conjunctival hyperemia will be assessed using the appropriate assessment guide (see the Procedure Manual for further details).

8.2.5.2. Best-corrected Visual Acuity

Visual acuity tests will be performed at all visits except on Day 1 and at the Sleep Lab visits. Manifest refraction using Snellen equivalent with a logMar chart (see Procedure Manual) will be performed at Screening, Baseline (Office visit), and Month 12/Study 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 best-corrected visual acuity performed, a repeat manifest refraction in both eyes and BCVA will be performed. See the Procedure Manual for further details.

8.2.5.3. Visual Field

Visual field examinations will be assessed using automated perimetry (using either Humphrey 24-2 full threshold program or 24-2 SITA Standard, or Octopus G1 or 24-2 and dynamic or normal strategy). The same test methodology must be used throughout the entire study for a given participant. If dilation is required to perform this test, then the visual field test should be performed after gonioscopy/angle assessment or with the scheduled dilated exams, if applicable. See the Procedure Manual for further details.

8.2.5.4. Specular Microscopy

Endothelial cell density will be assessed using specular microscopy performed on the central cornea. The determination of central endothelial cell density for study entry as well as study visit

measures will be by the study investigator using automated analysis. See the Procedure Manual for further details. The same instrument and analysis methodology must be used throughout the study for a given participant.

8.2.5.5. Biomicroscopy

Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, cornea, AC (with Van Herick anterior chamber depth assessment at Screening only), iris/pupil, and lens (lens assessment is performed using the modified AREDS procedure and is collected on dilated examination days through a dilated pupil, using the slit-lamp biomicroscope. Please see the Procedure Manual for details).

8.2.5.6. Gonioscopy/Angle Assessment

Gonioscopic examinations will be performed by the study investigator as described in the Procedure Manual. At Screening and the Baseline Office visits, the investigator's eligibility assessments must confirm participant eligibility for participation in the study. In subsequent gonioscopic examinations during the study, the investigator will evaluate the inferior iridocorneal angle and the Bimatoprost SR implant.

8.2.5.7. 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 participant. Pachymetry may be performed any time after non-contact exams. See the Procedure Manual for further details.

8.2.5.8. Dilated Ophthalmoscopy

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

8.2.5.9. Optic Disc Examination

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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs may be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

Additionally, the investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs from the signing of the ICF until the study exit visit will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study treatment, but after obtaining informed consent will be recorded in the AE section of the eCRF.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Allergan with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- If a pregnancy is confirmed after the participant has received the study treatment, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow up assessments through the study exit visit.
- Details of all pregnancies in female participants will be collected from the signing of the ICF and through the duration of the pregnancy.
- If a pregnancy is reported, the investigator should inform Allergan within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous or elective abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Medication Errors

Medication error refers to any unintended error in the dose strength and/or administration of the study treatment as per instructions in the protocol and/or the Procedure Manual. Medication errors generally fall into the categories as follows:

- Wrong study drug
- Wrong dose strength
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant) or wrong eye
- Study medication expired

8.4. Treatment of Overdose

Not applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

8.8.1. Anterior Segment Imaging

At selected sites/selected participants only, anterior segment imaging may be performed using Allergan-approved instruments. Please see the Procedure Manual for further details. The participant's decision about whether to allow anterior segment imaging will not affect their eligibility for participation in the study.

8.9. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

Two database locks are planned for this study. The first database lock, for the primary and secondary efficacy endpoint analysis, will occur when 100% of participants have completed the primary visit (ie, Week 8 Sleep Lab visit) or prematurely discontinued prior to the Week 8 Sleep Lab visit. Similarly, the second database lock for the full study database will occur after all participants have completed the study at Month 12 or prematurely discontinued from the study. Analyses will be performed after each lock: the primary and secondary efficacy analysis results are based on the first database lock, and the analyses based on the second database lock provides further efficacy and safety information. Prior to the first database lock a detailed analysis plan will be finalized.

