Title Page

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

Protocol Number: 1698-304-007

Product: Bimatoprost SR

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

Study Phase: 3b

Sponsor Name: Allergan (North America),

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SAP Version History

This Statistical Analysis Plan (SAP) for study 1698-304-007 is based on the protocol dated 20DEC2019.

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1			Original version

1. Introduction

This SAP provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in the study protocol 1698-304-007 of the Phase 3b study of the 24-Hour IOP-lowering effect of Bimatoprost SR in participants with open-angle glaucoma (OAG) or ocular hypertension (OHT).

1.1. Study Objectives

The purpose of this study is to obtain data on the 24-hour IOP lowering effect at Week 8 of Bimatoprost SR treatment, with safety assessed until Month 12. Each study objective is presented below with associated information.

Table 1-1 Study Objectives and Corresponding Endpoints

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

1.2. Study Design

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

1.2.1. Intervention Group and Study Duration

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

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

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

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

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

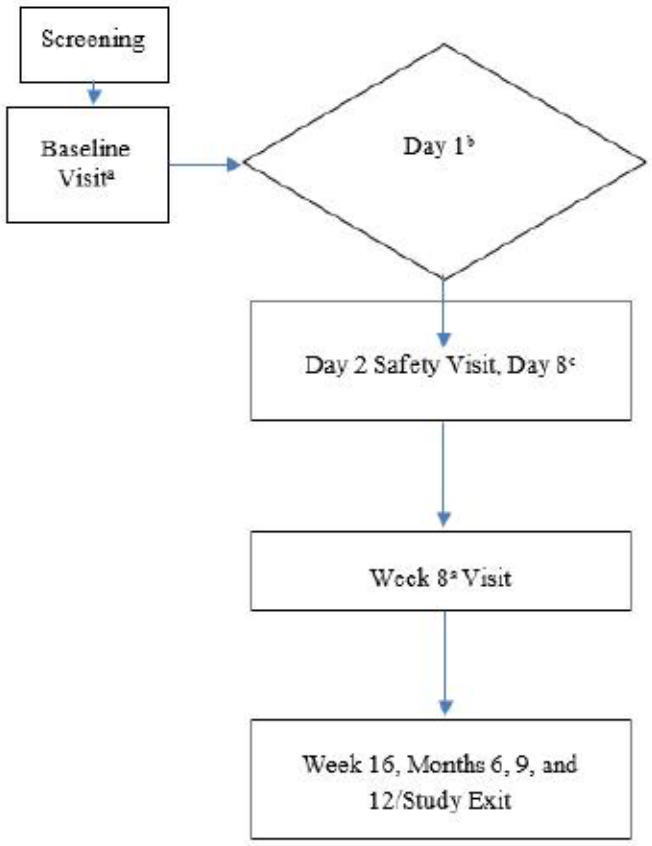
Participants who complete all regularly scheduled study visits should have 9 study office visits, 2 sleep lab visits, and 1 phone call. The schedule includes the following:

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

1.2.2. Schema

The study schema is presented in Figure 1–1.

Figure 1–1 Study Schema



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

1.2.3. Schedule of Activities (SoA)

Table 1-2 Schedule of Activities – Screening through Week 8

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

Visit	Screening		Baseline		Day 1	Day 2 Safety Visit	Day 8 Phone Call	Week 8	
			Office Visit	Sleep Lab Visit[d]				Office Visit	Sleep Lab Visit[d]
Visit Windows	**Up to 60 days[a]**		**-7 days from Sleep Lab Visit[c]**				**+14 days**	**-7 days from Sleep Lab Visit[c]**	**± 7 days**
Determination of Eligibility	X		X						
Contact IWRS[k]	X		X		X				
24-Hour IOP Measurements[l]				OU					OU
Study Treatment[m]					SE				

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 1-3 Schedule of Activities – Week 16 through Month 12/Study Exit

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

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

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

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

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

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

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

1.2.4. End of Study Definition

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

A participant assigned and treated with Bimatoprost SR is considered to have completed the study if he/she has completed all visits of the study to Month 12. At the Month 12/Study Exit visit, if the investigator determines that any safety concerns warrant participant follow-up, the participant may be followed post exit until safety concerns are resolved based on the investigator's discretion. Participants assigned and treated with LUMIGAN 0.01% may early

exit the study after completion of the Week 8 Sleep Lab visit, if there are no safety concerns in the opinion of the investigator. For the LUMIGAN cohort, an exit visit will be performed after the Week 8 Sleep Lab visit where all assessments scheduled for the Month 12/Study Exit visit will be performed.

