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A Comparison of Bimatoprost SR to Selective Laser Trabeculoplasty in Patients with Open-Angle Glaucoma or Ocular Hypertension

Protocol Number:	192024-093 Amendment 7
EudraCT Number:	2015-002131-18
Phase:	3
Name of Investigational Product:	Bimatoprost sustained release (SR)
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Allergan Signatory:	[redacted] Ophthalmology Allergan, Inc. Refer to the final page of this protocol for electronic signature and date of approval.

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

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

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

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

Investigator Printed Name	Signature	Date

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Protocol Summary

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

Phase: 3

Study Objective: To evaluate the intraocular pressure (IOP)-lowering effect and safety of Bimatoprost SR compared with selective laser trabeculoplasty (SLT) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence)

Clinical Hypotheses:

Bimatoprost SR will have an IOP-lowering effect that is noninferior to that of SLT in patients with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

Bimatoprost SR administered intracamerally will have an acceptable safety profile in patients with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

Study Design

Structure: multicenter, paired eye, randomized, masked, conducted in 2 stages:

- Stage 1: Bimatoprost SR 15 µg vs SLT; 2 administration cycles for patients who had not received a third administration cycle before implementation of Amendment 3
- Stage 2: Bimatoprost SR 10 µg vs SLT; 2 administration cycles

Duration: approximately 26 months, including screening period of up to 28 days before washout, washout period of up to 56 days before initial study treatment, plus 24 months of follow-up after initial Bimatoprost SR and SLT administration.

Study Treatment: Bimatoprost SR 15 µg (Stage 1) or 10 µg (Stage 2)

Controls: 360° SLT administration

Dosage/Dose Regimen:

Patients will receive a 360° administration of SLT in 1 eye on Day 1 and an administration of Bimatoprost SR in the contralateral eye on Day 4, with a repeat administration of Bimatoprost SR at Week 16 if the patient meets the retreatment criteria. For those patients not meeting retreatment criteria at Week 16, Cycle 2 may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met. (Note that for all patients who were enrolled and reached the Week 16 visit prior to implementation of Amendment 6, retreatment with Bimatoprost SR was fixed at Week 16.) In order to mask the patient to the treatment assigned to each eye, on Day 1, a sham SLT procedure will be performed in the eye that will receive Bimatoprost SR administrations (hereafter referred to as the "Bimatoprost SR eye"). Similarly, a sham needleless Bimatoprost SR administration (hereafter referred to as the "Sham Bimatoprost SR administration") that involves touching the eye at the area of insertion with a needleless applicator that does not deliver an implant into the anterior chamber, will be performed on the SLT-treated eye (hereafter referred to as the "SLT eye") on Bimatoprost SR administration visits.

Treatment schedule by eye is shown in

Table 1.

Table 1 Treatment Schedule by Eye

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

SLT = selective laser trabeculoplasty; SR = sustained release

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

Randomization/Stratification: The eye with the higher IOP at Baseline will be assigned to be the primary eye. If baseline IOP is the same in both eyes, the right eye will be the primary eye. The primary eye will be randomized to receive either Bimatoprost SR or SLT using a 1:1 ratio, stratified by primary eye baseline IOP (≤ 25 or > 25 mm Hg) [redacted] If the primary eye receives Bimatoprost SR, the contralateral eye will receive SLT. If the primary eye receives SLT, the contralateral eye will receive Bimatoprost SR.

Visit Schedule: Patients who complete all study treatments will have up to 28 visits and 5 phone calls. The schedule includes the following:

- Screening (up to 28 days); Washout period of up to 56 days for both eyes; and Baseline visit (up to 3 days)
- SLT treatment (Day 1) and phone call (Day 2)
- Bimatoprost SR Cycle 1 administration (Day 4); Cycle 1 Day 2 safety visit; Cycle 1 Day 4 and Week 2 phone calls; and follow-up study visits at Weeks 4, 8, 12, and 15
- Bimatoprost SR Cycle 2 administration (to occur at Week 16 for all patients who meet retreatment criteria); Cycle 2 Day 2 safety visit; and Cycle 2 Day 4 and Week 2 phone calls
    - Patients who do not receive Cycle 2 administration at Week 16 will not attend the Cycle 2 Administration Day visit on Week 16, or the Day 2 Safety or Day 4 and Week 2 phone calls associated with administration at Week 16. For these patients, Cycle 2 may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met; in this case, inadequate control of IOP should be confirmed at another scheduled or unscheduled visit prior to initiation of Cycle 2. All Cycle 2 visits will apply at the time of the Cycle 2 administration.
- Follow-up visits at Weeks 20, 24, 28, 31, 36, 40, 44, 47, and 52; and Months 13, 14, 15, 16, 18, 20, 22, and 24/Exit
    - Regardless of the timing of Cycle 2 administration, all regularly scheduled visits should be completed. Cycle 2 visits should be scheduled such that the Administration Day and the Day 2 Safety Visit do not occur on the day of a regularly scheduled study visit. However, if the Cycle 2 Day 4 or Week 2 Phone Calls overlap with a regularly scheduled visit, perform the regularly scheduled visit.
    - Patients who receive the second administration of Bimatoprost SR at Week 16 and patients who never receive a second administration may, at the investigator's discretion, skip the

visits at Months 13, 15 and 22 if the patient has received nonstudy IOP lowering medication in both eyes; has ≤ 25% of each implant remaining in the eye; and in the investigator's clinical judgment, has no safety or other concern that would require the patient to attend these visits. Please note: each eye should be evaluated on an individual basis when determining the need for additional nonstudy IOP-lowering treatments; initiation of treatment in one eye should not automatically lead to initiation of treatment in the contralateral eye.

- Intraocular pressure evaluations will occur at Hour 0 (08:00 am ± 1 hour). Selected patients at selected sites will have additional IOP measurements performed at Hour 2 (Hour 0 + 2 hours [± 30 minutes]) and Hour 8 (Hour 0 + 8 hours [± 30 minutes]).

Study Population Characteristics
Number of Patients:

Stage 1: approximately 50 patients

Stage 2: approximately 160 patients

Condition/Disease: patients with OAG or OHT who require IOP-lowering medications in both eyes

Key Inclusion Criteria:

- Male or female, 18 years of age or older
- 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 [United States (US) sites] and written Data Protection consent [European Union (EU) sites])
- In the investigator's opinion, patient's IOP is not adequately managed with topical medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence)

<u>Ocular</u>

- In the investigator's opinion, both eyes can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan®, Travatan®) eye drops as the sole therapy if medication was taken as directed
- In the investigator's opinion, patient's IOP can be adequately managed with SLT monotherapy
- In the investigator's opinion, patient is a suitable candidate for SLT
- Diagnosis of either OAG (ie, primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in each eye, requiring bilateral IOP-lowering treatment (Note: diagnosis does not have to be the same in both eyes)
- Central endothelial cell density by specular microscopy confirmed as being qualified by Reading Center assessment prior to beginning Washout
- The iridocorneal angle must be independently confirmed as being qualified by 2 ophthalmologists using the following criteria:
  - Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle
  - Peripheral anterior chamber depth by Van Herick examination ≥ 1/2 corneal thickness

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

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

Key Exclusion Criteria:

Ocular

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

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

  b. History of phakic IOL insertion for refractive error correction

Response Measures

Efficacy: IOP measured by Goldmann applanation tonometry

Safety: adverse events, visual fields, visual acuity, macroscopic conjunctival hyperemia, slit-lamp biomicroscopic assessments, dilated ophthalmoscopic assessments (including optic disc assessment), pachymetry, gonioscopy, and specular microscopy

Other: [redacted]

General Statistical Methods and Types of Analyses:

Three database locks will be performed: 1) when all patients treated with Bimatoprost SR 10 µg have completed the Week 24 visit or have prematurely discontinued before the Week 24 visit, 2) when all patients treated with Bimatoprost SR 10 µg have completed the Month 12 visit or prematurely discontinued before the Month 12 visit, and 3) when all patients treated with Bimatoprost SR 10 µg have completed the Month 24 visit or prematurely discontinued before Month 24.

Efficacy: The primary efficacy analysis will be performed for patients treated with Bimatoprost 10 µg in the intent-to-treat (ITT) population. The primary efficacy variable is IOP change from baseline and the primary time period is 24 weeks (measurements for the primary analysis are designated for the following timepoints: Weeks 4, 12, and 24). IOP change from baseline will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include IOP change from baseline as the response variable and treatment, visit, eye, baseline IOP, treatment-by-visit, visit-by-baseline, and visit-by-eyes interactions as covariates. Unstructured correlation for study visits and eyes will be used for repeated measures on the same patient. The mean difference between the Bimatoprost SR 10 µg eyes and SLT eyes (Bimatoprost SR 10 µg minus SLT) and the corresponding 95% confidence interval (CI) will be constructed at each visit from MMRM analysis. The noninferiority comparison for Bimatoprost SR 10 µg versus SLT at Weeks 4, 12, and 24 is the primary analysis. If the upper limit of the 95% CI is ≤ 1.5 mm Hg at all 3 visits, Bimatoprost SR 10 µg statistical noninferiority to SLT is demonstrated. In addition, Bimatoprost SR 10 µg is considered clinically noninferior to SLT if the upper limit of the 95% CI is ≤ 1.0 mm Hg at 2 out of the 3 visits of Weeks 4, 12, and 24.

Secondary efficacy analyses will be performed separately for patients treated with Bimatoprost SR 10 µg in the ITT populations. Secondary efficacy variables to compare Bimatoprost SR 10 µg eyes and SLT eyes include: time to initial use of nonstudy IOP-lowering treatment (as determined by the investigator); percentage of Bimatoprost SR 10 µg and SLT eyes achieving ≥ 20% reduction; and IOP changes from baseline at Weeks 8, 15, and 20.

Safety: Safety analyses will be performed separately for patients in the Bimatoprost SR 10 µg and Bimatoprost SR 15 µg safety populations. Adverse events and medical history will be coded using Medical Dictionary for

Regulatory Activities (MedDRA) nomenclature. The number and percentage of patients reporting treatment-emergent adverse events will be tabulated based on the system organ class and preferred term. Ocular safety variables attributable to each eye will be tabulated by Bimatoprost SR or SLT eye. Nonocular safety variables will be summarized.

Sample Size Calculation: The sample size calculation is based on paired-eye differences using a normal approximation with a 2-sided significance level of 0.05, assuming that there is no difference in mean IOP change from baseline between Bimatoprost SR 10 µg eyes and SLT eyes and that change from baseline in IOP has a standard deviation of 4 mm Hg. A sample size of 144 patients will provide approximately 98% power in showing noninferiority for 3 out of 3 timepoints with a noninferiority margin of 1.5 mm Hg, and 90% power in showing noninferiority for 2 out of 3 timepoints with a noninferiority margin of 1.0 mm Hg, assuming that both the between-eyes and the within-patient correlation coefficients are 0.5. Assuming a premature discontinuation rate of 10%, approximately 160 patients are to be enrolled into this study and treated with Bimatoprost SR 10 µg. Additionally, there are approximately 50 patients who were enrolled before implementation of Amendment 3.

Table 2 Administration Cycle 1 Schedule of Visits and Procedures: Screening through Day 2

Visit	**Screening**		**Baseline[b]**	**Day 1 (SLT Administration)**	**Day 2 Phone Call[c]**
Visit Windows	**Up to 28 days**		**Up to 3 days**		
Informed Consent/Authorization	X	Washout[a] Up to 56 days			
Demographic Data	X				
Medical/Ophthalmic History	X		X		
Adverse Events	X		X	X	X
Concomitant Medications/ Procedures	X		X	X	X
Visual Function Questionnaire-25			X		
Physical Examination	X				
Vital Signs (at rest ≥ 5 minutes)	X		X	X	
Pregnancy Test[d]			X		
Blood and Urine Sample Collection[e]	X[e]				
Ocular Examinations in **bold** should be performed in the order shown					
Pre-Hour 0 Exam (perform before Hour 0 IOP):					
Macroscopic Conjunctival Hyperemia Assessment[f]	OU	Washout[a] Up to 56 days	OU		
Manifest Refraction[g]	OU		OU		
Best-Corrected Visual Acuity	OU		OU		
Intraocular Pressure Measurement Hour 0	OU		OU		
Non-contact Exams (may perform in any order at any time before gonioscopy [before Hour 8 at Baseline[h]])					
Macroscopic Iris Color Assessment			OU		
Visual Field[i]	OU		OU		
Specular Microscopy	OU				
Anterior Segment Optical Coherence Tomography	OU				

Visit	Screening		Baseline[b]	Day 1 (SLT Administration)	Day 2 Phone Call[c]
Visit Windows	**Up to 28 days**		**Up to 3 days**		
[redacted]	OU				
Biomicroscopy[f]	OU		OU	OU[k]	
Gonioscopy/Angle Assessment	OU[l]				
Pachymetry: (may be done any time after gonioscopy)	OU				
Intraocular Pressure Hour 2 and Hour 8 (selected sites/patients[h])			OU		
Pupil Dilation (may perform post-dilation eye exams in any order)	OU		OU		
Dilated Ophthalmoscopy	OU		OU		
Optic Disc Examination	OU		OU		
Determination of Eligibility	X		X	X	
Contact Interactive Response System[m]	X		X	X	
Treatment and/or Sham Administration				X	

IOP = intraocular pressure; OU = both eyes; SLT = selective laser trabeculoplasty; X = do procedure; Hour 0 = 08:00 ± 1 hour; Hour 2 = Hour 0 + 2 hours (± 30 min); Hour 8 = Hour 0 + 8 hours (± 30 min)

[a] Washout may begin after all screening procedures have been completed and the Reading Center has confirmed central endothelial cell density.

