1.0 TITLE PAGE

STATISTICAL ANALYSIS PLAN

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

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Protocol Number:	192024-095
Development Phase:	Phase 3
Name of Investigational Product:	Bimatoprost sustained release (SR)
Study Statistician:	[redacted]

Sponsor:

Allergan (North America)
2525 Dupont Drive
Irvine, California USA
92612
+1-714-246-4500
+1-800-347-4500

Allergan Ltd.
1st Floor, Marlow
International,
The Parkway, Marlow
Buckinghamshire
SL7 1YL United Kingdom
Tel: +44 (0) 1628 494444
Fax: +44 (0) 1628 494449

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3.0 LIST OF ABBREVIATIONS

AC	anterior chamber
ACG	angle closure glaucoma
AE	adverse event
AREDS	age-related eye disease study
ATC	anatomical therapeutic chemical
BCVA	best-corrected visual acuity
Bim SR	Bimatoprost SR
CCT	central corneal thickness
CI	confidence interval
CV	coefficient of variation
dB	decibels
[redacted]	
ECD	endothelial cell density
eCRF	electronic case report form
IOP	intraocular pressure
ITT	intent-to-treat
K-M	Kaplan-Meier
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed effect model for repeated measurement
NA	not applicable
OAG	open-angle glaucoma
OD	right eye
OHT	ocular hypertension
OS	left eye
OU	both eyes
PAS	peripheral anterior synechiae
PID	patient identification

PP	per protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	*Le Système International d'Unités* (International System of Units)
SLT	selective laser trabeculoplasty
SMQ	standard MedDRA query
SOC	system organ class
SR	sustained release
SUN	standardization of the uveitis nomenclature
TEAE	treatment-emergent adverse event
TFLs	tables, figures and data listings
VA	visual acuity

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the Study Protocol 192024-095 (Amendment 3). Specifications of tables, figures, and data listings (TFLs) are contained in a separate document. Additionally, if data are to be excluded from per-protocol analyses, a separate document will provide detailed rules for the data exclusion.

Study 192024-095 is a multicenter, paired-eye, randomized, efficacy evaluator-masked 14-month study conducted in 2 stages (Stage 1 and 2). The safety and intraocular pressure (IOP)-lowering effect of Bimatoprost SR (Bim SR) will be compared with selective laser trabeculoplasty (SLT) in open-angle glaucoma (OAG) or ocular hypertension (OHT) patients who are not adequately managed with topical medication for reasons other than medication efficacy (e.g., due to intolerance or nonadherence).

After the screening visit procedures, patients currently being treated with IOP-lowering medication(s) in either eye will begin washout of these medication(s) for a medication-dependent minimum washout period. The maximum washout period is 42 days. Baseline visit occurs after the washout period has been completed. To be eligible to participate in the study, at the Baseline visit, patients must have an Hour 0 IOP of ≥ 22 and ≤ 34 mmHg in each eye with a difference between the eyes of ≤ 5 mmHg. 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 Bim SR or SLT using a 1:1 ratio, stratified by:

- primary eye baseline IOP (≤ 25 versus > 25 mmHg)

and

- [redacted]

If the primary eye receives Bim SR, the contralateral eye will receive SLT. If the primary eye receives SLT, the contralateral eye will receive Bim SR.

The study is being conducted in 2 stages because the protocol was amended (Amendment 2) to reduce the number from 3 to 2 cycles of Bim SR administration, which allows for longer duration of efficacy follow up after the second administration:

- **Stage 1**: Bim SR 15 µg vs SLT; 3 administration cycles for patients who were enrolled and reached the Week 32 administration visit prior to implementation of Protocol Amendment 2

- **Stage 2**: Bim SR 15 µg vs SLT; 2 administration cycles for patients who had not reached Week 32 prior to implementation of Amendment 2; and all patients enrolled under Protocol Amendment 2

Patients will receive a 360° administration of SLT in 1 eye on Day 1, and administration of Bim SR in the contralateral eye on Day 4 (Bim SR Cycle 1 Day 1), with a repeat administration of Bim SR at Week 16 (Bim SR Cycle 2 Day 1). Patients who were enrolled and reached Week 32 prior to implementation of Protocol Amendment 2 received a third administration of Bim SR at Week 32 (Bim SR Cycle 3 Day 1). Therefore, the planned number of treatment cycles for Stage 1 patients is 3, and the planned treatment cycles for Stage 2 patients is 2.