2. Statistical Hypotheses

There are no statistical hypotheses for this study.

3. Sample Size Determination

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

Twenty-five to 30 participants will be enrolled in the Bimatoprost SR cohort to achieve a minimum total of 20 evaluable participants, defined as participants with sufficient data at baseline and Week 8 to evaluate the 24-hour IOP-lowering effect of Bimatoprost SR. This assumes a premature discontinuation rate of up to 33%. Participants who prematurely discontinue from the study will not be replaced. Participants will be assigned to the Bimatoprost SR or LUMIGAN 0.01% cohort [redacted].

4. Populations for Analysis

4.1. Safety Analysis Set (SAF)

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

4.2. Full Analysis Set (FAS)

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

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

5. Statistical Analyses

5.1. General Considerations

Two database locks are planned for this study. The first database lock (referred to as primary DBL), for the primary and secondary efficacy endpoint analysis, will occur when 100% of participants have completed the primary visit (ie, Week 8 Sleep Lab visit) or prematurely discontinued prior to the Week 8 Sleep Lab visit. Similarly, the second database lock (referred to as final DBL) for the full study database will occur after all participants have completed the study at Month 12 or prematurely discontinued from the study. Analyses will be performed after each lock and this SAP will cover both primary and final analysis.

5.1.1. Statistical Notation and Presentation

Continuous variables will be summarized by cohort (Bimatoprost SR or LUMIGAN 0.01%) for number of participants, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of participants within each treatment cohort.

All statistical analyses will be performed using Statistical Analysis Software (SAS®) version 9.4.

5.2. Participant Disposition

Number of participants screened for the study will be provided. Counts of the participants in the two analysis populations will be summarized by treatment cohorts. The number and percentages of participants who completed or discontinued from the study in the eCRF open label form, as well as the discontinuation reasons, will be summarized by treatment cohorts.

5.3. Efficacy Analysis

The efficacy analyses will be based on the FAS population. Data handling conventions are described in Section 6.3 Appendix 3.

Time-matched IOP will be collected at 12 timepoints across the 24-hour period (08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00, 00:00, 02:00, 04:00 and 06:00). The diurnal IOP will be collected between 08:00 to 22:00 and the nocturnal IOP will be collected between 00:00 and 06:00. The diurnal IOP will be performed in supine and sitting positions while the nocturnal IOP will be performed only in a supine position. The primary and secondary efficacy analysis will be performed based on the habitual IOP (the diurnal IOP in a sitting position and the nocturnal IOP in a supine position).

Hour 0 IOP examinations will be scheduled at 08:00 ± 1 hour and all Hour 0 IOP examinations will be performed with the participants in a sitting position.

5.3.1. Analysis Endpoint(s)

- The primary efficacy endpoint is the time-matched IOP change from baseline at the Week 8 Sleep Lab visit from the 24-hour IOP data collected at the Baseline Sleep Lab visit in the study eye for the Bimatoprost SR cohort.
- The secondary efficacy endpoint is the change from baseline in range of IOP in eyes treated with Bimatoprost SR at Week 8 Sleep Lab visit.
- Other efficacy endpoints include:
  - Time-matched IOP change from baseline in a supine position.
  - Hour 0 IOP change from baseline through Month 12.
  - Time to initial use of nonstudy IOP-lowering treatment.

Refer to Section 6.3 Appendix 3 for details on IOP measurement conventions and corresponding time windows.

5.3.2. Primary Efficacy Analyses

The habitual IOP values at various hours of the Baseline Sleep Lab visit will be considered as the time-matched baseline values for the corresponding timepoints of Week 8 Sleep Lab visit. For example, the habitual IOP time-matched change from baseline at timepoint 06:00 of Week 8 Sleep Lab visit will be calculated as: habitual IOP at timepoint 06:00 of Week 8 Sleep Lab visit – habitual IOP at timepoint 06:00 of Baseline Sleep Lab visit.

The habitual IOP raw values and the corresponding time-matched change from baseline in habitual IOP will be summarized descriptively by visit and by timepoint for the study eye in the Bimatoprost SR and Lumigan 0.01% cohorts as well as for the fellow eye in the pooled treatment cohorts. Ninety-five percent CIs based on a paired t-test statistic will be provided for the mean time-matched habitual IOP change from baseline at 12 timepoints across the 24-hour period for the study eye in the Bimatoprost SR cohort.