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Sample Size Determination

The sample size is based on practical considerations. Approximately 35 participants will be enrolled: 25 to 30 in the Bimatoprost SR cohort and 5 in the LUMIGAN 0.01% cohort.

Twenty-five to 30 participants will be enrolled in the Bimatoprost SR cohort to achieve a minimum total of 20 evaluable participants, defined as participants with sufficient data at baseline and Week 8 to evaluate the 24-hour IOP-lowering effect of Bimatoprost SR. This assumes a premature discontinuation rate of up to 33%. Participants who prematurely discontinue from the study will not be replaced.

Participants will be assigned to the Bimatoprost SR or LUMIGAN 0.01% cohort by the investigator.

9.3. Populations for Analyses

Safety Analysis Set (SAF): All participants who have received study intervention (ie, Bimatoprost SR administration or LUMIGAN 0.01%) will contribute to the SAF. All safety data collected from these participants will be included in the SAF.

Full Analysis Set (FAS): All participants who have received study intervention (ie, Bimatoprost SR administration or LUMIGAN 0.01%) with at least 1 postbaseline IOP assessment will contribute to the FAS. All efficacy data collected from these participants will be included in the FAS with the following exception:

- To avoid confounding of efficacy data, IOP measurements obtained after initiating the use of nonstudy rescue IOP-lowering treatment (medication[s] or procedure[s] or both) in an eye will be excluded from FAS.

9.4. Statistical Analyses

In general, continuous variables will be summarized by cohort (Bimatoprost SR or LUMIGAN 0.01%) for number of participants, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

An SAP will be developed and finalized before the first database lock. The details of the planned statistical analyses will be provided in the SAP. This section is a summary of the planned statistical analyses.

9.4.1. Efficacy Analyses

The efficacy analyses will be based on the FAS.

9.4.1.1. Analysis Endpoints

The primary efficacy endpoint is the time-matched IOP change from baseline at the Week 8 Sleep Lab visit from the 24-hour IOP data collected at the Baseline Sleep Lab visit in the study eye for the Bimatoprost SR cohort.

As described in Section 8.1, the median of the IOP measurements at each timepoint will be the value used for analysis for the study eye.

9.4.1.2. Primary Efficacy Analyses

Sleep Lab visit collected IOP raw values and the corresponding time-matched change from baseline in IOP will be summarized descriptively by timepoint for the study eye in the Bimatoprost SR cohort. Ninety-five percent CIs based on a paired t-test will be provided for the mean time-matched IOP change from baseline. Mean IOP and mean time-matched IOP change from baseline across time during diurnal/wake period and nocturnal/sleep period will be presented graphically for the study eye in the Bimatoprost SR cohort.

9.4.1.3. Secondary Efficacy Analyses

IOP fluctuation will be evaluated by the range of IOP collected from the Sleep Lab visit during diurnal/wake period and nocturnal/sleep period, as well as over a 24-hour period in the Bimatoprost SR cohort. The range of IOP at baseline and Week 8, as well as the change from baseline to Week 8 in IOP range will be summarized descriptively.

9.4.1.4. Other Efficacy Analyses

Other efficacy analyses will include descriptive summary for IOP (Hour 0) values at baseline with corresponding change from baseline by visit through Month 12/Study Exit. In addition, time from Day 1 to initial use of nonstudy rescue IOP-lowering treatment (medication[s] or procedure[s] or both) in the study eye will be analyzed using Kaplan-Meier methods.

Summary statistics calculating change from baseline in IOP will also be presented for the LUMIGAN 0.01% cohort.

9.4.2. Safety Analyses

The safety analyses will be performed using the safety analysis set and will be fully defined in the SAP. General safety parameters will include AEs (including pregnancy) and vital signs. Ocular safety parameters will include visual fields, best-corrected visual acuity, conjunctival hyperemia, biomicroscopy, dilated ophthalmoscopy (including optic disc assessment), pachymetry, gonioscopy, and specular microscopy.