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 Bim SR. A Sham Bim SR administration will be performed in the eye that underwent SLT on each Bim SR administration visit (Day 4 [Bim SR Cycle 1 Day 1] and Week 16 [Bim SR Cycle 2 Day 1]) (see Table 4-1). For brevity, the eye administered Bim SR will be referred to as the "Bim SR eye", and the eye that underwent SLT will be referred to as the "SLT eye".

Due to the paired-eye design of the study, the experimental units for treatment effects are individual eyes of each patient. Therefore, data summaries will primarily be done by randomized treatment (Bim SR and SLT). Where appropriate, data summaries at patient level will be provided.

Table 4-1 Treatment Schedule by Eye

Treatment Visit	Bim SR Eye	SLT Eye
SLT administration (Day 1)	Sham SLT	360° SLT
Bim SR Cycle 1 administration (Day 4)	Bim SR	Sham Bim SR
Bim SR Cycle 2 administration (Week 16)	Bim SR	Sham Bim SR

SLT = selective laser trabeculoplasty; SR = sustained release
Note: Patients who were enrolled and reached the Week 32 administration visit prior to implementation of Protocol Amendment 2 received a third administration of Bim SR at Week 32.

Schedule of visits and procedures to be performed on randomized patients are presented in Tables 4-2 to 4-6.

Table 4-2 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 42 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 Up to 42 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				
[redacted]	OU				
Biomicroscopy[f]	OU		OU	OU[k]	
Gonioscopy/Angle Assessment	OU[l]				
Pachymetry: (may be done any time after gonioscopy)	OU				

Visit	Screening		Baseline[b]	Day 1 (SLT Administration)	Day 2 Phone Call[c]
Visit Windows	Up to 28 days		Up to 3 days		
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 42 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/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 of the protocol.

[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 4-3 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
	Day 4							
Visit Windows	+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[b]		OU			OU	OU	OU	OU
Best-Corrected Visual Acuity[c]		OU			OU	OU	OU	OU
Intraocular Pressure H0	SC/T[d]	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	
Specular Microscopy					OU		OU	
Biomicroscopy[b]	SC/T[d]	OU			OU	OU	OU	OU
Intraocular Pressure H2 and H8 (selected sites/patients)[e]							OU[e]	
Gonioscopy/Angle Assessment					OU[f]	OU	OU[f]	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 Day 4	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
Visit Windows	+3 days				±4 days	± 4 days	±4 days	± 4 days
Dilated Ophthalmoscopy							OU	
Optic Disc Examination							OU	
Contact Interactive Response System[g]	X							
Treatment and/or Sham Administration[h]	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 [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 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.

e 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]).

f [redacted]. See Procedure Manual for details.

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

h [redacted]

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

Visits	Bimatoprost SR Cycle 2 Day 1 Administration Week 16	Cycle 2 Day 2 Safety Visit[k] 	Cycle 2 Day 4 Phone Call[a, k] 	Cycle 2 Week 2 Phone Call[a, k] 	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[b]		OU			OU	OU	OU	OU
Best-Corrected Visual Acuity[c]		OU			OU	OU	OU	OU
Intraocular Pressure H0	SC/T[d]	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[c]						OU		
Visual Field[e]						OU		
Specular Microscopy						OU		
Biomicroscopy[b]	SC/T[d]	OU			OU	OU	OU	OU
Intraocular Pressure H2, H8 (selected sites/patients)[f]						OU[f]		
Gonioscopy/Angle Assessment					OU	OU[g]	OU	OU

Visits	Bimatoprost SR Cycle 2 Day 1 Administration Week 16	Cycle 2 Day 2 Safety Visit[k]	Cycle 2 Day 4 Phone Call[a, k]	Cycle 2 Week 2 Phone Call[a, k]	Week 20	Week 24	Week 28	Week 31
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[h]	X							
Treatment and/or Sham Administration[i]	X[j]							

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 [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 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.

e For a given patient, the same test methodology must be used for fields that are historical as well as fields performed throughout the study.

f 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]).

g [redacted] See Procedure Manual for details.