The mean habitual IOP and the mean time-matched habitual IOP change from baseline across the 24-hour period will be presented graphically with the timepoint of IOP measurements on the x-axis for the study eye in the Bimatoprost SR cohort. The diurnal/wake period and nocturnal/sleep period within the 24-hour measurement period will be clearly marked in the figure.

5.3.3. Secondary Efficacy Analyses

The habitual IOP fluctuation will be evaluated by the range of habitual IOP values for each participant collected from the Sleep Lab visit during diurnal/wake period and nocturnal/sleep period, as well as over a 24-hour period in the Bimatoprost SR and Lumigan 0.01% cohorts. Descriptive summary statistics on the analysis variable (range of IOP) at baseline and Week 8, as well as its corresponding changes from baseline at Week 8, will be presented by treatment cohorts for the study eye and the pooled treatment cohorts for the fellow eye. The same analysis will be performed for the IOP in a supine position.

5.3.4. Other Efficacy Analyses

Other efficacy analyses will include IOP analysis by body positions, time-to-event of the initial use of nonstudy IOP-lowering treatment and Hour 0 IOP analysis in a sitting position.

5.3.4.1. IOP Analysis by Body Positions

The same analysis of the habitual IOP analysis will be performed for the IOP in a supine position for the study eye in Bimatoprost SR and Lumigan 0.01% cohorts as well as for the fellow eye in the pooled treatment cohorts. For the diurnal IOP, the mean difference of time-matched IOP between sitting and supine positions will be summarized.

For IOP in a supine position, the mean IOP and the mean time-matched IOP change from baseline across the 24-hour period will be presented graphically.

5.3.4.2. Time-to-Event Analysis

Time to the event of the initial use of nonstudy rescue IOP lowering treatment (medication and/or procedure) in the study eye from the date of Bimatoprost SR treatment will be estimated using Kaplan-Meier (KM) method with graphical display.

Time to initial use of nonstudy rescue IOP lowering treatment = (Date of initial use of non-study IOP-lowering treatment – Date of the Bimatoprost treatment) + 1.

In the calculation of time to initial use of nonstudy rescue IOP lowering treatment, if a participant did not use any nonstudy rescue IOP lowering treatment in the study eye, then the event (initial use of nonstudy rescue IOP lowering treatment) time will be censored at the study exit date or the last visit date if the study exit date is not available.

5.3.4.3. Hour 0 IOP Analyses

The descriptive summary for Hour 0 IOP values in a sitting position at baseline with corresponding change from baseline by visit through Month 12/Study Exit will be performed by treatment cohorts for the study eye in Bimatoprost SR and Lumigan 0.01% cohorts and pooled treatment cohorts for the fellow eye. The mean of the Hour 0 IOP and the Hour 0 IOP change from baseline for each visit will be presented graphically for the study eye in the Bimatoprost SR cohort.

5.4. Safety Analysis

Descriptive statistics will be used to summarize the safety data by cohorts based on the SAF. The safety parameters will include the following non-ocular safety parameters: non-ocular AEs and vital signs; ocular safety parameters: visual field examination, visual acuity, macroscopic conjunctival hyperemia assessment, biomicroscopy, dilated ophthalmoscopy (including optic disc assessment), pachymetry, gonioscopy (including angle assessment), and specular microscopy. Results from ocular safety assessments will be summarized by participants and listed, including scheduled and unscheduled assessments (if any). The results will be presented by treatment cohorts for the study eye and pooled treatment cohorts for the fellow eye. Unless

otherwise stated, the last nonmissing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety parameter.

5.4.1. Study Duration

The study treatment duration will be calculated as the number of days between the study exit date and Day 1 treatment administration day, inclusively (date of study exit or last visit available – Day 1 + 1).

5.4.2. Adverse Events (AEs)

Adverse Events will be coded using the MedDRA.

An AE is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment, whether or not considered related to the study treatment. An AE will be considered a treatment emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first administration of study treatment. An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any SAE criterion.

Adverse events will be classified into ocular AEs and non-ocular AEs. An ocular AE will be determined by the location information on the adverse event page in eCRF and thus are not limited to AEs with primary SOCs of eyes. Additionally, questions about adverse event relationships to study treatment and study administration procedure will be asked in eCRF, and the answers to these questions will be used together to derive the treatment related TEAE.