Ocular AEs and safety variables will be tabulated by cohort for the study eye and fellow eye, and nonocular safety variables will be summarized at the participant level.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first administration of study treatment.

An AE will be considered a treatment-emergent SAE if it is a TEAE that additionally meets any SAE criterion.

MedDRA nomenclature will be used to code AEs. Adverse events will be coded from the verbatim text into PT and SOC. AEs will be collected for both eyes and will be displayed separately where appropriate. Ocular AEs and safety variables will be summarized by cohort for the study eye or fellow eye, and nonocular safety variables will be summarized by participant.

The number and percentage of participants reporting AEs will be tabulated by cohort based on primary SOC and PTs. Participants with multiple occurrences of a PT will be counted once in the calculation of the rate for that PT. Similarly, participants with multiple events within an SOC will be counted once in the incidence rate for that SOC.

Summary tables will be generated for all AEs regardless of causality as well as treatment-related AEs for the entire study. Related AEs will be displayed as those related to study treatment or procedures. Summaries will also be displayed by severity.

9.4.2.2. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) at Baseline and changes from Baseline at each assessment will be presented by cohort.

9.5. Interim Analyses

Two database locks will occur as described under Section 9. Analyses will be performed after each lock. The primary and secondary efficacy analysis based on the first database lock will be considered as final analysis. The analyses based on the second database lock provide further efficacy and safety information.

Additional safety analyses may be periodically performed based on relevant data snapshots.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the CIOMS International Ethical Guidelines
  - Applicable ICH/ISO GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor with sponsor permission.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and must follow ALCOA, ie, records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- 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.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study treatment accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by a central laboratory or designated regional facility, including any repeat laboratory tests.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Refer to the Central Laboratory Manual for further details regarding central laboratory collection and shipment procedures.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.

Laboratory test results will be forwarded from the central laboratory or designated regional facility to the study site and to Allergan or its designee. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. 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.

Table 10-1 Protocol Required Safety Laboratory Assessments

Laboratory Assessments[a]	Parameters			
Hematology	Platelets RBC count Hemoglobin Glycated hemoglobin Hematocrit	RBC indices: MCV MCH MCHC Morphology	WBC count with differential (absolute): Neutrophils Bands Lymphocytes Monocytes Eosinophils Basophils	
Serum Chemistry	BUN, uric acid	Potassium	AST	Total, direct, and indirect bilirubin
	Creatinine	Sodium	ALT	Total protein
	Creatinine kinase	Magnesium, phosphorus	Bicarbonate	Total cholesterol
	Glucose	Calcium	Alkaline phosphatase	Chloride, albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Clarity, color, presence of blood • Microscopic examination (WBCs, RBCs, casts, bacteria, crystals, epithelial cells)			

[a] No laboratory assessments require fasting.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events Meeting the AE Definition
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to provide pertinent documentation related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Allergan in lieu of completion of the AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Allergan. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Allergan.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the investigator's brochure and/or product information, for marketed products, in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Allergan. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Allergan.** • The investigator may change his/her opinion of causality in light of follow up information and send an SAE follow up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
• Any SAE must be immediately reported but no later than 24 hours after learning of the SAE. • Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

Abbreviation/Term	Definition
ABMD	Anterior Basement Membrane Disease
AC	anterior chamber
AE	adverse event
AGIS	Advanced Glaucoma Intervention Study
ALT	Alanine aminotransferase
AMD	age-related macular degeneration
AREDS	Age-related Eye Disease Study
ASC	ambulatory surgical center
AST	Aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
eCRF	electronic case report form
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follical stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IOL	intraocular lens implant
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
ISO	International Organization for Standardization
IWRS	interactive web response system
LT	laser trabeculoplasty
MCHC	mean corpuscular hemoglobin concentration
MCH	mean corpuscular hemoglobin