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

i [redacted]

j With the implementation of Amendment 3, patients who are enrolled and have not yet reached Week 16 will not receive Cycle 2 administration and will be followed up at the regularly scheduled follow-up visits through Week 52/exit. Therefore, the Week 16 will not be required for these patients.

k These visits are not required if Cycle 2 is not received.

Table 4-5 Administration Cycle 3 Schedule of Visits and Procedures (Stage 1 Patients Only)

	Bimatoprost SR Cycle 3 Day 1 Administration	Cycle 3 Day 2 Safety Visit	Cycle 3 Day 4 Phone Call[a]	Cycle 3 Week 2 Phone Call[a]
Visits	Week 32			
Visit Windows	-2/+4 days			
Adverse Events	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X		
Pregnancy Test				
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		
Best-Corrected Visual Acuity[c]		OU		
Intraocular Pressure H0	SC/T[d]	OU		
Non-contact Exams (may perform in any order at any time before gonioscopy)				
Macroscopic Iris Color Assessment				
Manifest Refraction[c]				
Visual Field[e]				
Specular Microscopy				
[redacted]				
Biomicroscopy[b]	SC/T[d]	OU		

	Bimatoprost SR Cycle 3 Day 1 Administration	Cycle 3 Day 2 Safety Visit	Cycle 3 Day 4 Phone Call[a]	Cycle 3 Week 2 Phone Call[a]
Visits	Week 32			
Visit Windows	-2/+4 days			
Gonioscopy/Angle Assessment				
Pachymetry (may be done any time after gonoiscopy)				
Dilated Ophthalmoscopy				
Pupil Dilation (perform post-dilation eye exams in any order)				
Optic Disc Examination				
Contact Interactive Response System[g]	X			
Treatment and/or Sham Administration[h]	X			

H = Hour; Hour 0 = 08:00 ± 1 hour; IOP = intraocular pressure; 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] [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] 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.

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

[f] [redacted] Assessment will be performed at Week 52/Exit in patients who underwent assessment at Screening. Perform any contact assessments following completion of IOP measurements. See Procedure Manual for details.

[g] Contact at Week 32 pretreatment for kit allocation (and posttreatment to confirm kit assignment, if applicable). Contact at Week 52/Exit to report patient's exit status

[h] [redacted]

Table 4-6 Schedule of Visits and Procedures: Week 36 through Week 52/Exit

Visits	Week 36	Week 40	Week 44	Week 47	Week 52/ Exit
Visit Windows	±4 days	±4 days	±4 days	±4 days	±7 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
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[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/ Exit
Visit Windows	±4 days	±4 days	±4 days	±4 days	±7 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
Contact Interactive Response System[f]					X

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/Exit in patients who underwent assessment at Screening. Perform any contact assessments following completion of IOP measurements. See Procedure Manual for details.

e [redacted]. See Procedure Manual for details.

f Contact at Week 52/Exit to report patient's exit status.

5.0 STUDY OBJECTIVES AND CLINICAL HYPOTHESES

5.1 STUDY OBJECTIVES

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

Two database locks will occur at the following two timepoints: 1) when all patients in Stage 2 complete the Week 24 visit or have prematurely discontinued before the Week 24 visit (primary analysis), and 2) when all patients in Stage 2 complete the Week 52 visit or exit the study (final analysis). Analyses will be performed after each lock on unmasked data. The analysis based on the first database lock will be considered as the primary analysis of the study. The analyses based on the second database lock will provide further efficacy and safety information.