[b] Baseline visit procedures can be performed over a 3-day period. Perform pupil dilation/diagnostic procedures after the completion of the final IOP measurement or a different day. If, after initial washout, the investigator believes the IOP does not meet entry criteria due to inadequate washout and if time remains in the washout period, he/she may perform additional washout up to a total of 56 days.

[c] If the patient reports symptoms or findings of concern in the Day 2 phone call (including but not limited to photophobia, blurred vision, eye pain, vitreous floaters), the investigator must bring the patient in for ophthalmic examination.

[d] In countries/institutions where required by local institution or health authority, an additional serum test may be done any time between Baseline and Bimatoprost SR administration, with negative results for all tests confirmed prior to the time of Bimatoprost SR/sham injection. Pregnancy testing at Baseline is required regardless.

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

[f] The examination may also include, [redacted] See Procedure Manual for details.

[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/patients, additional IOP measurements will be performed at Hour 2 and Hour 8.

[i] Two visual field tests are required prior to the administration procedure. The first can be performed up to 10 months prior to or at Screening, and the second during Washout or at the Baseline visit. For a given patient, the same test methodology must be used for historical fields and all fields performed throughout the study.

j [redacted] See Procedure Manual for details. Assessment will be repeated at Week 52 and Month 24/Exit and may be performed at any interim study visit at the discretion of the investigator.

k Biomicroscopy on the SLT Administration Day is performed following treatment as described in Section 8.4.3.1.

l [redacted] See Procedure Manual for details.

m Screening: patient #; Day 1: **randomization** after eligibility confirmation (may be done at end of Baseline visit if needed); Baseline: H0 IOP

Table 3 Administration Cycle 1 Schedule of Visits and Procedures: Day 4 through Week 15

Visit	Bimatoprost SR Cycle 1 Day 1 Administration	Cycle 1 Day 2 Safety Visit	Cycle 1 Day 4 Phone Call[a]	Cycle 1 Week 2 Phone Call[a]	Week 4	Week 8	Week 12	Week 15[b]
Visit Windows	**Day 4 +3 days**				**±4 days**	**± 4 days**	**±4 days**	**± 4 days**
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications/ Procedures	X	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X			X	X	X	X
Ocular Examinations in **bold** should be performed in the order shown								
Pre-Hour 0 exams (may perform in any order before Hour 0 IOP)								
Macroscopic Conjunctival Hyperemia Assessment[c]		OU			OU	OU	OU	OU
Best-Corrected Visual Acuity[d]		OU			OU	OU	OU	OU
Intraocular Pressure H0	SC/T[e]	OU			OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)								
Macroscopic Iris Color Assessment					OU		OU	
Manifest Refraction[d]							OU	
Specular Microscopy					OU		OU	
Biomicroscopy[c]	SC/T[e]	OU			OU	OU	OU	OU
Intraocular Pressure H2 and H8 (selected sites/patients)[f]							OU[f]	
Gonioscopy/Angle Assessment					OU[g]	OU	OU[g]	OU
Pachymetry (may be done any time after gonioscopy)					OU		OU	
Pupil Dilation (may perform post-dilation eye exams in any order)							OU	

Visit	Bimatoprost SR Cycle 1 Day 1 Administration	Cycle 1 Day 2 Safety Visit	Cycle 1 Day 4 Phone Call[a]	Cycle 1 Week 2 Phone Call[a]	Week 4	Week 8	Week 12	Week 15[b]
Visit Windows	**Day 4**				**±4 days**	**± 4 days**	**±4 days**	**± 4 days**
	+3 days							
Dilated Ophthalmoscopy							OU	
Optic Disc Examination							OU	
Contact Interactive Response System[h]	X							
Treatment and/or Sham Administration[i]	X							

H = Hour; IOP = intraocular pressure; Hour 0 = 08:00 ± 1 hour; OU = both eyes; SC/T = applies to only patients with sickle cell disease or trait or other hemoglobinopathies; X = perform procedure

[a] If the patient reports symptoms or findings of concern in the Day 4 or Week 2 phone call (including but not limited to photophobia, blurred vision, eye pain, vitreous floaters), the investigator must bring the patient in for ophthalmic examination.

[b] Patients who meet the retreatment criteria will receive Cycle 2 administration at Week 16 (Table 4). Patients who do not receive Cycle 2 administration at Week 16 will not attend the Cycle 2 Administration Day visit at Week 16, or the Day 2 Safety and Day 4 and Week 2 phone call visits (visits shaded in grey in Table 4). For these patients, the second administration of Bimatoprost SR may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met.

[c] [redacted]. See Procedure Manual for details.

[d] 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.

[e] Optional biomicroscopy and IOP measurement in both eyes may be performed 4 hours after study treatment for patients with sickle cell/trait or other hemoglobinopathies.

[f] At selected sites in consenting patients, additional IOP measurements will be performed at Hour 2 (Hour 0 + 2 hours [± 30 minutes]) and Hour 8 (Hour 0 + 8 hours [± 30 minutes]).

[g] [redacted] See Procedure Manual for details.

[h] Contact pretreatment for kit allocation (and posttreatment to confirm kit assignment, if applicable).

[I] [redacted]

Table 4 Administration Cycle 2 Schedule of Visits and Procedures: Week 16 through Week 31

Visits	Bimatoprost SR Cycle 2 Day 1 Administration[b] Week 16[b]	Cycle 2 Day 2 Safety Visit[b]	Cycle 2 Day 4 Phone Call[a, b]	Cycle 2 Week 2 Phone Call[a, b]	Week 20	Week 24	Week 28	Week 31
Visit Windows	**-2/+4 days**				**± 4 days**	**±4 days**	**± 4 days**	**±4 days**
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X			X	X	X	X
Ocular Examinations in **bold** should be performed in the order shown								
Pre-Hour 0 Exams (may perform in any order before Hour 0 IOP)								
Macroscopic Conjunctival Hyperemia Assessment[c]		OU			OU	OU	OU	OU
Best-Corrected Visual Acuity[d]		OU			OU	OU	OU	OU
Intraocular Pressure H0	SC/T[e]	OU			OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)								
Macroscopic Iris Color Assessment						OU		
Manifest Refraction[d]						OU		
Visual Field[f]						OU		
Specular Microscopy						OU		
Biomicroscopy[c]	SC/T[e]	OU			OU	OU	OU	OU
Intraocular Pressure H2, H8 (selected sites/patients)[g]						OU[g]		
Gonioscopy/Angle Assessment					OU	OU[h]	OU	OU

Visits	Bimatoprost SR Cycle 2 Day 1 Administration[b]	Cycle 2 Day 2 Safety Visit[b]	Cycle 2 Day 4 Phone Call[a, b]	Cycle 2 Week 2 Phone Call[a, b]	Week 20	Week 24	Week 28	Week 31
	Week 16[b]							
Visit Windows	-2/+4 days				± 4 days	±4 days	± 4 days	±4 days
Pachymetry (may be done any time after gonioscopy)						OU		
Pupil Dilation (may perform post-dilation eye exams in any order)						OU		
Dilated Ophthalmoscopy						OU		
Optic Disc Examination						OU		
Contact Interactive Response System[i]	X							
Treatment and/or Sham Administration[j]	X							

H = Hour; IOP = intraocular pressure; Hour 0 = 08:00 ± 1 hour; OU = both eyes; SC/T = applies to only patients with sickle cell disease or trait or other hemoglobinopathies; X = perform procedure

[a] If the patient reports symptoms or findings of concern in the Day 4 or Week 2 phone call (including but not limited to photophobia, blurred vision, eye pain, vitreous floaters), the investigator must bring the patient in for ophthalmic examination.

[b] Cycle 2 visits in grey are performed at Week 16 for all patients who meet retreatment criteria. Patients who do not receive Cycle 2 administration at Week 16 will not attend the Cycle 2 Administration Day visit on Week 16, or the Day 2 Safety or Day 4 and Week 2 phone calls associated with administration at Week 16 (visits shaded in gray). For those patients not meeting retreatment criteria at Week 16, Cycle 2 may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met; in this case, inadequate control of IOP should be confirmed at another scheduled or unscheduled visit prior to initiation of Cycle 2. For patients who receive a Cycle 2 administration after Week 16 and before Month 12, the Cycle 2 visits in grey will apply at the time of the Cycle 2 administration. Regardless of the timing of Cycle 2 administration, all regularly scheduled visits (visits not shaded in grey) should be completed. Cycle 2 visits should be scheduled such that the Administration Day and the Day 2 Safety Visit do not occur on the day of a regularly scheduled study visit. However, if the Cycle 2 Day 4 or Week 2 Phone Calls overlap with a regularly scheduled visit, perform the regularly scheduled visit.

[c] [redacted] See Procedure Manual for details.

[d] 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.

e Optional biomicroscopy and IOP measurement in both eyes may be performed 4 hours after study treatment for patients with sickle cell/trait or other hemoglobinopathies.
f For a given patient, the same test methodology must be used for fields that are historical as well as fields performed throughout the study.
g For all patients, IOP measurements will be performed at Hour 0 [8:00 AM ± 1 hour]. At selected sites in consenting patients, additional IOP measurements will be performed at Hour 2 (Hour 0 + 2 hours [± 30 minutes]) and Hour 8 (Hour 0 + 8 hours [± 30 minutes]).
h [redacted] See Procedure Manual for details.
i Contact pretreatment for kit allocation (and posttreatment to confirm kit assignment, if applicable).
j [redacted]

Table 5 Schedule of Visits and Procedures: Week 36 through Week 52

Visits	**Week 36**	**Week 40**	**Week 44**	**Week 47**	**Week 52**
Visit Windows	**±4 days**	**±4 days**	**±4 days**	**±4 days**	**±4 days**
Adverse Events	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X	X	X
Ocular Examinations in **bold** should be performed in the order shown					
Pre-Hour 0 Exams (may perform in any order before Hour 0 IOP)					
Macroscopic Conjunctival Hyperemia Assessment[a]	OU	OU	OU	OU	OU
Best-Corrected Visual Acuity[b]	OU	OU	OU	OU	OU
Intraocular Pressure H0	OU	OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)					
Macroscopic Iris Color Assessment					OU
Manifest Refraction[b]					OU
Visual Field[c]					OU
Specular Microscopy		OU			OU
[redacted]					OU
Biomicroscopy[a]	OU	OU	OU	OU	OU

Visits	**Week 36**	**Week 40**	**Week 44**	**Week 47**	**Week 52**
Visit Windows	**±4 days**	**±4 days**	**±4 days**	**±4 days**	**±4 days**
Gonioscopy/Angle Assessment	OU[e]	OU	OU	OU	OU[e]
Pachymetry (may be done any time after gonioscopy)		OU			OU
Pupil Dilation (perform post-dilation eye exams in any order)		OU			OU
Dilated Ophthalmoscopy		OU			OU
Optic Disc Examination		OU			OU

H = Hour; Hour 0 = 08:00 ± 1 hour; IOP = intraocular pressure; OU = both eyes; X = perform procedure

[a] [redacted] See Procedure Manual for details.

[b] 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.

[c] For a given patient, the same test methodology must be used for historical fields and all fields performed throughout the study.

[d] [redacted] Assessment will be performed at Week 52 and Month 24/Exit in patients who underwent assessment at Screening and may also be performed at any interim study visit at the discretion of the investigator. Perform any contact assessments following completion of IOP measurements. See Procedure Manual for details.