Abbreviation/Term	Definition
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MIGS	minimally invasive glaucoma surgery
NSAID	nonsteroidal anti-inflammatory drugs
OAG	open-angle glaucoma
OHT	ocular hypertension
OU	both eyes
PLA	polylactic acid
PLGA	polylactic-co-glycolic acid
POAG	primary open-angle glaucoma
PT	preferred term
RBC	red blood cell
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SLT	selective laser trabeculoplasty
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SR	sustained release
SUSARS	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
US/USA	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)

CDISC Submission Value	CDISC Definition
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	An Evaluation of the 24-Hour IOP-lowering Effect of Bimatoprost SR in Participants with Open-Angle Glaucoma or Ocular Hypertension
	Clinical Study Sponsor	Allergan Sales LLC
	Trial Phase Classification	Phase 3b Trial
	Trial Indication	Open-angle glaucoma or ocular hypertension
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	15 months
	Planned Country of Investigational Sites	United States
	Planned Number of Subjects	30
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	Open-angle glaucoma or ocular hypertension
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	Not specified
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not specified

Parameter Group	Parameter	Value	
Treatments	Investigational Therapy or Treatment	Bimatoprost SR	LUMIGAN 0.01%
	Intervention Type	Drug	Drug
	Pharmacological Class of Investigational Therapy	Prostaglandin analog	Prostaglandin analog
	Dose Strength per Administration	10 µg	0.01%
	Dose Units	1 implant	Drop
	Dosing Frequency	Single dose	Once daily in the evening
	Route of Administration	Intracameral	Topical ophthalmic
	Current Therapy or Treatment	No	No
	Added on to Existing Treatments	No	No
	Control Type	None	None
	Comparative Treatment Name	N/A	N/A
Trial design	Study Type	Interventional	
	Intervention Model	2 arm	
	Planned Number of Arms	2	
	Trial is Randomized	No	
	Randomization Quotient	N/A	
	Trial Blinding Schema	Open-label	
	Stratification Factor	N/A	
	Adaptive Design	No	
	Study Stop Rules	None	

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

WOCBP

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following cate**gories are not considered WOCBP:**

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods or acceptable contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female Participants

WOCBP are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective and Acceptable Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) Bilateral tubal occlusion Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test at Baseline.
- Additional pregnancy testing should be performed at study exit, and as required locally.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Urine pregnancy testing will be used unless the study site requires the use of serum testing, in which case serum testing will be used.

Collection of Pregnancy Information:

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Allergan within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on the participant and the neonate, and the information will be forwarded to Allergan. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to Allergan as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- If a pregnancy is confirmed after the participant has received study treatment, the participant may choose to exit the study after appropriate safety follow up or to remain in the study for all safety and efficacy follow up assessments through study exit visit.

10.8. Appendix 8: Study Schedule Supplement

10.8.1. Screening

After informed consent and other documentation have been obtained, the procedures listed below are carried out. IOP measurements must be performed in 1 day; however, other procedures (eg, post dilation procedures) may be performed on a different day as long as the screening procedures are completed within a 60-day period, and procedures completed on the same day follow the schedule as set out in the protocol. Pupil dilation/diagnostic procedures are to be performed after the completion of the final IOP measurement of the day or on a different day. Screening procedures may be repeated for eligibility confirmation at any time prior to and during washout, at the discretion of the investigator

- Collection of demographic data
- Collection of medical and ophthalmic history
- Collection of AEs
- Collection of concomitant medications and procedures
- Collection of alcohol/caffeine/smoking consumption and sleep habits
- Physical examination
- Vital signs (at rest ≥ 5 minutes)
- Collection of blood and urine samples

The following procedures should be performed in both eyes in the order below (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examination** (perform before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
- **Manifest refraction** (Manifest refraction will be used to provide a correction for best corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.)
- **BCVA**
- **IOP measurement at Hour 0**
- Anterior segment imaging (perform any time after Hour 0 IOP; select sites/participants only)

- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Visual field (If dilation is required to perform this test, then the visual field test should be performed after gonioscopy/angle assessment with the scheduled dilated exams.)
    - Specular microscopy
    - Biomicroscopy
- **Gonioscopy/angle assessment**
- Pachymetry (may be performed at any time after non-contact exams)
- **Pupil Dilation** (post dilation examinations below may be performed in any order)
    - Dilated ophthalmoscopy
    - Optic disc examination

Eligibility is then determined and the IWRS is contacted.