Ocular AEs will be tabulated by treatment cohorts for the study eye and pooled treatment cohorts for the fellow eye, and non-ocular AEs will be summarized by treatment cohorts for participants.

Overall summaries of adverse events will be provided on a per-participant basis by treatment cohorts for categories including the following:

- All TEAEs
- Treatment-related TEAEs
  - Related to study drug
  - Related to study drug administration procedure
- All serious TEAEs
- Treatment-related serious TEAEs
  - Related to study drug
  - Related to study drug administration procedure
- Any TEAE leading to Bimatoprost SR implant removal
- Any TEAE leading to study discontinuation
- Deaths

Any non-ocular TEAEs will be summarized by the primary SOC,PT, and severity including serious TEAEs by the primary SOC and PT, treatment related by SOC and PT and those leading to study discontinuation by the primary SOC and PT.

For incidences of treatment emergent ocular adverse events, summaries will be provided for the following categories:

- Any ocular TEAEs by SOC, PT, and severity
- Any treatment related ocular TEAEs by SOC and PT
- Any serious ocular TEAEs by SOC and PT
- Any ocular TEAEs leading to study discontinuation by SOC and PT
- Any ocular TEAEs resulting in Bimatoprost SR implant removal by PT
- Any corneal TEAEs of interest by PT (Related AEs of interest will be identified separately prior to database lock.)
- Any anterior segment inflammation TEAEs of interest by SOC and PT (Related AEs of interest will be identified separately prior to database lock.)

5.4.3. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) will be collected, but not analyzed.

5.4.4. Clinical Safety Laboratory Assessment

Laboratory assessments (blood and urine samples) will be collected at the Screening visit, but will not be analyzed.

5.4.5. Pregnancy Test

Pregnancy test will be performed but will not be analyzed.

5.4.6. Additional Safety Assessments

5.4.6.1. Best Correct Visual Acuity

Visual acuity tests will be performed at all visits except on Day 1 and at the Sleep Lab visits. Best corrected visual acuity (BCVA) is recorded in Snellen equivalent units on eCRF as 20/8, 20/10, 20/12.5, 20/16 ... or 20/800. An increase in the second number (denominator) in Snellen equivalent unit indicates worsening of visual acuity (VA) and a decrease indicates an improvement. For example, change from 20/32 to 20/40 is a worsening of VA by one line, 20/32 to 20/20 (note that 20/25 is in between) is an improvement by 2 lines.

The line change from baseline at each post-baseline evaluation can be calculated using the formula:

$$Line\ Change = 10\ \times [log_{10}\left(\frac{d_{BL}}{d_{PBL}}\right)]$$

where d_{BL}= denominator of the Snellen equivalent unit at baseline,

d_{PBL}= denominator of the Snellen equivalent unit at post-baseline.

The logarithmic value in the formula above needs to be rounded to the nearest tenth before proceeding to the calculation of the line change. A positive value indicates an improvement, a negative value indicates a worsening, and a zero indicates no change. For example, the line change for a Snellen equivalent unit at baseline of 20/25 followed by a Snellen equivalent unit of 20/80 at a post-baseline visit would be:

$$Line\ Change = 10\ \times \left[log_{10}\left(\frac{25}{80}\right)\right] = 10 \times (-0.5) = \ -5$$

representing a worsening of 5 lines in VA. Note that there are 4 Snellen equivalent units (20/32, 20/40, 20/50 and 20/63) between 20/25 and 20/80, thus moving from 20/25 to 20/80 is a worsening by 5 lines in VA because the denominator has increased.

The greatest line change in BCVA from baseline will be summarized with respect to number of line change categories. Categories will be summarized as change < -2, -2 ≤ change ≤ 2, and change > 2. The number and percentage of participant in each category will be presented by treatment cohorts.

5.4.6.2. Visual Field

Visual field examinations will be assessed by automated perimetry (using either Humphrey 24-2 full threshold program or 24-2 SITA Standard, or Octopus G1 or 24-2 and dynamic or normal strategy) at Screening, Baseline, Month 6, and Month 12/Exit. The same test methodology should be used throughout the entire study for a given participant. Visual field overall results will be recorded on the eCRF as normal or abnormal. Abnormal findings include enlargement of blind spot, superior arcuate scotoma, interior arcuate scotoma, paracentral scotoma, nasal step, central scotoma, generalized depression, and temporal scotoma and other. An eye may exhibit multiple abnormalities. Any post-baseline abnormal findings on visual field will be summarized by eye and by visit regardless of the machine type using number and percentage format to calculate incidences.