[e] [redacted] See Procedure Manual for details.

Table 6 Schedule of Visits and Procedures: Month 13 through Month 24/Exit

Visits	**Month 13[a]**	**Month 14**	**Month 15[a]**	**Month 16**	**Month 18**	**Month 20**	**Month 22[a]**	**Month 24/Exit**
Visit Windows	**±4 days**	**±4 days**	**±4 days**	**±4 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X	X	X	X	X	X
Pregnancy Test								X
Ocular Examinations in **bold** should be performed in the order shown								
Pre-Hour 0 Exams (may perform in any order before Hour 0 IOP)								
Macroscopic Conjunctival Hyperemia Assessment[b]	OU	OU	OU	OU	OU	OU	OU	OU
Best-Corrected Visual Acuity[c]	OU	OU	OU	OU	OU	OU	OU	OU
Intraocular Pressure H0	OU	OU	OU	OU	OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)								
Macroscopic Iris Color Assessment					OU			OU
Manifest Refraction[c]					OU			OU
Visual Field[d]					OU			OU
Specular Microscopy				OU		OU		OU
[redacted]								OU
Biomicroscopy[b]	OU	OU	OU	OU	OU	OU	OU	OU

Visits	Month 13[a]	Month 14	Month 15[a]	Month 16	Month 18	Month 20	Month 22[a]	Month 24/Exit
Visit Windows	**±4 days**	**±4 days**	**±4 days**	**±4 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
Gonioscopy/Angle Assessment	OU	OU	OU	OU	OU[f]	OU	OU	OU[f]
Pachymetry (may be done any time after gonioscopy)				OU		OU		OU
Pupil Dilation (perform post-dilation eye exams in any order)				OU		OU		OU
Dilated Ophthalmoscopy				OU		OU		OU
Optic Disc Examination				OU		OU		OU
Contact Interactive Response System[g]								X

H = Hour; Hour 0 = 08:00 ± 1 hour; IOP = intraocular pressure; OU = both eyes; X = perform procedure

[a] Patients who receive the second administration of Bimatoprost SR at Week 16 and patients who never receive a second administration may, at the investigator's discretion, skip the visits at Months 13, 15 and 22 if the patient has received nonstudy IOP lowering medication in both eyes; has ≤ 25% of each implant remaining in the eye; and in the investigator's clinical judgment, has no safety or other concern that would require the patient to attend these visits. Please note: as described in Section 4.5.2, each eye should be evaluated on an individual basis when determining the need for additional nonstudy IOP-lowering treatments; initiation of treatment in one eye should not automatically lead to initiation of treatment in the contralateral eye.

[b] [redacted] See Procedure Manual for details.

[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 patient, the same test methodology must be used for historical fields and all fields performed throughout the study.

[e] [redacted] Assessment will be performed at Week 52 and Month 24/Exit in patients who underwent assessment at Screening and may also be performed at any interim study visit at the discretion of the investigator. Perform any contact assessments following completion of IOP measurements. See Procedure Manual for details.

[f] [redacted] See Procedure Manual for details.

[g] Contact at Month 24/Exit to report patient's exit status.

1. Background and Clinical Rationale

1.1 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 (OAG) (Stamper et al, 2009). Open-angle glaucoma is further categorized into primary OAG (POAG, sometimes also referred to as chronic OAG) and secondary OAG (which includes pigmentary and pseudoexfoliation glaucoma), the former being the predominant form of OAG. Primary OAG is characterized as a 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 anterior chamber (AC) angles, and manifesting characteristic visual field abnormalities (American Academy of Ophthalmology, 2010a). 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 and Broman, 2006; Varma et al, 2011; Cook and Foster, 2012). Approximately 10% of eyes with elevated intraocular pressure (IOP) will progress to OAG over the course of a decade (Quigley et al, 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 et al, 2009). A number of controlled trials have demonstrated that lowering IOP will slow or delay the appearance or progression of glaucomatous damage. Large, randomized clinical trials such as the Ocular Hypertension Treatment Study (Kass et al, 2002) and the Early Manifest Glaucoma Trial (Heijl et al, 2002) addressed the value of early detection and lowering of elevated IOP in ocular hypertension (OHT) or POAG. The effects and parameters of various interventions in eyes with established glaucomatous damage were addressed by the Collaborative Initial Glaucoma Treatment Study (Lichter et al, 2001) and the Advanced Glaucoma Intervention Study (AGIS) (AGIS, 2000). The currently available approaches to lowering IOP include topical pharmacological therapy, laser trabeculoplasty (LT), incisional surgery, and cyclodestructive procedures. Each of these approaches has its own risk-benefit ratio. Because the risk-benefit ratio with drug therapy appears to be lower than that of surgical procedures, both historical and contemporary practice has been to attempt pharmacological treatment before resorting to other more invasive alternatives.

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 et al, 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 have been developed and provided to clinicians for assisting patients with being adherent (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 controversial (Realini, 2008). Patients will often require adjunctive therapy after LT, and may eventually require incisional surgery to control their IOP (Francis et al, 2005; Koucheki and Hashemi, 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 et al, 2009). As a result, Allergan has developed a sustained-release (SR) bimatoprost implant as an ocular antihypertensive therapy for patients with OAG and OHT who are not adequately managed by topical medication due to medication adherence or tolerability issues.

1.2 Bimatoprost (LUMIGAN®)

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

The IOP-lowering efficacy of LUMIGAN (bimatoprost ophthalmic solution) 0.03% is well established. In phase 3 studies in patients with POAG or OHT, LUMIGAN administered once daily as monotherapy was superior to timolol at all timepoints (Higginbotham et al, 2002). This was further substantiated in the extension studies which followed patients in a masked manner for up to 4 years (Cohen et al, 2004; Williams et al, 2008; Study 192024-014). In clinical studies of patients with OAG or OHT with a mean baseline IOP of 26 mm Hg, the IOP-lowering effect of LUMIGAN administered once daily in the evening was 7 to 8 mm Hg (Cohen et al, 2004; LUMIGAN® Package Insert, 2012; Williams et al, 2008). LUMIGAN was approved by the United States (US) Food and Drug Administration (FDA) in 2001. Worldwide, LUMIGAN 0.03% is currently licensed and marketed in more than 80 countries and LUMIGAN 0.01% is licensed and marketed in more than 40 countries. Preservative-free bimatoprost ophthalmic solution 0.03% has been approved since November 2012 for lowering IOP, and is currently marketed in 10 countries.

A sustained-release (SR) formulation of bimatoprost was developed at Allergan, Inc. to evaluate ocular antihypertensive therapies that do not require patient self-administration. Bimatoprost SR refers to the biodegradable, sustained-release, preservative-free bimatoprost implant which is preloaded in an applicator for administration; together they comprise the Bimatoprost SR product. The Bimatoprost SR implant is injected into the AC via the corneal limbus using the prefilled applicator. The biodegradable polymer matrix gradually degrades to carbon dioxide and water so that there is no need to remove the Bimatoprost SR implant once the drug has been released. The Bimatoprost SR implant used in this study contains a total preservative-free bimatoprost load of 10 µg, and intracameral administration of this dose strength is expected to reduce the total daily drug exposure to the eye by approximately 126-fold compared with topical LUMIGAN 0.03% application over 4 months, as well as possibly reducing the adverse effects observed with topical glaucoma medications. The Bimatoprost SR implant is expected to release drug over approximately 4 months, and [redacted] polymer matrix degradation is expected within approximately 12 months. Although the biodegradation process of the Bimatoprost SR implant exceeds the drug release duration, experience from preclinical studies, the phase 1/2 (Study 192024-041D), and approved intravitreal implants composed of similar biodegradable polymers provide support for the anticipated safety in a phase 3 clinical trial with repeated administration.

1.2.1 Nonclinical Studies with Bimatoprost SR

Pharmacology, toxicology, and pharmacokinetic studies with multiple dose strengths, implant sizes, and formulations (Generation 1 and Generation 2) of Bimatoprost SR were completed

in 2 species (Beagle dogs and Cynomolgus monkeys) with a range of AC angle sizes in order to support the clinical program. These studies build on the already considerable amount of nonclinical and clinical information available for topical bimatoprost (see Investigator's Brochure [IB] for additional details).

Nonclinical studies with pharmacology endpoints (Reports BIO-09-803, BIO-11-920, PK09109-PK, BIO-09-785) showed dose-related reductions in IOP in normotensive Cynomolgus monkeys and Beagle dogs, as well as in laser-induced ocular hypertensive Cynomolgus monkeys following single doses. Toxicology studies, of at least 6 to 12 months duration and including single and repeat Bimatoprost SR administration, were conducted in Cynomolgus monkeys and Beagle dogs (Studies TX09051-TX, TX09066-TX, TX10016-TX, TX11076-TX, TX12012-TX, TX12018-TX, and TX12102-TX). Monkeys, which have a characteristically small AC angle compared to both dogs and humans, did not tolerate Bimatoprost SR dose strengths tested (≥ 10 µg Bimatoprost SR) due to chronic contact of the implant with corneal endothelium. Single and repeat ocular toxicity studies with Generation 2 Bimatoprost SR in dogs with varying AC angle sizes demonstrated acceptable safety and ocular tolerability with single doses ≤ 20 µg (Studies TX11076-TX, TX12012-TX, TX12018-TX) and with repeat doses of ≤ 15 µg (Studies TX12012-TX and TX12018-TX). Furthermore, no adverse drug- or implant-related ocular findings have been seen following 3 intracameral injections of up to 20 µg (two 10 µg implants) Bimatoprost SR in the 18-month repeat-dose Good Laboratory Practice (GLP) study in dogs (Study TX12102-TX).

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

limit of quantitation (BLQ) or near the detection limit in bulbar conjunctiva, eyelid margin, and periorbital fat while the highest bimatoprost and bimatoprost acid concentrations were observed in the target tissue, the iris ciliary body. Retinal concentrations were BLQ following both topical and Bimatoprost SR administration.

1.2.2 Other Biodegradable Ocular Implants

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

1.2.3 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 this study was to evaluate the safety and IOP-lowering efficacy of Bimatoprost SR in patients with OAG.

A total of 109 patients received at least a single administration of Bimatoprost SR, and 24 patients received a repeat administration of Bimatoprost SR. A trend in dose response was observed across the 4 dose strengths that were tested.

Data suggest that the implant may provide topical prostaglandin analog-like efficacy up to 3 to 4 months post-implantation in the majority of patients. Data following the second administration in the retreated patients showed similar IOP lowering efficacy to that observed following the first administration of Bimatoprost SR. In addition, efficacy was maintained longer than the expected 3- to 4-month duration in many patients in this completed study. By Month 6, most patients (> 66%) were still maintained on monotherapy with the initial Bimatoprost SR implant administered. Among all Generation 2 dose strengths, at least 33% of patients had not received rescue or a second Bimatoprost SR treatment by Month 12. At Month 24, at least 23% of patients had not received rescue or a second treatment.

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

Two identical global phase 3 studies (Studies 192024-091 and 192024-092) were initiated in late 2014. These studies are assessing the safety and efficacy of Bimatoprost SR in multicenter, randomized, masked, parallel-group comparison studies of 2 dose strengths of Bimatoprost SR (10 and 15 μg) to an active control (timolol maleate 0.5%).

1.3 Study Rationale

Results of the completed phase 1/2 study, 192024-041D, showed that Bimatoprost SR provides a prostaglandin analog-like IOP-lowering efficacy when used at the dose strengths being used in this phase 3 investigation. Additionally, the safety profile of Bimatoprost SR at dose strengths of 20 μg (2 × 10 μg) or less in the phase 1/2 study was acceptable and supports additional clinical studies in humans. Study 192024-093 was designed as a randomized, patient and efficacy evaluator-masked, paired-eye comparison evaluating the safety and IOP-lowering effects of repeated administrations of 15 μg Bimatoprost SR in patients with OAG or OHT who are not adequately managed with topical medication (eg, due to intolerance or nonadherence).