10.8.2. Baseline

10.8.2.1. Office Visit

The Baseline Office visit occurs after the washout period has been completed. Baseline Office visit procedures must be performed in 1 day with the exception of anterior segment imaging, which may be performed on a different day. Pupil dilation/diagnostic procedures are to be performed after the completion of the final Hour 0 IOP measurement. The following procedures are performed at the Baseline Office visit:

- Collection of medical and ophthalmic history
- Collection of AEs
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Pregnancy test for WOCBP

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examination** (perform before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
- **Manifest refraction** (Manifest refraction will be used to provide a correction for best corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.)
- **BCVA**
- **IOP measurement at Hour 0**
- Anterior segment imaging (perform any time after Hour 0 IOP; select sites/participants only)
- **Non-contact examinations**: The following may be performed at any time after IOP at Hour 0:
    - Visual field (If dilation is required to perform this test, then the visual field test should be performed after gonioscopy/angle assessment with the scheduled dilated exams.)
    - Specular microscopy
    - Biomicroscopy
- **Gonioscopy/angle assessment**
- Pachymetry (may be performed at any time after non-contact exams)
- **Pupil Dilation** (post dilation examinations below may be performed in any order)
    - Dilated ophthalmoscopy
    - Optic disc examination

Eligibility is then determined and Hour 0 IOP is entered into the IWRS.

10.8.2.2. Sleep Lab Visit

Sleep Lab visit procedures must be performed on a different day from Baseline Office visit procedures. The following procedures are performed at the Baseline Sleep Lab visit:

- Collection of AEs
- Collection of concomitant medications and procedures
- Collection of alcohol/caffeine/smoking consumption and sleep habits
- Vital signs (at rest ≥ 5 minutes)

- Perform 24-hour Sleep Lab visit on a different day from all other Baseline Office visit study procedures.

All 24-hour Sleep Lab visit IOP exams will be performed with an Allergan-specified tonometer. Diurnal IOP measurements will be taken supine ≥ 5 minutes at rest then sitting ≥ 5 minutes at rest at 08:00 ± 30 min, 10:00 ± 30 min, 12:00 ± 30 min, 14:00 ± 30 min, 16:00 ± 30 min, 18:00 ± 30 min, 20:00 ± 30 min, and 22:00 ± 30 min. Nocturnal IOP measurements will be taken supine only ≥ 5 minutes at rest 00:00 ± 30 min, 02:00 ± 30 min, 04:00 ± 30min, and 06:00 ± 30 min. Lights in individual sleep rooms will be turned off at 23:00 and nocturnal IOP measurements will be performed under a dim lighting with monitoring of the participant's sleep status. Please see Procedure Manual for details.

10.8.3. Day 1

The following procedures are performed on Day 1:

- Collection of AEs
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Contact IWRS for kit allocation (this contact may take place one day prior to Bimatoprost SR Administration [Day 1], if needed)
- Administer study treatment (Bimatoprost SR 10 µg) in study eye or at selected sites/patients, begin LUMIGAN 0.01% in the study eye

All participants must remain in the surgical facility for bilateral eye examination at least 1 hour after the Bimatoprost SR administration procedure.

Each participant will be supplied a bottle of topical ophthalmic antibiotic drops and instructions to use them for the next 3 days (including the day of the administration) in the Bimatoprost SR treated eye and to follow up with the study site as per protocol.