In addition, mean deviation or mean defect (MD) and change from baseline will also be recorded in decibels (dB), and will be analyzed by visit by machine type (Humphrey and Octopus respectively). If the machine type is different between baseline and post baseline visit, no change from baseline will be derived. If machine type is missing at post-baseline, but available at baseline, then it will be assumed using same machine type. For participants whose visual field were assessed by one machine type as recorded, the mean deviation or mean defect assessment with missing machine type will be imputed as assessments by the corresponding unique machine type.

5.4.6.3. Macroscopic Conjunctival Hyperemia

Macroscopic conjunctival hyperemia assessment will be performed at all scheduled visits except on the administration day. Conjunctival hyperemia severity is assessed as 0 (None), +0.5 (Trace), +1 (Mild), +2 (Moderate), +3 (Severe) or 'Not Evaluable.' These data will be summarized overall by treatment cohort and associated eye using the worst severity of hyperemia observed.

In addition, worst severity grade increases greater than 1 (worsening ie, a change from 0 to 2 and above, from 0.5 to 2 and above, or from 1 to 3 and above) in hyperemia from baseline will also be summarized overall and by treatment cohort. If the worst severity grade during a period is less severe compared to baseline, it will be considered as 'no increase.'

5.4.6.4. Specular Microscopy

Central endothelial cell density (CECD) mean (cells/mm^2) will be assessed using specular microscopy performed on the central cornea at Screening, Baseline, Week 16, Month 6, Month 9 and Month 12/Exit. At each examination, 3 measurements of CECD will be reported, and the average of the 3 measurements will be calculated and used for analysis. CECD at baseline and raw values and their changes from baseline will be summarized descriptively by visit and for last visit by treatment cohorts.

Note that the same model of the specular microscopy machine must be used for all patient visits. If a different model is used at post-baseline visit, the data will be excluded from the analysis.

The number and percentage of participants will be tabulated by loss categories for each visit, including the last visit (ie, last assessment), and during the entire study, eg, 15% loss (percent change from baseline $\leq$ -15%). The last visit of a participant for final analysis is defined as the assessment at exit visit (ie, the last assessment during the study).

By visit tabulation will be based on the analysis value. A participant will be counted in a loss category for the entire study if any assessment during the study meeting the criteria. The loss categories are listed but not limited to the below:

- Percent change from baseline > -10%
- Percent change from baseline $\leq$ -10%
- Percent change from baseline $\leq$ -15%
- Percent change from baseline $\leq$ -20%
- Percent change from baseline $\leq$ -30%
- Percent change from baseline $\leq$ -40%
- Percent change from baseline $\leq$ -50%

A listing of patients with $\geq$ 20% CECD loss will be provided.

5.4.6.5. Pachymetry

Corneal thickness using contact pachymetry will be performed on the central cornea at Screening, Baseline, Week 16, Month 6, Month 9 and Month 12/Exit visits. At each examination, 3 measurements of central corneal thickness (CCT) and associated standard deviation will be reported, and the average of the 3 measurements will be calculated and used for analysis. CCT raw values and their changes from baseline at each post-baseline visit will be summarized descriptively by visit and by treatment cohorts.

5.4.6.6. Biomicroscopy and Dilated Ophthalmoscopy

Biomicroscopic examinations will be performed for each eye at baseline and post-baseline visits. All findings will be coded using MedDRA dictionary.

Number and percentage of participants with findings showing more than one grade increase in severity from baseline or a positive status change, at 1 or more post-baseline visits, will be presented by coded PT in descending order of incidence rate. For findings that are associated with a severity grade, more than 1 severity grade increase in severity from baseline is defined as a change from no finding to 2 and above, from 0.5 to 2 and above, or from 1 to 3 and above from baseline at any of the follow-up visits. Number and percentage of participants with findings that not associated with a severity grade, a positive status change is defined as a finding present at post-baseline which did not present at baseline will be summarized.

Change from baseline in severity grade for gradable findings and status change from baseline for non-gradable findings will be derived at each post-baseline visits. The method to compare with baseline will be by eye, eye area, finding and MedDRA PT. When conducting comparison from baseline, "Other" is consider as a specific finding itself that is different from findings under any pre-defined terms. If the same PT appears under a pre-defined finding and "Other" within the same eye and eye area, they will be compared with baseline separately.