Based on the interim data from phase 1/2 study 192024-041D, the higher of the two dose strengths being evaluated in the other global phase 3 studies, 15 μg, was selected for the 2 phase 3 studies against an SLT comparator (192024-093 and 192024-095). After additional data from later-stage studies became available, the protocol in one of these studies (192024-093) was amended (Amendment 3) to reduce the dose strength for newly enrolled patients to 10 μg, in order to broaden the range of dose strengths evaluated in the 2 phase 3 studies with the SLT comparator arm. In addition, the number of administration cycles was reduced from 3 to 2 (eliminating Week 32 administration for newly enrolled patients and ongoing patients who had not yet received the Week 32 administration). The number of administration cycles was reduced based on the duration of effect observed in completed 24-month Study 192024-041D as well as the analysis of data from the first 3 months of treatment (primary analysis) in Study 192024-091, which suggested that the majority of patients do not require rescue treatment for an extended duration following their last Bimatoprost SR administration. The results of both studies suggest that efficacy may be

maintained with fewer administration cycles. In Amendment 6, an IOP-based retreatment criterion was added as a requirement for the second administration of Bimatoprost SR at Week 16 (patients not meeting retreatment criteria at Week 16 may receive the second administration of Bimatoprost SR at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met). The change from 3 to 2 administration cycles and the addition of the IOP-based retreatment criterion will not change the primary efficacy analysis, which is planned to occur after all patients treated with Bimatoprost SR 10 µg complete the Week 24 visit or discontinue the study and allows for assessment of the duration of effect of 2 Bimatoprost SR administration cycles throughout the study.

The comparator that is to be administered in the contralateral eye is selective laser trabeculoplasty (SLT), which is also indicated for this patient population. SLT, one of the most frequently used LT modalities, is commonly used as an intermediate step between topical medications and incisional glaucoma surgery and is comparable in efficacy and durability to argon laser trabeculoplasty (ALT) (Damji et al, 1999; Damji et al, 2006; Martinez-de-la-casa et al, 2004; Rolim de Moura et al, 2007; Wang et al, 2013). SLT causes minimal tissue destruction compared with ALT and is increasingly being adopted as the LT standard of care (Realini, 2008). SLT has been reported to reduce IOP effectively in eyes with OHT and OAG, as reports often suggest IOP reduction to be similar to topical prostaglandin analogues (Katz et al, 2012; Nagar et al, 2009; McAlinden 2014). This study is 1 of 2 phase 3 studies that will compare the IOP-lowering effects and safety profiles of Bimatoprost SR and SLT.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

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

2.2 Clinical Hypotheses

Bimatoprost SR will have an IOP-lowering effect that is noninferior to that of SLT in patients with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

Bimatoprost SR administered intracamerally will have an acceptable safety profile in patients with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

3. Study Design

This study is a multicenter, paired-eye, randomized, efficacy evaluator-masked 26-month study conducted in 2 stages and evaluating 2 different dose strengths of Bimatoprost SR (Stage 1: 15 µg; Stage 2: 10 µg). The safety and IOP-lowering effect of Bimatoprost SR will be compared with SLT in OAG and OHT patients who are not adequately managed with topical medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

The study is being conducted in 2 stages because the protocol was amended (Amendment 3) to reduce the dose strength for newly enrolled patients to 10 µg in order to broaden the range of dose strengths evaluated in the 2 phase 3 studies with the SLT comparator arm. The primary efficacy analysis will be performed for patients in Stage 2 only.

The eye with the higher IOP at Baseline will be assigned as the primary eye. If baseline IOP is the same in both eyes, the right eye will be the primary eye. The primary eye will be randomized to receive either Bimatoprost SR or SLT using a 1:1 ratio, stratified by primary eye baseline IOP (≤ 25 versus > 25 mm Hg) [redacted] If the primary eye receives Bimatoprost SR, the contralateral eye will receive SLT. If the primary eye receives SLT, the contralateral eye will receive Bimatoprost SR.

Patients will receive a 360° administration of SLT in 1 eye on Day 1, and administration of Bimatoprost SR in the contralateral eye on Day 4, with a repeat administration of Bimatoprost SR at Week 16 for all patients who meet retreatment criteria. For those patients not meeting retreatment criteria at Week 16, Cycle 2 may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met. (Note that for all patients who were enrolled and reached the Week 16 visit prior to implementation of Amendment 6, retreatment with Bimatoprost SR was fixed at Week 16.) In order to mask the patient to the treatment assigned to each eye, on Day 1 a Sham SLT procedure will be performed in the eye to be administered Bimatoprost SR (hereafter refer to as the "Bimatoprost SR eye"). A Sham Bimatoprost SR administration will be performed in the eye that underwent SLT (hereafter referred to as the "SLT eye") on each Bimatoprost SR administration visit (Day 4 and Week 16) (see

Table 1).

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 160 patients will be enrolled and treated with Bimatoprost SR 10 µg at approximately 70 sites, in order to have an estimated 144 patients treated with Bimatoprost SR 10 µg complete the study based on a premature discontinuation rate of 10%. Approximately 50 patients enrolled before implementation of Amendment 3 and received Bimatoprost SR 15 µg.

4.2 Study Population Characteristics

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

4.2.1 Patients with Sickle Cell Trait/Disease or Other Hemoglobinopathies

Patients with sickle cell trait or disease or other hemoglobinopathies may be enrolled at the discretion of the investigator based on an individual risk-benefit assessment. Because of a slightly higher risk of IOP elevation and intraocular complications in the setting of a microhyphema, patients with these disorders may undergo optional additional safety monitoring (biomicroscopy and IOP measurement) after Bimatoprost SR administration at the investigator's discretion. Additional information about the previous experience with the use of Bimatoprost SR in patients with sickle cell trait is provided in the IB.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, 18 years of age or older

2. 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 [Unites States (US) sites] and written Data Protection consent [European Union (EU) sites])

3. Patient is willing to withhold his/her IOP treatments according to the study requirements, and in the opinion of the investigator, can do so without significant risk. Note: If patients cannot discontinue their currently prescribed therapy for up to 8 weeks to meet the Washout period for study entry, the investigator may switch the patient's medication to one that requires a shorter washout interval during the washout of the original medication (see Section 8.2 and Table 7)

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

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

6. Negative pregnancy test at Baseline for females of childbearing potential

Ocular Inclusion Criteria for Both Eyes:

7. In the investigator's opinion, both eyes can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy if medication was taken as directed

8. In the investigator's opinion, patient's IOP can be adequately managed with SLT monotherapy

9. In the investigator's opinion, patient is a suitable candidate for SLT

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

11. Central endothelial cell density by specular microscopy confirmed as being qualified by Reading Center assessment prior to beginning Washout

12. The iridocorneal angle must be independently confirmed as being qualified by 2 ophthalmologists using the following criteria:
    a. Shaffer Grade $\geq$ 3 on clinical gonioscopy of the inferior angle
    b. Peripheral anterior chamber depth by Van Herick examination $\geq$ 1/2 corneal thickness

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

13. At the Baseline visit, patient has been appropriately washed out of all IOP-lowering medications

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

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

4.4 Exclusion Criteria

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

1. Uncontrolled systemic disease

2. Females who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not using a reliable means of contraception during the study (see Section 4.5.3)

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

4. Any condition which would preclude the patient's ability to comply with study requirements (including completion of the study)

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

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

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

8. Known history of bleeding disorder or prolonged bleeding after surgery (in the opinion of the investigator). Note: Patients receiving pharmacologic blood thinners (eg, aspirin, Coumadin) may be enrolled at the investigator's discretion.

Ocular Exclusion Criteria for Both Eyes:

9. History of previous laser trabeculoplasty

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

11. The following surgical history:

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

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

    b. History of phakic IOL insertion for refractive error correction

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

13. 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

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

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

16. Any history of external ocular or intraocular malignancy, and/or any history of benign ocular neoplasia that in the investigator's opinion resulted in clinically significant ocular morbidity

17. History of herpetic ocular diseases (including herpes simplex virus and varicella zoster virus)

18. The following ocular surface findings:

    a. Bulbar conjunctival hyperemia, on either macroscopic or slit-lamp examination, > +1 (mild) at baseline

    b. Active ocular surface findings other than bulbar conjunctival hyperemia, on either macroscopic or slit-lamp examination, > +1 (mild) at Baseline

19. History of moderate or worse (≥ +2) bulbar conjunctival hyperemia due to marketed prostaglandin, prostamide, or prostaglandin analog use

20. The anticipated wearing of contact lenses 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 an Administration Day 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 Administration Day visit

    c. Use of contact lenses of any kind should be discontinued for 1 week following any Bimatoprost SR (or Sham) administration

21. Central corneal thickness of < 480 or > 620 micrometers

22. Anticipated need for any incisional or laser ocular surgery during the study

23. History of anatomically narrow angle resulting in evidence of angle changes or any history of closed angle glaucoma. Note: historically narrow angled patients whose angle has been opened by cataract surgery or peripheral iridotomy may be eligible for enrollment if they have no evidence of angle abnormalities.

24. History or evidence of a peripheral iridotomy/iridectomy in the inferior iris

25. Any history of trabeculectomy or other types of glaucoma surgery, including a glaucoma seton or aqueous bypass stents

26. Peripheral anterior synechiae (PAS) in the inferior iridocorneal angle on gonioscopic examination at Screening

27. Visual field loss that, in the opinion of the investigator, is functionally significant (eg, split fixation, field defect within the central 10 degrees that is visually significant or likely to cause central visual impairment upon progression) or shows evidence of progressive visual field loss within the year prior to baseline (Note: Two visual fields are required for qualification, 1 performed within the 10 months prior to or at Screening, and 1 performed at baseline or during the washout period using the protocol-required testing method [see Procedure Manual]. The same test methodology should be used for all historical and study-related examination for a given patient.)

28. Evidence of macular edema during screening or in patient's medical history

29. Anticipated use of corticosteroids in either eye (except as described in Section 4.5.1 [Permissible Medications/Treatments]) 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 corticosteroids applied to skin of the eyelid(s), around the eye, or adnexa

30. Anticipated use of other topical ocular medications except as described in Section 4.5.1 (Permissible Medications/Treatments)

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Ophthalmic Medications/Treatments

Intermittent use of artificial tear products is allowed if they are taken > 15 minutes before any study procedure or if they are required for a study procedure. Intermittent use of ocular decongestants or antihistamines is allowed if not taken within 2 days prior to a scheduled visit.

Use of artificial tear products and ocular decongestants or antihistamines may be restarted 3 days after any study administration (Bimatoprost SR, Sham Bimatoprost SR, SLT, or Sham SLT) procedure.

> Note: post-procedural use of artificial tear products following SLT/Sham SLT administration is allowed at the investigator's discretion; patients should be instructed to wait at least 15-20 minutes after instilling required medication (eg, NSAID) drops before instilling artificial tear products. Use of artificial tears is not allowed following Bimatoprost SR/Sham Bimatoprost SR administration except as described above (restart 3 days after).

Use of post-Bimatoprost SR administration topical ocular antibiotics for 3 days, and corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) for up to 7 days following the administration days is permissible.

Use of immediate pre- and post-SLT topical ocular antihypertensive medication (ie, brimonidine or apraclonidine) is permissible. Post-SLT topical NSAIDS are also permissible for 3 days following the procedure. The medications instructed for use pre- and post-SLT are described in detail in Section 5.9.2.

Systemic Medications

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

The use of systemic NSAIDS is also permitted.

In addition, therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. If possible, the concurrent therapy (ocular and systemic) administered should not have an effect on study outcomes. However, if concurrent medications may have an effect on study outcomes, these medications should be administered in dosages that remain constant throughout the duration of the study. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

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

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

4.5.2 Prohibited Medications/Treatments

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

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

Nonstudy IOP-lowering Treatments

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

In order to maintain patient masking to treatments assigned to each eye, patients who have received nonstudy topical IOP-lowering treatment in a Bimatoprost SR eye will receive Sham Bimatoprost SR administration in that eye on the Bimatoprost SR Cycle 2 administration day(s). If nonstudy topical IOP-lowering medication is initiated in an SLT eye, the patient will continue to receive Sham Bimatoprost SR administration in the SLT eye on the administration day(s). In all cases, the contralateral eye that does not require nonstudy topical IOP-lowering medication will maintain the same treatment regimen assigned at randomization. Patients who have received nonstudy IOP-lowering treatment in both eyes will not receive Bimatoprost SR administration or Sham Bimatoprost SR administration in either eye, and therefore do not need to attend the Bimatoprost SR (or Sham Bimatoprost SR) administration visits and immediate postadministration visits (ie, Bimatoprost SR Cycle 2

administration [Week 16], Cycle 2 Day 2 safety visit, and Cycle 2 Day 4 and Week 2 phone calls).