Participants assigned to LUMIGAN 0.01% will begin self-administration in the study eye once daily in the evening (at 20:00 ± 1 hour) starting with the evening dose on Day 1, and will continue daily self-administration through the duration of the study.

10.8.4. Day 2 Safety Visit

The following procedures are performed on the Day 2 Safety visit:

- Collection of AEs
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may perform in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
- **BCVA**
- **IOP measurement at Hour 0**
- **Non-contact examination**: The following may be performed at any time after IOP at Hour 0:
    - Biomicroscopy

10.8.5. Day 8 Phone Call

On Day 8, the participant will be contacted by telephone to collect the following:

- Collection of AEs
- Collection of concomitant medications and procedures

10.8.6. Week 8 Visits

10.8.6.1. Office Visit

Week 8 Office visit procedures must be performed in 1 day with the exception of anterior segment imaging, which may be performed on a different day. The following procedures are performed at the Week 8 Office visit:

- Collection of AEs
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may be performed in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
- **BCVA**
- **IOP measurement at Hour 0**
- Anterior segment imaging (perform any time after Hour 0 IOP; select sites/participants only)
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Biomicroscopy
- **Gonioscopy/angle assessment**

10.8.6.2. Sleep Lab Visit

Sleep Lab visit procedures must be performed on a different day from Week 8 Office visit procedures. The following procedures are performed at the Week 8 Sleep Lab visit:

- Collection of AEs
- Collection of concomitant medications and procedures
- Collection of alcohol/caffeine/smoking consumption and sleep habits
- Vital signs (at rest ≥ 5 minutes)
- Perform 24-hour Sleep Lab visit on a different day from all other Week 8 Office visit study procedures.

All 24-hour Sleep Lab visit IOP exams will be performed with an Allergan-specified tonometer. Diurnal IOP measurements will be taken supine ≥ 5 minutes at rest then sitting ≥ 5 minutes at rest at 8:00 ± 30 min, 10:00 ± 30 min, 12:00 ± 30 min, 14:00 ± 30 min, 16:00 ± 30 min, 18:00 ± 30 min, 20:00 ± 30 min, and 22:00 ± 30 min. Nocturnal IOP measurements will be taken supine only ≥ 5 minutes at rest 00:00 ± 30 min, 02:00 ± 30 min, 04:00 ± 30min, and 06:00 ± 30 min. Lights in individual sleep rooms will be turned off at 23:00 and nocturnal IOP measurements will be performed under a dim lighting with monitoring of the participant's sleep status. At the Week 8 Sleep Lab visit, participants assigned to LUMIGAN 0.01% must take their evening dose at 20:00 ± 1 hour. Caution must be taken not to unmask the IOP assessor. Please see Procedure Manual for details.

10.8.7. Week 16 and Months 6, 9, and 12/Study Exit Visits

At all visits, procedures must be performed in 1 day with the exception of anterior segment imaging, which may be performed on a different day at applicable visits. The following procedures are performed at Week 16 and Months 6, 9, and 12/Study Exit:

- Collection of AEs
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Pregnancy test for WOCBP (Month 12/Study Exit only)

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examination** (perform before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**
- Anterior segment imaging (perform any time after Hour 0 IOP; select sites/participants only; Months 6 and 12/Study Exit only)
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Visual field (If dilation is required to perform this test, then the visual field test should be performed after gonioscopy/angle assessment with the scheduled dilated exams; Months 6 and 12/Study Exit only)
    - Manifest refraction (Manifest refraction will be used to provide a correction for best corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed; Month 12/Study Exit only)
    - Specular microscopy
    - Biomicroscopy
- **Gonioscopy/angle assessment**
- Pachymetry (may be performed at any time after non-contact exams)

- **Pupil Dilation** (post dilation examinations below may be performed in any order; Month 12/Study Exit only)
    - Dilated ophthalmoscopy
    - Optic disc examination

IWRS is contacted to register early termination or study completion (Month 12/Study Exit only)

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