Dilated ophthalmoscopy including vitreous, macula, retina periphery, lens status and opacification and optic nerve will be performed at Screening, Baseline and Month 12/Exit visits. No severity grade will be assigned for vitreous, retina periphery and macula findings, and summarized together with biomicroscopy findings as non-gradable findings.

5.4.6.6.1. Optic Disc Examination

Optic Nerve cup/disc ratio will be evaluated using a 0.0 to 1.0 scale, with larger values indicating glaucoma or other pathologies, thus a reduction from baseline is considered an improvement. Categorical changes in cup/disc ratio from baseline will be summarized for post-Baseline visit. Change from baseline at the follow-up visit (visit value –baseline values) will be categorized as an improvement of 0.2 or more ($\leq$ -0.2), no change -between 0.2 and -0.2 ($>$ -0.2 to $<$ 0.2), or a worsening if the ratio increases by 0.2 or more (ie, change $\geq$ 0.2). The number and percentage of participants in each category will be provided for treatment cohorts.

5.4.6.6.2. Lens Status and Opacification

At follow-up visits, the lens opacity will be assessed only for eyes evaluated as phakic at baseline. The presence and severity of nuclear, cortical, and posterior subcapsular cataract lens

opacities using a 3-point scale (< standard photo #2, and ≥ standard photo #2) will be summarized by treatment cohorts and by visit.

5.4.6.7. Gonioscopy and Bimatoprost SR Implant Assessment

Gonioscopy will be performed to assess the inferior iridocorneal (anterior chamber) angle. Participants presenting with peripheral anterior synechiae on gonioscopy at any time during the study will be presented in a listing with the time in which it occurred.

Number and percentage of participants with an implant visible during the study will be summarized in a tabular format further breaking down by the categorical percentage visible of the implant. Also, the number and percentage of participants who have an implant in contact with corneal endothelium at any visit will be summarized. Implant assessment will be presented as data listings displaying the location of implant (12 zones) and status of contact with corneal endothelium for each participant.

5.5. Interim Analyses

There are no planned interim analyses. Safety analyses may be periodically performed based on relevant data snapshots.

There will be two database locks as described in Section 5.1. Analyses will be performed after each lock. The primary and secondary efficacy analysis based on the first database lock will be considered as the final analysis. The analyses based on the second database lock provide further efficacy and safety information.

5.5.1. Data Monitoring Committee

A data monitoring committee is not required for this study.

6. Supporting Documentation

Additional baseline characteristics, and pre-defined safety criteria can be found in Section 6.2 Appendix 2.

6.1. Appendix 1: List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
BMI	Body mass index
BUN	blood urea nitrogen
CCT	central corneal thickness
CECD	Central endothelial cell density
CI	Confidence interval
CV	Coefficient of variation
eCRF	Electronic case report form
FAS	Full analysis set
HEX	Pleomorphism
IOP	Intraocular pressure
IWRS	Interactive web response system
KM	Kaplan-Meier
MCHC	Mean corpuscular hemoglobin concentration
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MD	Mean defect
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
OAG	Open-angle glaucoma
OHT	Ocular hypertension
OU	Both eyes
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SAF	Safety analysis set
SAS	Statistical Analysis Software

Abbreviation	Definition
SD	Standard deviation
SE	Study eye
SoA	Schedule of activities
SOC	System organ class
SR	Sustained release
SUN	Standardization of the Uveitis Nomenclature
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
USA	United States
VA	Visual Acuity
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential

6.2. Appendix 2: Supporting Study Information

6.2.1. Demographics

Demographic parameters (age, sex, race, ethnicity) will be summarized descriptively by treatment cohort for the FAS population.

6.2.2. Baseline and Disease Characteristics

Baseline characteristics will be summarized descriptively (height, weight, BMI) by treatment cohort for the FAS population including general and ocular inclusion criteria. The following ocular baseline and disease characteristics will be presented for the study eye in both treatment cohorts: diagnosis (of OAG or OHT), Baseline Hour 0 IOP, iridocorneal angle Shaffer grade, Baseline central endothelial cell density, and Baseline lens status.

6.2.3. Protocol Deviations

Unique participants reporting significant protocol deviations will be summarized in total and by treatment cohort for the FAS population. A listing of any significant protocol deviations will be provided.

6.2.4. Medical History

Abnormalities in participants' medical and surgical history data will be coded using the MedDRA dictionary. Ophthalmic and non-ophthalmic medical and surgical history will be summarized by treatment cohort for the SAF population.