Contact Lenses

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

Other Medications

The following medications (or classes of medications) and treatment procedures are not permitted as concurrent therapy during the study unless the patient has already received nonstudy IOP-lowering medication or treatment in both eyes:

- Subconjunctival, sub-Tenon's, intravitreal, or other ophthalmic injections of any medications in either eye
- Use of any topical ophthalmic medications (except as described above and in Section 4.5.1) in either eye
- Surgical (incisional and laser) procedures that are not related to study-specific Bimatoprost SR (or Sham) and SLT administration procedures in either eye; patients may exit the study early if an ophthalmic incisional procedure is required
- Oral, intramuscular, or intravenous corticosteroids from 2 months prior to the Baseline visit through study exit
- Use of bimatoprost for hypotrichosis during the study period in either eye
- Use of cyclosporine ophthalmic solution during the study period in either eye
- Systemic use of carbonic anhydrase inhibitor
- Any initiation of or alterations in systemic regimen of beta-blocker containing medications from 2 months prior to screening through the study exit
- Use of corticosteroids in either eye (except as described in Section 4.5.1 for postoperative 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

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

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

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

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug (and unmask the study treatment as needed for pregnancy monitoring), and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

5. Study Treatments

5.1 Study Treatments and Formulations

The clinical formulation of Bimatoprost SR contains preservative-free bimatoprost dispersed in a biodegradable polymer matrix (including PLA and PLGA). The biodegradable implants are preloaded in the applicator. The formulations used in this study are Bimatoprost SR 15 µg (11048X, for Stage 1) and 10 µg (11047X, for Stage 2).

5.2 Control Treatment

The control treatment is a 360° administration of SLT.

5.3 Methods for Masking

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

The patient and the site staff will be masked to the treatment assignment for each eye. Only the site coordinator and designated staff will be unmasked to the patient's treatment assignment for each eye. Efficacy IOP measurements will be masked using a 2-person reading method as described in Section 6.1.1.

The site staff who perform IOP readings will be masked to the treatment assignment for each eye. Site personnel and patients will be instructed and reminded throughout the study not to discuss study medication assignments to ensure masking is maintained.

In the event that the patient requires postoperative topical eyedrops in only 1 eye following a Bimatoprost SR administration (eg, topical corticosteroids or anti-inflammatory eyedrops) or SLT administration (eg, treatment of acute post-SLT IOP spike), in order to maintain masking of the eye receiving study treatment, the investigator will be instructed to dispense the required medication without disclosing which eye is the Bimatoprost SR or SLT eye or the etiology of the signs/symptoms that require the medication.

5.4 Treatment Allocation Ratio and Stratification

The eye with the higher IOP at baseline will be assigned as primary eye and randomized to receive either Bimatoprost SR or SLT using a 1:1 ratio, stratified by the primary eye baseline IOP (≤ 25 or > 25 mm Hg) [redacted]. If the primary eye receives Bimatoprost SR, the contralateral eye will receive SLT. If the primary eye receives SLT, the contralateral eye will receive Bimatoprost SR. If baseline IOP is the same in both eyes, the right eye will be the primary eye.

5.5 Method for Assignment to Treatment Groups/Randomization

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

For determination of stratification group assignment for the primary eye for each patient, sites will be required to enter Baseline IOP (at Hour 0) data for both eyes into an automated interactive response system.

At the time of randomization (Day 1 SLT Administration Day), an automated interactive response system will be used to manage the randomization and treatment assignment for the Bimatoprost SR and SLT. A randomization number will be assigned to a patient according to the order of enrollment within each IOP stratum (Baseline primary eye Hour 0 IOP ≤ 25 or > 25 mm Hg) [redacted] across the study. That is, the interactive response system will assign the next available randomization number to the patient at the time when the investigator requests randomization.

The interactive response system will provide the site with the specific treatment assignment for each randomized patient/eye at the time of randomization (Day 1 SLT Administration Day). Sites will contact the interactive response system at subsequent visits to obtain a study medication kit number for dispensing study medication (Bimatoprost SR and Sham). Study medication kits for Bimatoprost SR and Sham administration will be labeled with medication kit numbers. Sites will receive interactive response system confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

5.6 Treatment Regimen

The treatment assignments are summarized in

Table 1. The eye randomized to receive Bimatoprost SR will receive an intracameral administration of Bimatoprost SR on Day 4 and at Week 16 (if retreatment criteria are met), plus Sham SLT administration on Day 1 only. For those patients who do not meet retreatment criteria at Week 16, the second Bimatoprost SR administration may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met. The contralateral eye will receive one 360° SLT administration on Day 1 only, plus Sham Bimatoprost SR administration on Day 4 and Week 16 (or at the time of the second Bimatoprost SR administration for patients who receive it later than Week 16). Patients will receive the same dose strength throughout the study (ie, patients in Stage 1 received 15 µg and patients in Stage 2 will receive 10 µg).

For patients who still have any visible Bimatoprost SR implants or have not received nonstudy IOP-lowering medications by the time of study discontinuation or completion, poststudy evaluations including the need for IOP-lowering medications should be conducted according to the treating physician's clinical opinion. Further patient follow-up will be determined by the treating physician's clinical opinion.

5.7 Storage of Study Medications

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol. Only assigned study personnel authorized by the investigator may have access to study medication. Bimatoprost SR and Sham needleless applicators must be stored in the original sealed foil pouch. Investigational medicinal product must be stored as described in the Investigator's Brochure. Sites must report any temperature excursions as described in the Procedure Manual or contact Allergan or its designee for further instructions.

For further details on storage, including requirements for study-provided eye drops, please refer to the Procedure Manual and/or contact Allergan.

5.8 Preparation of Study Medications/Treatments

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

5.9 Study Treatment Administration

Study medication must only be administered to patients who meet the eligibility criteria in accordance with the conditions specified in this protocol. Medication will be labeled with either a single panel label or booklet label. Records of use of medication kit numbers for each patient will be maintained by the site and recorded in the electronic case report form (eCRF) as appropriate.

5.9.1 Bimatoprost SR Administration

5.9.1.1 Patient 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 should be administered to each eye approximately every 5 minutes beginning approximately 15 minutes prior to the procedure. With the patient 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.

5.9.1.2 Study Treatment Location

At the discretion of the investigator, Bimatoprost SR (or Sham) administration may be performed at an Ambulatory Surgical Center (ASC; free standing or hospital based) or in the office setting (eg, in a procedure room with an operating microscope). 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 standard operating procedures (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.

5.9.1.3 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 a 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 patient. The entrance site for the applicator needle is just anterior to the insertion of the conjunctiva through the clear cornea in the superior or temporal quadrant. The trajectory of the needle should be parallel to the iris plane. The eye is stabilized by either counter traction with a sterile toothed forceps or counter pressure with a cotton tipped applicator as the needle is advanced through the cornea. The actuator button is depressed until an audible and/or palpable click is heard. The Bimatoprost SR implant should be visible exiting the needle bevel into the aqueous 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.

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

The preparation and procedure for all sham administrations is the same; however, the sham applicator will not have a needle and thus will not enter the AC (but should touch the eye at the area of recommended insertion).

5.9.1.4 Immediate Posttreatment Observation

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

The patient 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 both eyes and to follow up as per protocol.

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

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

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

5.9.1.5 Retreatment with Bimatoprost SR

For all patients who meet retreatment criteria at Week 16, Cycle 2 Bimatoprost SR administration will occur at Week 16.

For patients who do not meet retreatment criteria at Week 16, Cycle 2 Bimatoprost SR administration may occur at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit based on the investigator's clinical judgment regarding the patient's IOP control and if the retreatment criteria are met. Note: beyond Week 16, Cycle 2 administration is not mandatory even if the retreatment criteria are met.

Patients who have received nonstudy IOP-lowering treatment (prohibited during the study except for pre- and post-SLT administration, Section 4.5.1) in only 1 eye will still attend administration visits regardless of whether the eye receiving additional medication is the Bimatoprost SR eye or the SLT eye. If the eye treated with additional nonstudy IOP lowering medication is the Bimatoprost SR eye, the eye will receive Sham Bimatoprost SR administrations at the administration visits. If the eye treated with additional nonstudy IOP lowering medication is the SLT eye, that eye will continue to receive Sham Bimatoprost SR administrations. Patients who have been treated with nonstudy IOP-lowering medication in both eyes will not attend the administration day visits, nor will they attend the Day 2, Day 4 (phone call), and Week 2 (phone call) visits following an administration. Patients who have received nonstudy IOP-lowering medication in one or both eyes will be followed for the duration of the study through the Month 24/Exit visit.

Retreatment of an eligible implanted eye is permitted if the following criteria are met in that eye:

- IOP > 17 mm Hg
- There is no evidence of any of the following:

- Significant corneal findings related to presence of the implant (including corneal edema, peripherally adjacent to the implant location and/or central) at any visit
- Endothelial cell density less than 1800 cells/mm^2 by specular microscopy, confirmed at 2 consecutive visits on separate days
- Persistent and progressive corneal endothelial cell density decrease $\geq$ 15% from baseline confirmed at 2 consecutive visits on separate days (scheduled or unscheduled)
- Remaining implant size or position from prior administration that, based on the investigator's evaluation, precludes placement of another implant (eg, may cause chronic contact of the implants with the corneal endothelium)
- Clinically significant intraocular inflammatory findings (eg, PAS, uveitis, iridocyclitis, macular edema, etc) at any visit. Note: mild AC cells/iritis related to the administration procedure itself that resolves rapidly (with or without NSAIDs or steroids) is not prohibitive

- In the investigator's opinion, it is safe for the study eye to receive an additional administration of Bimatoprost SR

Signs or symptoms will be documented in the eCRF.

5.9.2 SLT Administration

5.9.2.1 Pre-SLT Patient Preparation

Measure the IOP in both eyes and record the result. Because this is a preoperative measurement and not used for efficacy analyses, this measurement does not need to be masked and only 1 measurement needs to be performed.

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

5.9.2.2 SLT and Sham SLT Procedure

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

5.9.2.3 Post-SLT

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

The patient will be supplied a bottle of topical NSAID eyedrops and instructions to use them as directed for the next 3 days (including the day of the administration) in both eyes and to follow up as per protocol.

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

6. Response Measures and Summary of Data Collection Methods

Detailed information on equipment and methodology to be used is provided in the Procedure Manual.

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

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

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

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

for the given eye will be the average of the 2 readings. If the difference between the first 2 measurements is > 1 mm Hg, the IOP for the given eye will be the median of the 3 readings.

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

6.2 Safety Measures

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

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

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

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

Blood and Urine Sample Collection: Blood and urine samples will be collected for blood chemistry, hematology panels, and urinalysis by a central laboratory or designated regional facility.

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

Measures of Ocular Safety:

Best Corrected Visual Acuity: Visual acuity tests will be performed at all scheduled visits except on any of the Bimatoprost SR administration days or SLT Administration Day. Manifest refraction using Snellen equivalent with a logMar chart (see Procedure Manual) will be performed at Screening; Baseline; Weeks 12, 24, and 52; and Months 18 and 24/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 best-corrected visual acuity will be performed.

Macroscopic Iris Color Assessment: Iris color will be assessed visually at each designated visit using the appropriate assessment guide (see the Procedure Manual for further details).

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

Gonioscopy/Angle Assessment: Gonioscopic examination for eligibility at Screening (only) will be independently performed by 2 ophthalmologists as described in the Protocol Procedure Manual. The independent eligibility assessors should not share their assessments with each other until the assessment is recorded. The 2 ophthalmologists' independent eligibility assessments must confirm patient eligibility for participation in the study. Subsequent gonioscopic examinations will be performed by the study investigator. Using gonioscopy, the investigator will evaluate the inferior iridocorneal angle and the Bimatoprost SR implant.

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).

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

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

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

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

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

Anterior Segment-Optical Coherence Tomography: Anterior segment-optical coherence tomography measurements will be performed at all sites and a Reading Center will be used to examine angle size for investigational purposes. See the Anterior Segment Optical Coherence Tomography Image Acquisition manuals from the Reading Center for further details on the use of optical coherence tomography. In the event that the anterior segment-optical coherence tomography type as specified in the manuals is not available, a suitable alternative may be approved by Allergan and the designated reading center for use. The same instrument should be used throughout the study for a given patient.

Visual Field: Visual field examinations will be assessed using automated perimetry (using either Humphrey 24-2 full threshold program or 24-2 Swedish Interactive Thresholding Algorithm (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 patient. Visual field data may also be submitted to an Allergan designated vendor for additional evaluation.

6.3 Other Measures

[redacted]

6.3.1 Medical History, Physical Examination, and Vital Signs

6.3.1.1 Medical History

A standard medical history (including all relevant conditions that the patient has had in the past or currently has) will be captured in the patient source documents. All surgical procedures should have an associated medical history entry. Current medications as well as those stopped within 60 days prior to the Screening visit and procedures within 90 days prior to the Screening visit will be recorded. In addition, all previous medications taken for OAG or OHT for at least 3 months prior to study entry will be recorded on the appropriate source document and/or eCRF page.

6.3.1.2 Physical Examination

The patient will be examined by qualified medical personnel for any physical abnormality of the following systems: general appearance; head, eyes, ears, nose, and throat; heart/cardiovascular; lungs; abdomen; neurologic; extremities; back; musculoskeletal;

lymphatic; and skin. The patient's height and weight will be recorded at the Screening visit only.

6.3.1.3 Vital Signs

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

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

6.3.2 Pregnancy Testing

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

Further, in countries/institutions where required by local institution or health authority, an additional serum test may be done any time between Baseline and Bimatoprost SR (or Sham) administration. Negative results for all pregnancy tests are required to be confirmed prior to the time of Bimatoprost SR (or Sham) administration.

6.3.3 Laboratory Procedures

A central laboratory or designated regional facility will analyze blood and urine specimens for this study; including any repeat laboratory tests. Blood and urine samples will be obtained for the analysis of blood chemistry, hematology, and urinalysis.

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

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

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

6.3.3.1 Hematology

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

6.3.3.2 Serum Chemistry

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

6.3.3.3 Urinalysis

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

6.4 Other Study Supplies

The following will be provided by Allergan or designated suppliers:

- All supplies needed for central laboratory blood and urine sampling (urinalysis, blood chemistry, and hematology), urine pregnancy test kits, and ocular fluid collection kits
- Shipping materials for shipment of laboratory samples to central laboratory
- [redacted]

- As needed: anterior segment-optical coherence tomography, anterior segment-optical coherence tomography software and/or module, Specular Microscope, contact (ultrasound) pachymetry equipment
- [redacted]
- Ancillary administration procedure supplies and postoperative topical ophthalmic antibiotics may be supplied

Sites that are not able to receive supplies from Allergan due to country regulations will need to provide their own supplies.

Allergan will not provide any nonstudy IOP-lowering medications.

6.5 Summary of Methods of Data Collection

This study will use eCRFs using remote electronic data capture through a qualified third party vendor. The data will be entered on the eCRFs in a timely manner on an ongoing basis. The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the case report forms (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. A certified electronic copy of the eCRF including data corrections will be provided to the site for archiving at the end of the study.

A central laboratory or designated regional facility will be used for analysis of blood chemistry and hematology, urinalysis, and ocular fluid sample analysis (if ocular fluid is obtained). Laboratory data will be transferred to Allergan on a periodic basis throughout the study.

7. Statistical Procedures

The study is being conducted in 2 stages. In Stage 1, patients are treated with Bimatoprost SR 15 µg and SLT. In Stage 2, patients are treated with Bimatoprost SR 10 µg and SLT.

Three database locks will be performed: 1) when all patients treated with Bimatoprost SR 10 µg complete the Week 24 visit or have prematurely discontinued before the Week 24 visit, 2) when all patients treated with Bimatoprost SR 10 µg have completed the Month 12 visit or

prematurely discontinued before the Month 12 visit, and 3) when all patients treated with Bimatoprost SR 10 µg have completed the Month 24 visit or prematurely discontinued before the Month 24 visit. Analyses will be performed after each lock. Prior to the first database lock a detailed analysis plan will be finalized. To maintain the integrity of the ongoing study, Allergan study personnel who are directly involved in data handling and supporting the trial (such as the clinical study team) will remain masked to treatment assignment of individual patients during the study. To avoid potential data unmasking between locks and to protect trial integrity, study statistical personnel who have been unmasked after each lock will no longer be involved directly in any ongoing masked study conduct. Another statistician, who is still masked to study treatment, will assume these responsibilities until the next lock. Unmasked data handling and appropriate data and results access will be specified prior to each lock.

7.1 Analysis Populations

The intent-to-treat (ITT) population is defined as all patients randomized to receive Bimatoprost SR 15 µg, Bimatoprost SR 10 µg, or SLT.

The per-protocol (PP) population is defined as all patients in the Bimatoprost SR 10 µg ITT population who have no protocol deviations affecting the data for primary efficacy analysis for all visits (Week 4, Week 12, and Week 24). The PP population will be used for selected efficacy analyses. A list of patients with data excluded from the PP population will be finalized prior to database lock.

The Bimatoprost SR 15 µg, Bimatoprost SR 10 µg, and SLT safety populations are defined as all patients who received any study treatments and will be used for safety analyses.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

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

To avoid confounding of efficacy data, IOP measurements obtained after initiating the use of nonstudy IOP-lowering medication in an eye will be included in the study database but will be excluded from efficacy analyses.

7.2.1 Primary Efficacy Variable

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

7.2.2 Secondary Efficacy Variables

Secondary efficacy variables include:

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

7.2.3 Other Efficacy Variables

[redacted]

7.3 Hypothesis and Methods of Analysis

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

Data collected from patients treated with Bimatoprost SR 10 µg and Bimatoprost SR 15 µg will be analyzed separately. Specifically, efficacy analysis for patients treated with Bimatoprost SR 15 µg will be limited to Hour 0 IOP descriptive summary statistics. Safety summaries will be generated for Bimatoprost SR 10 µg and Bimatoprost SR 15 µg using the same analysis methods, but will be presented separately.

7.3.1 Primary Efficacy Analyses

The primary efficacy analysis will be performed for patients treated with Bimatoprost SR 10 µg in the ITT population. The primary efficacy variable is IOP change from baseline and Weeks 4, 12, and 24 are the primary analysis timepoints.

The null and alternative hypotheses for the comparison between Bimatoprost SR 10 µg-treated eyes and SLT-treated eyes at each visit of Weeks 4, 12, and 24 are:

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

IOP change from baseline will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include IOP change from baseline as the response variable and treatment, visit, eye, baseline IOP, treatment-by-visit, visit-by-baseline, and visit-by-eyes interactions as covariates. Unstructured correlation for study visits and eyes will be used for repeated measures on the same patient.

The mean difference between the Bimatoprost SR 10 µg eyes and SLT eyes (Bimatoprost SR 10 µg minus SLT) and the corresponding 95% confidence interval (CI) will be constructed at each visit from MMRM analysis. The noninferiority comparison for Bimatoprost SR 10 µg versus SLT at Weeks 4, 12, and 24 is the primary analysis. If the upper limit of the 95% CI is ≤ 1.5 mm Hg at all 3 visits, Bimatoprost SR 10 µg statistical noninferiority to SLT is demonstrated. In addition, Bimatoprost SR 10 µg is considered clinically noninferior to SLT if the upper limit of the 95% CI is ≤ 1.0 mm Hg at 2 out of the 3 visits of Weeks 4, 12, and 24.

As part of the sensitivity analysis for the primary efficacy analysis, a PP analysis using the same MMRM model as the one used in the primary efficacy analysis will be performed. The PP analysis will be based on the data from PP population.

Additionally, a by-visit analysis using an ANCOVA model will be conducted using the data from Bimatoprost SR 10 µg ITT population, where the between-eye correlation will be included in the same way as the MMRM model used for the primary analysis.

Finally, handling of missing data will be supplemented by sensitivity analyses using multiple imputation and tipping point (adding different penalties to the imputed values) approach.

7.3.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be performed for patients treated with Bimatoprost SR 10 µg in the ITT populations.

Superiority Test of Bimatoprost SR 10 µg Versus SLT

A superiority test of Bimatoprost SR 10 µg versus SLT will be performed once noninferiority is demonstrated in the primary efficacy analysis. Superiority of Bimatoprost SR 10 µg versus SLT is considered achieved if the upper limit of the 95% CI is < 0 mm Hg at Weeks 4, 12, and 24.

Time to Initial Use of Nonstudy IOP-lowering Treatment (As Determined by the Investigator)

Time to initial use of nonstudy IOP-lowering treatment from the date of the first study treatment will be estimated separately for Bimatoprost SR 10 µg and SLT .

Additionally, time to initial use of nonstudy IOP-lowering treatment from the second injection, will be analyzed similarly for Bimatoprost SR 10 µg.

Percentage of Bimatoprost SR and SLT Eyes Achieving ≥ 20% Reduction in IOP

Number and percent of Bimatoprost SR 10 µg and SLT eyes that have achieved a ≥ 20% reduction in IOP by visit in each eye will be summarized.

IOP Change from Baseline at Weeks 8, 15, and 20

Summary statistics for Bimatoprost SR 10 µg and SLT eyes will be tabulated for IOP change from baseline at Weeks 8, 15 and 20; [redacted]

7.3.3 Other Efficacy Analyses

[redacted]

7.3.4 Safety Analyses

Safety analyses will be performed separately for patients in the Bimatoprost SR 15 µg and Bimatoprost SR 10 µg safety populations. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events and medical history. The number and percent of patients reporting treatment emergent adverse events will be tabulated based on the primary SOC and preferred terms. Summary tables will be generated for all adverse events regardless of causality as well as treatment-related adverse events for the entire study and by treatment cycle. Other safety variables include vital signs (blood pressure, pulse rate, and temperature) and pregnancy test results. Ocular safety will be evaluated through assessment of visual acuity and visual field, evaluation of macroscopic bulbar conjunctival hyperemia and iris color, assessment of endothelial cell density and corneal thickness, IOP measurement, and biomicroscopic and ophthalmoscopic examinations (including gonioscopy with Bimatoprost SR implant assessment, optic disc examination, and dilated fundus examination).

Ocular adverse events and safety variables attributable to each eye will be summarized by Bimatoprost SR or SLT eye, and nonocular safety variables will be summarized by patient.

7.4 Subgroup Analyses

A subgroup analysis will be conducted for patients who received Bimatoprost SR 10 µg administration under the flexible dosing regimen as specified in the protocol. This will include patients enrolled under Amendment 6 and patients who were reconsented to Amendment 6 before receiving the second Bimatoprost SR administration.

The details of this subgroup analysis will be provided in the Statistical Analysis Plan.

7.5 Sample Size Calculation

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

Assuming a premature discontinuation rate of 10%, approximately 160 patients are to be enrolled into this study and treated with Bimatoprost SR 10 µg. Additionally, there are approximately 50 patients who were enrolled before implementation of Amendment 3.

7.6 Interim Analyses

No interim analyses are planned.

8. Study Visit Schedule and Procedures

Patients who complete all study treatments will have up to 28 visits and 5 phone calls. The schedule includes the following:

- Screening (up to 28 days); Washout period of up to 56 days for both eyes; and Baseline visit (up to 3 days)
- SLT treatment (Day 1) and phone call (Day 2)
- Bimatoprost SR Cycle 1 administration (Day 4); Cycle 1 Day 2 safety visit; Cycle 1 Day 4 and Week 2 phone calls; and follow-up study visits at Weeks 4, 8, 12, and 15

- Bimatoprost SR Cycle 2 administration (to occur at Week 16 for all patients who meet retreatment criteria); Cycle 2 Day 2 safety visit; and Cycle 2 Day 4 and Week 2 phone calls

    - Patients who do not receive Cycle 2 administration at Week 16 will not attend the Cycle 2 Administration Day visit on Week 16, or the Day 2 Safety or Day 4 and Week 2 phone calls associated with administration at Week 16. For these patients, Cycle 2 may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met; in this case, inadequate control of IOP should be confirmed at another scheduled or unscheduled visit prior to initiation of Cycle 2. All Cycle 2 visits will apply at the time of the Cycle 2 administration.

- Follow-up visits at Weeks 20, 24, 28, 31, 36, 40, 44, 47, and 52; and Months 13, 14, 15, 16, 18, 20, 22, and 24/Exit
    - Regardless of the timing of Cycle 2 administration, all regularly scheduled visits should be completed. Cycle 2 visits should be scheduled such that the Administration Day and the Day 2 Safety Visit do not occur on the day of a regularly scheduled study visit. However, if the Cycle 2 Day 4 or Week 2 Phone Calls overlap with a regularly scheduled visit, perform the regularly scheduled visit.
    - Patients who receive the second administration of Bimatoprost SR at Week 16 and patients who never receive a second administration may, at the investigator's discretion, skip the visits at Months 13, 15 and 22 if the patient has received nonstudy IOP lowering medication in both eyes; has ≤ 25% of each implant remaining in the eye; and in the investigator's clinical judgment, has no safety or other concern that would require the patient to attend these visits. Please note: as described in Section 4.5.2, each eye should be evaluated on an individual basis when determining the need for additional nonstudy IOP-lowering treatments; initiation of treatment in one eye should not automatically lead to initiation of treatment in the contralateral eye.