6.2.5. Prior/Concomitant Medications

The medication data will be coded using the most recent version of World Health Organization (WHO) Drug Dictionary Enhanced.

Prior medication is defined as any medication taken prior to the start of study intervention regardless of stop date of the medication. Concomitant medication is defined as any medication taken after the start of study intervention regardless of the start date of the medication.

Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical code (4th level, or most specific level available if 4th level is unavailable).

The number and percentage of participants reporting prior or concomitant medications will be summarized by treatment cohort, ATC class and code, and preferred drug name. If more than one medication is coded to the same preferred drug name for the same participant, the participant will be counted only once for that preferred drug name. Prior and concomitant medications will be summarized separately.

6.3. Appendix 3: Data Handling Convention

6.3.1. Visit Timepoints

Table 6-1 and Table 6-2 present the analysis visits assigned for efficacy and safety assessments for participants for both the Bimatoprost SR and LUMIGAN 0.01% cohorts. Depending on safety assessments schedule, either Table 6-1 or Table 6-2 will be used for by visit analysis. If the assessment date is on or after the date of the administration of Bimatoprost SR (or date of the first self-administration of LUMIGAN 0.01%), the study day is calculated by assessment date – date of the first administration or dose of study treatment + 1. If the assessment date is before the date of the first administration or dose of study treatment, the study day is calculated by assessment date – date of the first administration or dose of study treatment. Therefore, a negative day indicates a day before the start of the study treatment.

Table 6-1 Efficacy and Safety Visit Window

Visit Name	Target Day of the visit[a]		Analysis Visit Window
Baseline Office	-7 to -1 from Baseline Sleep Lab visit		≤ Baseline Sleep Lab-1
Baseline Sleep Lab	0[b]		≤ Administration Day 1-1
Administration Day 1	1		1
Day 2 Safety	2		2
Week 8 Office	-7 to -1 from Week 8 Sleep Lab visit		≤ Week 8 Sleep Lab visit - 1
Week 8 Sleep Lab	56[c]		[42, 70]
Week 16	112		[71, 142]
Month 6	180		[143, 225]
Month 9	270		[226, 315]
Month 12/Study Exit	360		≥ 316

a Relative to the date of treatment administration.
b Must be different than Baseline Office visit.
c Different than Week 8 Office visit.

Table 6-2 Safety Visit Windows

Visit Name	Target Day of the visit[a]		Analysis Visit Window
Baseline Office	-7 to -1 from Baseline Sleep Lab visit		≤ Baseline Sleep Lab-1
Administration Day 1	1		1
Week 16	112		[2, 142]
Month 6	180		[143, 225]
Month 9	270		[226, 315]
Month 12/Study Exit	360		≥ 316

a Relative to the date of treatment administration.

If multiple assessments (scheduled or unscheduled visits) were taken within an analysis window, the assessment obtained on the day closest to the target day will be used; in the case of a tie, the assessment obtained on the later day will be used in the analysis. For participants treated with Lumigan, the exit visit assessments will be summarized in Month 12/study exit regardless of the last visit falls into. Be noted, IOP values will be also measured for safety, and these safety IOP values recorded on unscheduled IOP eCRF page. Unscheduled IOP values in an analysis windows will not be used for efficacy analysis, unless the IOP value is the only one in the analysis visit window. For 24 hour time-match IOP analysis, IOP assessments at Week 8 sleep lab visit will be used and unscheduled visit assessments will not be used.

Table 6-3 presents the time window for IOP measurements during the Office and Sleep Lab visits at Baseline and Week 8 for both the Bimatoprost SR and LUMIGAN 0.01% cohorts. During each assessment, two consecutive IOP measurements will be taken of study 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.

Table 6-3 IOP Measurement Time Windows

Visit Name	Assessment Name	Assessment Type	Target Time of the Assessment	Analysis Time Window
Sleep Lab[a]	24-hour IOP Measurements	Diurnal	08:00	07:15 to 08:45
			10:00	09:15 to 10:45
			12:00	11:15 to 12:45
			14:00	13:15 to 14:45
			16:00	15:15 to 16:45
			18:00	17:15 to 18:45
			20:00	19:15 to 20:45
			22:00	21:15 to 22:45
		Nocturnal	00:00	23:15 to 00:45
			02:00	01:15 to 02:45
			04:00	03:15 to 04:45
			06:00	05:15 to 06:45
Office[b]	Hour 0 IOP Measurement	N/A	08:00	06:30 to 09:30

a For both Baseline and Week 8

b For Baseline office visit, Day 2 safety visit, Week 8 office visit, Week 16, Month 6, 9, and 12/Exit

6.3.2. Repeated or Unscheduled Assessments of Safety Parameters

If a participant has repeated assessments before the administration of treatment, unless otherwise stated, the results from the latest non-missing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for safety evaluation, and all assessments will be presented in the data listings.