IOP evaluations will occur at Hour 0 (08:00 AM ± 1 hour) in all patients. Selected patients at selected sites will have additional IOP measurements performed at Hour 2 (Hour 0 + 2 hours [± 30 minutes]) and Hour 8 (Hour 0 + 8 hours [± 30 minutes]).

The study visits should adhere as closely as possible to the schedule shown in Table 2, Table 3, Table 4, Table 5, and Table 6.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

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

8.1.2 Informed Consent and Patient Privacy

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

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

8.2 Washout Intervals

All patients must provide informed consent prior to beginning any drug washout for the purposes of inclusion in this study. Patients currently being treated with IOP-lowering medication(s) in either eye will begin washout of these medication(s) following completion of the screening procedures and Reading Center confirmation of endothelial cell density by specular microscopy. The screening and washout periods may not be concurrent. The washout period will be up to 56 days depending on the minimum washout period schedule below.

If patients cannot discontinue their prescribed therapy for up to 8 weeks to meet the washout period for study entry, the investigator may switch the patient's medication to one that requires a shorter washout interval during the washout of the original medication (Table 7). Nonetheless, the investigator should adhere to the minimum washout period for all IOP-lowering medications as indicated in Table 7.

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 56 days.

Table 7 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 analogues, 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], etc)	longest minimum duration of any component based on medication class

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

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

8.3 Procedures for Final Study Entry

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

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

8.4 Visits and Associated Procedures

The following sections provide a list of procedures for each scheduled visit. Additional information on the examination procedures, equipment, and techniques for the measures listed in this section is presented in the Procedure Manual.

Ocular examination procedures should be performed in the order listed at each visit. Flexibility in procedure order is allowed, as indicated in the tables (Table 2, Table 3, Table 4, Table 5, and Table 6). Noncontact examinations may be performed at any time prior to gonioscopy (including before or after Hour 0 IOP). Intraocular pressure should be measured at approximately the same time of day at each visit. Hour 0 is defined as 8:00 AM ± 1 hour. All IOP measurements for a given visit day must be completed prior to performing any examination procedures that require pupil dilation.

Examiners performing IOP measurements should be masked to the patient's treatment group. Effort should be made to keep IOP examiners masked to the patient's other evaluation results.

8.4.1 Screening Visit

After informed consent and other documentation have been obtained (as described in Section 8.1.2), the procedures listed below are carried out. Intraocular pressure measurements must be performed in 1 day; however, other procedures (eg, postdilation and imaging procedures) may be performed on a different day as long as the screening procedures are completed within a 28-day period. Perform pupil dilation/diagnostic procedures after the completion of the final IOP measurement of the day or on a different day.

- Collection of demographic data
- Collection of medical and ophthalmic history
- Collection of adverse events
- Collection of concomitant medications and procedures
- Physical examination
- Vital signs (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.)
- **Best-corrected visual acuity**
- **Intraocular pressure measurement at Hour 0**
- **Non-contact examinations:** The following may be performed in any order, at any time before gonioscopy (including prior to Hour 0 IOP):
  - Visual field (Two visual field tests are required prior to the administration procedure. The first can be performed up to 10 months prior to or at Screening, and the second during the washout period or at the Baseline visit. For a given patient, the same test methodology must be used for fields that are historical as well as fields performed throughout the study.)
  - Specular microscopy
  - Anterior segment-optical coherence tomography
  - [redacted] Assessment will be repeated at Week 52 and Month 24/Exit and may be performed at any interim study visit at the discretion of the investigator.)
  - Biomicroscopy
- **Gonioscopy/angle assessment** (The examination at Screening will be independently performed by 2 ophthalmologists for eligibility purposes. Examination will also include, [redacted]
- Pachymetry (may be performed at any time after gonioscopy)
- **Pupil dilation** (Post-dilation examinations below may be performed in any order)
  - Dilated ophthalmoscopy
  - Optic disc examination

Eligibility is then determined and the interactive response system is contacted.

Washout may begin after Screening visit procedures have been completed and the Reading Center has confirmed central endothelial cell density (see Section 8.2 for a description of washout).

8.4.2 Baseline Visit

The Baseline visit occurs after the washout period has been completed. Baseline visit procedures, excluding IOP measurements (which must be performed in 1 day), can be performed over a 3-day period; all must be completed by the day before the administration day. Perform pupil dilation/diagnostic procedures after the completion of the final IOP measurement or on a different day.

- Collection of medical and ophthalmic history (confirmation)
- Collection of adverse events
- Collection of concomitant medications and procedures
- Completion of Visual Field Questionnaire-25 (VFQ-25)
- Vital signs (at rest ≥ 5 minutes)
- Pregnancy test for females of childbearing potential (as defined in Section 4.5.3)

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 (The examination may also include, [redacted]
- **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.)
- **Best-corrected visual acuity**
- **Intraocular pressure measurement at Hour 0**
- **Non-contact examinations**: The following may be performed in any order, at any time before Hour 8 IOP (including prior to Hour 0 IOP):
    - Macroscopic iris color assessment
    - Visual field (If dilation is required to perform this test, then the visual field test should be performed after the last IOP measurement of the day.)

  - Biomicroscopy (The examination may also include, [redacted])

- **Intraocular pressure measurements at Hours 2 and 8** (at selected sites in consenting patients)
- **Pupil dilation** (post-dilation examinations below may be performed in any order)
  - Dilated ophthalmoscopy
  - Optic disc examination

Determine eligibility and enter Hour 0 IOP into the interactive response system.

8.4.3 Treatment Period

8.4.3.1 Day 1 SLT Administration

The following procedures are performed on the day of SLT or Sham SLT administration:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Confirm eligibility
- Contact interactive response system for randomization (this contact may take place 1 day prior to the administration day, if needed)
- Preoperative IOP measurement (measurement does not need to be masked and only 1 measurement needs to be performed)
- Administer assigned study treatment (360° or Sham SLT; see details in Section 5.9.2)
- Postoperative biomicroscopy
- Postoperative IOP measurement (measurement does not need to be masked and only 1 measurement needs to be performed)

All patients must remain at the surgical facility for at least 1 hour for bilateral eye examination after 360° or Sham SLT administration.

Each patient will be supplied a bottle of topical NSAID eyedrops and instructions to use them 4 times daily for the next 3 days (including the day of the administration) in both eyes and to follow up as per protocol.

8.4.3.2 Day 2 (Phone Call)

On the day after study treatment administration, the patient will be contacted by telephone to collect the following:

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

If the patient reports symptoms or findings of concern in the Day 2 phone call (including but not limited to photophobia, blurred vision, eye pain, vitreous floaters), the investigator must bring the patient in for ophthalmic examination.

8.4.3.3 Day 4 (Bimatoprost SR Cycle 1 Administration)

The following procedures are performed on the day of Bimatoprost SR administration:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Contact interactive response system for kit allocation (this contact may take place 1 day prior to the administration day, if needed)
- Administer assigned study treatment (Bimatoprost SR or Sham Bimatoprost SR; see details in Section 5.9)
- Contact interactive response system to confirm kit assignment if applicable

All patients must remain at the surgical facility for bilateral eye examination at least 1 hour after Bimatoprost SR administration or sham administration procedure. For patients with sickle cell disease or trait (or other hemoglobinopathies), the investigator may perform optional biomicroscopy and measure IOP in both eyes 4 hours after the administration procedure as desired. This IOP examination is for postoperative purposes only, and as such does not require a masked, 2-person reading method. The IOP should be taken only once to avoid excessive postadministration (or sham administration) manipulation of the eye, and should be taken by the investigator (or other unmasked, qualified personnel). This postadministration (or sham administration) examination may be performed using a Goldmann applanation tonometer or a hand-held tonometer. See full procedure instructions in the Procedure Manual.

Each patient 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 both eyes and to follow up as per protocol.

8.4.3.4 Cycle 1: Day 2 (Cycle 1 Safety Visit)

The following procedures are performed on Cycle 1 Day 2:

- Collection of adverse events
- 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 (The examination may also include, [redacted])
  - Best-corrected visual acuity
- **Intraocular pressure measurement at Hour 0**
- **Non-contact examination:** The following may be performed at any time after the pre-Hour 0 examinations (including prior to Hour 0 IOP):
  - Biomicroscopy (The examination may also include, [redacted].)

8.4.3.5 Cycle 1: Day 4 and Week 2 (Cycle 1 Phone Calls)

On Cycle 1 Day 4 and Cycle 1 Week 2, the patient will be contacted by telephone to collect the following:

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

If the patient reports symptoms or findings of concern in the Day 4 or Week 2 phone call (including but not limited to photophobia, blurred vision, eye pain, vitreous floaters), the investigator must bring the patient in for ophthalmic examination.

8.4.3.6 Cycle 1: Weeks 4, 8, 12, and 15

The following procedures are performed at Weeks 4 (±4 days), 8 (± 4 days), 12 (±4 days), and 15 (±4 days):

- Collection of adverse events
- 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 (The examination may also include, [redacted].)
  - Best-corrected visual acuity
- **Intraocular pressure measurement at Hour 0**
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy (including prior to Hour 0 IOP):
  - Macroscopic iris color assessment (Weeks 4 and 12 only)
  - Manifest refraction (Week 12 only)
  - Specular microscopy (Weeks 4 and 12 only)
  - Biomicroscopy (The examination may also include, [redacted].)
- **Intraocular pressure measurement at Hours 2 and 8** (at selected sites in consenting patients; Week 12 only)
- **Gonioscopy/angle assessment** (The examination will also include, [redacted]. Perform gonioscopy at least 2 hours prior to H8 IOP measurement at Week 12.)
- Pachymetry (may be done any time after gonioscopy; Weeks 4 and 12 only)
- **Pupil dilation** (Week 12 only) (post dilation examinations below may be performed in any order)
  - Dilated ophthalmoscopy (Week 12 only)
  - Optic disc examination (Week 12 only)

8.4.3.7 Bimatoprost SR Cycle 2 Day 1 Administration

The following procedures are performed at Week 16 (-2/+4 days) for all patients who meet retreatment criteria.

Patients who do not receive Cycle 2 administration at Week 16 will not attend the Cycle 2 Administration Day visit on Week 16, or the Day 2 Safety or Day 4 and Week 2 phone calls associated with administration at Week 16. For those patients not meeting retreatment criteria at Week 16, Cycle 2 may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met; in this case, inadequate control of IOP should be confirmed at another scheduled or unscheduled visit prior to initiation of Cycle 2. For patients who begin Cycle 2 after Week 16 and before Month 12, the Cycle 2 visits (Administration Day, Day 2 Safety Visit, and Day 4 and Week 2 Phone Calls) will apply at the time that Cycle 2 occurs. Regardless of the timing of Cycle 2, all regularly scheduled visits should be completed. Cycle 2 should be scheduled such that the Administration Day and the Day 2 Safety Visit do not occur on the day of a regularly scheduled study visit. However, if the Cycle 2 Day 4 or Week 2 Phone Calls overlap with a regularly scheduled visit, perform the regularly scheduled visit.

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Contact interactive response system for kit allocation (this contact may take place 1 day prior to the Cycle 2 administration day, if needed)
- Administer assigned study treatment
- Contact interactive response system to confirm kit assignment if applicable

All patients must remain at the surgical facility for bilateral eye examination at least 1 hour after Bimatoprost SR administration or sham administration procedure. For patients with sickle cell disease or trait (or other hemoglobinopathies), the investigator may perform optional biomicroscopy and measure IOP in both eyes 4 hours after the administration procedure as desired. This IOP examination is for postoperative purposes only, and as such does not require a masked, 2-person reading method. The IOP should be taken only once to avoid excessive postadministration (or sham administration) manipulation of the eye, and should be taken by the investigator (or other unmasked, qualified personnel). This postadministration (or sham administration) examination may be performed using a Goldmann applanation tonometer or a hand-held tonometer. See full procedure instructions in the Procedure Manual.

8.4.3.8 Cycle 2: Day 2 (Cycle 2 Safety Visit)

The following procedures are performed on Cycle 2 Day 2:

- Collection of adverse events
- 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**:
  - Macroscopic conjunctival hyperemia assessment (The examination may also include, [redacted])
  - Best-corrected visual acuity
- **Intraocular pressure measurement at Hour 0**
- **Non-contact examination:** The following may be performed at any time after the pre-Hour 0 examinations (including prior to Hour 0 IOP):
  - Biomicroscopy (The examination may also include, [redacted])

8.4.3.9 Cycle 2: Day 4 and Week 2 (Cycle 2 Phone Calls)

On Cycle 2 Day 4 and Cycle 2 Week 2, the patient will be contacted by telephone to collect the following:

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

If the patient reports symptoms or findings of concern in the Day 4 or Week 2 phone call (including but not limited to photophobia, blurred vision, eye pain, vitreous floaters), the investigator must bring the patient in for ophthalmic examination.

8.4.3.10 Weeks 20, 24, 28, and 31

The following procedures are performed at Weeks 20 (± 4 days), 24 (±4 days), 28 (± 4 days), and 31 (± 4 days):

- Collection of adverse events
- 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:**
  - Macroscopic conjunctival hyperemia assessment (The examination may also include, [redacted])
  - Best-corrected visual acuity
- **Intraocular pressure measurement at Hour 0**
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy (including prior to Hour 0 IOP):
  - Macroscopic iris color assessment (Week 24 only)
  - Manifest refraction (Week 24 only)
  - Visual field (If dilation is required to perform this test, then the visual field test should be performed after the last IOP measurement of the day.) (Week 24 only)
  - Specular microscopy (Week 24 only)
  - Biomicroscopy (The examination may also include, [redacted])
- **Intraocular pressure measurement at Hours 2 and 8** (at selected sites in consenting patients; Week 24 only)
- **Gonioscopy/angle assessment** (The examination will also include, [redacted])
- Pachymetry (Week 24 only) (may be done any time after gonioscopy)
- **Pupil dilation** (may perform post-dilation eye exams in any order; Week 24 only)
  - Dilated ophthalmoscopy (Week 24 only)
  - Optic disc examination (Week 24 only)

8.4.3.11 Weeks 36, 40, 44, 47, and 52; and Months 13, 14, 15, 16, 18, 20, 22, and 24/Exit

The following procedures are performed at Weeks 36 (± 4 days), 40 (± 4 days), 44 (± 4 days), 47 (± 4 days), and 52 (± 4 days) and Months 13 (± 4 days), 14 (± 4 days), 15 (± 4 days), 16 (± 4 days), 18 (± 7 days), 20 (± 7 days), 22 (± 7 days), and 24/Exit (± 7 days).

Patients who receive the second administration of Bimatoprost SR at Week 16 and patients who never receive a second administration may, at the investigator's discretion, skip the visits at Months 13, 15 and 22 if the patient has received nonstudy IOP lowering medication in both eyes; has ≤ 25% of each implant remaining in the eye; and in the investigator's clinical judgment, has no safety or other concern that would require the patient to attend these visits. Please note: as described in Section 4.5.2, each eye should be evaluated on an individual basis when determining the need for additional nonstudy IOP-lowering treatments; initiation of treatment in one eye should not automatically lead to initiation of treatment in the contralateral eye.

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Pregnancy test for females of childbearing potential (as defined in Section 4.5.3) (Month 24/Exit only)

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 (The examination will also include, [redacted] may be performed at interim visits for appearance of or increase/decrease in hyperemia.)
  - Best-corrected visual acuity
- **Intraocular pressure measurement at Hour 0**
- **Non-contact examinations:** The following may be performed in any order, at any time before gonioscopy (including prior to Hour 0 IOP)**:**
  - Macroscopic iris color assessment (Week 52 and Months 18 and 24/Exit only)
  - Manifest refraction (Week 52 and Months 18 and 24/Exit only)

  - Visual field (If dilation is required to perform this test, then the visual field test should be performed after the last IOP measurement of the day.) (Week 52 and Months 18 and 24/Exit only)
  - Specular microscopy (Weeks 40 and 52 and Months 16, 20, and 24/Exit only)
  - [redacted] (at Week 52 and Month 24/Exit at selected sites in both eyes of all consenting patients who underwent assessment at Screening; may be done at interim visits at the discretion of the investigator. Perform any contact assessments following IOP measurements.)
  - Biomicroscopy (The examination will also include, [redacted] may be performed at interim visits for appearance of or increase/decrease in hyperemia.)
- **Gonioscopy/angle assessment** (The examination will also include, [redacted])
- Pachymetry (Weeks 40 and 52 and Months 16, 20, and 24/Exit only) (may be done any time after gonioscopy)
- **Pupil dilation** (Weeks 40 and 52 and Months 16, 20, and 24/Exit only) (post dilation exams below may be performed in any order)
  - Dilated ophthalmoscopy (Weeks 40 and 52 and Months 16, 20, and 24/Exit only)
  - Optic disc examination (Weeks 40 and 52 and Months 16, 20, and 24/Exit only)
- Contact interactive response system at Month 24/Exit to report patient's exit status

8.5 End of Study

The end of the clinical phase of the study will be considered achieved when last patient has completed his or her last study visit.

8.6 Instructions for the Patients

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

Instruction should be given to the patient to maintain a stable dose of any concomitant medication used chronically, or any new medications initiated during the study whenever possible. Patients should be instructed to communicate any changes to their medication at

their next study visit. Patients should also be reminded to contact the study site if they are experiencing any difficulties during their study participation.

Patients should be instructed to remove their contact lenses before instillation of any topical ophthalmic medication, and to keep contact lenses out for at least 15 minutes after instillation of eye drops.

8.7 Unscheduled Visits

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

8.8 Compliance with Protocol

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

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

8.9 Early Discontinuation (Early Exit) of Patients

Patients may voluntarily withdraw from the study at any time.

Patients who have received nonstudy IOP-lowering medication in one or both eyes, or who do not undergo Cycle 2 administration, will be followed for the duration of the study through the Month 24/Exit visit. If the implant has been removed, the patient may discontinue the study if based on investigator assessment the eye is in stable condition, at which time they should complete the Month 24/Exit visit procedures.

Notification of early patient 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.

When patients discontinue before Month 24/Exit, the site should complete all procedures for the Month 24/Exit visit at the patient's last visit.

8.10 Withdrawal Criteria

After the first administration (or Sham), failure to undergo an Administration Day visit does not indicate total withdrawal from the study. Patients who have received nonstudy IOP-lowering treatment in one or both eyes, or who do not undergo Cycle 2 administration, will continue through the duration of the study.

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

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

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

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

8.11 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification. In the event that the study is stopped, patients will be followed for 16 weeks after their last Bimatoprost SR (or Sham) administration, after which they will return to standard of care as per the investigator's discretion.

9. Adverse Events

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

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This definition includes events related to the medical (investigational) product (Bimatoprost SR implant and applicator combination) or comparator medical device (SLT), and events related to the procedures involved, and also includes any malfunction or deterioration in the characteristics and/or performance of a device. During the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

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

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

IOP return to baseline following the cessation of the Bimatoprost SR treatment effect should not be considered an adverse event.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, nondirected question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a

congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

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

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

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

9.1.3 Severity

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

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

9.1.4 Relationship to Study Drug, Device, or Procedure

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

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

Note: A study procedure occurring during the screening/baseline period can include a washout of medication or study required diagnostic procedure.

9.2 Procedures for Reporting Adverse Events

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

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

9.3 Procedures for Reporting a Serious Adverse Event

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

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

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and Study Contacts Page.

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

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

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

9.4 Procedures for Unmasking of Study Treatment

The primary investigator and select site staff (eg, study coordinator) are unmasked. When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient and/or other site personnel.

When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unmasking the patient and/or other site personnel. In instances where this is not possible, the sponsor should be notified as soon as possible thereafter.

The reason for unmasking the patient and/or other site personnel must be recorded in the patient's source documents.

10. Administrative Items

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

10.1 Protection of Human Patients

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

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

signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

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

10.1.2 Compliance With IRB or IEC Regulations

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

10.1.3 Compliance With Good Clinical Practice

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

10.1.4 Quality Assurance

Compliance with the ethical and scientific ICH GCP quality standard, along with Allergan SOPs, on the design, conduct, recording, and reporting of clinical trials provides protection for the wellbeing and rights of patients as well as assuring the quality and credibility of the clinical trial data. Quality Control activities will be undertaken within the quality assurance system to verify that the requirements for the quality of trial-related activities have been fulfilled.

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

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

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the

IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

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

10.3.1 Patient Privacy

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

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

10.4 Documentation

10.4.1 Source Documents

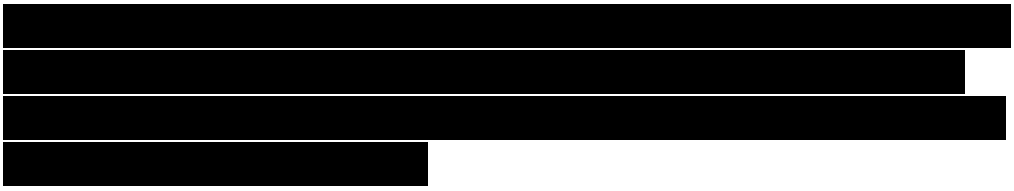
Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- Patient's name
- Patient's contact information

- The date that the patient entered the study, patient number, and patient medication kit number.
- The study title and/or the protocol number of the study and the name of Allergan.
- A statement that informed consent was obtained (including the date). A statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date).
- Dates of all patient visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any adverse events (including any procedure-related adverse events due to complications)
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation.
- The results of laboratory tests performed by the site (eg, blood chemistry and hematology, urinalysis, and pregnancy tests)
- Key study variables

  Documentation of the patient's medical history
  Vital signs, physical examination findings
  IOP and ophthalmic examination findings
  Dates of SLT or Sham SLT administration procedure
  Dates of Bimatoprost SR or Sham administration procedure
  Documentation of whether any procedure including study treatment administration was performed according to the protocol, noting any deviations (if applicable)



Source documentation practices must follow Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and ALCOA, ie, records must be Attributable, Legible, Contemporaneous, Original, and Accurate.

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

10.4.3 Study Summary

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

10.4.4 Retention of Documentation

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

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

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

10.5.1 Labeling/Packaging

Packaged and labeled study medication will be supplied by Allergan.

The assembled Bimatoprost SR (or Sham applicator) is individually packaged into a laminated foil pouch with desiccant and sealed. The entire foil pouch package is terminally sterilized. Each pouch will be placed into its own carton. The medication will be identified as an investigational product. The study number and medication kit number will be identified on the medication labels.

The study medication contents are described in Section 5.1 and Section 5.2.

10.5.2 Clinical Supply Inventory

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

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

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction. Used applicators will be disposed of immediately in a sharps container.

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

10.6 Monitoring by the Sponsor

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

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

10.7 Handling of Biological Specimens

Laboratory specimens for blood chemistry panel, hematology including complete blood count with differential, and urinalysis will be sent to a centralized clinical laboratory or a designated regional facility with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification) to be assayed using validated methods. All blood and urine samples will be stored at the centralized clinical laboratory following testing, and will be discarded after a time period indicated by Allergan. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.

See the Covance Laboratory Manual and the Procedure Manual for procedural details.

10.8 Publications

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

10.9 Coordinating Investigator

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

10.10 [redacted]

11. References

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12. Attachments

Not applicable

12.1 Glossary of Abbreviations

Term/Abbreviation	Definition
ABMD	Anterior Basement Membrane Disease
AC	anterior chamber
AGIS	Advanced Glaucoma Intervention Study
ALT	argon laser trabeculoplasty
ANCOVA	analysis of covariance
ARMD	Age-related macular degeneration
ASC	Ambulatory Surgical Center
BLQ	below the limit of quantitation
bpm	beats per minute
CFR	Code of Federal Regulations
CI	confidence interval
DMEK	Descemet's Membrane Endothelial Keratoplasty
DSEK	Descemet's Stripping Endothelial Keratoplasty
eCRF	electronic case report form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
H	hour
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IOL	intraocular lens
IOP	intraocular pressure
IRB	institutional review board
ITT	intent-to-treat
LOCF	last observation carried forward
LT	laser trabeculoplasty

Term/Abbreviation	Definition
MDF	Map-Dot-Fingerprint
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	mixed effect model for repeated measures
NSAID	nonsteroidal anti-inflammatory drug
OAG	open-angle glaucoma
OHT	ocular hypertension
OU	both eyes
PAS	peripheral anterior synechiae
PLA	polylactic acid
PLGA	polylactic-*co*-glycolic acid
POAG	primary open-angle glaucoma
PP	per protocol
RBC	red blood cell
SC/T	patients with sickle cell disease or trait or other hemoglobinopathies
SLT	selective laser trabeculoplasty
SOC	system organ class
SOP	standard operating procedures
SR	sustained release
US	United States
WBC	white blood cell
WOCF	worst (postrandomization) observation carried forward
X	perform procedure