6.3.3. Missing Date of the Last Dose of Study Intervention

For participants who did not received the LUMIGAN 0.01% at the Week 8 Sleep Lab visit or missed at the Week 8 Sleep Lab visit, the date will be imputed with the last non-missing date of treatment self-administration prior to Week 8 Sleep Lab visit.

6.3.4. Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of study treatment, severity of mild will be assigned. If severity is missing for an AE that started on or after the date of study treatment, severity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summaries; the values will be shown as missing in the data listings.

6.3.5. Missing Causal Relationship to Study Intervention for Adverse Events

If the causal relationship to a study treatment is missing for an AE that started on or after the date of the study treatment, a causality of 'yes' will be assigned. The imputed values for causal relationship will be used for the incidence summaries; the values will be shown as missing in the data listings.

6.3.6. Missing Date Information for Adverse Events

In cases of incomplete dates for AE, the missing component(s) will be assumed as the most conservative value(s) possible. The imputation rule is aimed at conservatively capturing AEs with missing start dates as treatment-emergent AEs (TEAEs).

Table 6-4 Imputing Rule for Partially Missing AE Start Dates

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D only	M and Y same as M and Y of first dose of study treatment	Date of first dose of study treatment
		Y is before the Y of first dose of study treatment or if Y same but M is before the M of first dose of study treatment	Last day of non-missing month
		Y is after the Y of first dose of study treatment or if Y same but M is after the M of first dose of study treatment	First day of non-missing month
	D and M	Y same as Y of first dose of study treatment	Date of first dose of study treatment
		Y before the Y of first dose of study treatment	Use Dec 31
		Y after the Y of first dose of study treatment	Use Jan 1
	M only	Treat D as missing as well	Use same procedure as D and M missing

Notes: D=Day, M=Month, Y=Year.

If the stop date is complete and the imputed start date computed using the rules in Table 6-4 is after the stop date, the start date will be imputed by the stop date. If the start date is completely missing and the stop date is complete, the following rule will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date.
- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date.

6.3.7. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including washout and IOP-lowering medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

6.3.7.1. Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Table 6-5 Imputing Rule for Missing Prior or Concomitant Medications Start Date

Parameter	Missing	Additional Conditions	Imputation
Start date for non-prior or concomitant medications	D only	M and Y same as M and Y of first dose of study treatment	Date of first dose of study treatment
		Y is before the Y of first dose of study treatment or if Y same but M is before the M of first dose of study treatment	Last day of non-missing month
		Y is after the Y of first dose of study treatment or if Y same but M is after the M of first dose of study treatment	First day of non-missing month
	D and M	Y same as Y of first dose of study treatment	Date of first dose of study treatment
		Y before the Y of first dose of study treatment	Use Dec 31
		Y after the Y of first dose of study treatment	Use Jan 1
	M only	Treat D as missing as well	Use same procedure as D and M missing

Notes: D=Day, M=Month, Y=Year.

6.3.7.2. Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date unless the stop date is marked as ongoing. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date. If the stop date is marked as ongoing, the study exit date will be assigned to the missing fields. If the study exit date is not available, the last visit date will be used for imputation.

Table 6-6 Imputing Rule for Missing Prior or Concomitant Medications Stop Date

Parameter	Missing	Additional Conditions	Imputation
Stop date for non-prior or concomitant medications	D only	M and Y same as M and Y of study exit date	Day of the study exit date
		Y is before the Y of study exit date or if Y same but M is before the M of study exit date	Last day of non-missing month
		Y is after the Y of study exit date or if Y same but M is after the M of study exit date	First day of non-missing month
	D and M	Y same as Y of study exit date	Month and day of the study exit date
		Y before the Y of study exit date	Use Dec 31
		Y after the Y of study exit date	Use Jan 1
	M only	Treat D as missing as well	Use same procedure as D and M missing

Notes: D=Day, M=Month, Y=Year.

6.3.8. Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable, the appropriately determined coded value will be used in the statistical analysis.

6.4. Appendix 4: Changes to Protocol-planned Analyses

There are no changes from the protocol-planned analyses.