5.2 CLINICAL HYPOTHESES

Bim 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 (e.g., due to intolerance or nonadherence). Bim 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 (e.g., due to intolerance or nonadherence).

6.0 ANALYSIS POPULATIONS

The primary eye of each patient will be randomized to receive either Bim SR or SLT treatment. Based on treatment randomization, the contralateral eye will receive SLT if the primary eye receives Bim SR (or vice versa). Per study design, each eye of every patient will provide data for the two study treatments separately, and the experimental units for treatment effect are individual eyes.

6.1 INTENT-TO-TREAT POPULATION

Patients whose primary eyes were randomized to receive either Bim SR or SLT treatment will be referred to as randomized patients. The intent-to-treat (ITT) population is defined as all randomized patients, and will be referred to as “ITT population” in this SAP and

TFLs. Analyses using the ITT population will be based on the randomized treatment assigned to each eye.

The modified intent-to-treat (mITT) population is defined based on ITT population, but will exclude patients who could not receive the second implant due to the discontinuation for the Bim SR 15µg dose strength implemented in protocol Amendment 3. The exclusion algorithm is as follows:

- If a patient had a missing Cycle 2 Day 1 Bim SR administration date with study exit date after March 19, 2020 (IWRS deactivation date), unless the patient had AE leading to drug withdrawn or received a rescue medication before March 19, 2020 in planned Bim SR eye, then the patients will be excluded from the mITT.

The reason for a missing Cycle 2 Day 1 Bim SR administration date is only due to the discontinuation for the Bim SR 15µg dose strength in protocol Amendment 3, not due to AE leading to drug withdrawn or rescue medications.

The mITT population will be used for the primary analysis.

6.2 PER-PROTOCOL POPULATION

The per-protocol (PP) population is defined as all patients in ITT population who have no protocol deviations affecting the data for the primary efficacy analysis for all visits (Week 4, Week 12, and Week 24) in both eyes, and will be referred to as the "PP population" in this SAP and TFLs.

Since the primary eye and contralateral eye of a patient will contribute data separately for the two different treatments in the study, the data from one eye can be excluded from PP analysis due to a protocol deviation, but the patient can still be included in PP population because of valid data from the other eye.

Examples of protocol deviations that will result in removal of data from PP analysis include but are not limited to the following cases:

- For eyes with no study treatment, post-baseline data will be excluded from PP analysis, and
- For eyes that received both study treatments, data after the wrong treatment will be excluded from PP analysis.

A separate document will be prepared to describe data exclusion algorithm for PP analysis. All patients with data excluded from the PP analysis will be identified and

finalized prior to each database lock and will be displayed in a data listing with reason(s) for exclusion.

6.3 SAFETY POPULATION

The safety population is defined as all patients who had received at least one treatment regardless of whether it was the planned treatment or not, and will be used for the safety analyses. Both eyes in the safety population are included in the ocular safety analyses. Ocular safety assessments will be based on the treatment received in each eye at the first administration. However, one patient received both SLT and Bim SR in the same eye. Safety assessment for the patient will be summarized under the Bim SR treatment group.

6.4 DATA COLLECTED BUT NOT ANALYZED

Clinical lab test data, vital signs, pregnancy test, national eye institute visual functioning questionnaire, and general (non-ophthalmic) physical examination are collected only at Screening and will not be analyzed. Other data collected but not analyzed, will be described in the clinical study report.

7.0 PATIENT ENROLLMENT, DISPOSITION AND COMPLIANCE

The number of patients in analysis populations (ITT, mITT, Safety, and PP) will be summarized for the overall study. The numbers and percentages of patients randomized by county and site will be presented. The numbers and percentages of patients who complete the study and the numbers and percentages of patients who prematurely discontinue the study will be presented overall and by analysis cycle defined in Figure 11-1.

The study completers will be defined as the patients who received at least one study treatment and marked as completed in the eCRF disposition page. A patient who received study treatment in the relevant cycle will be considered to have completed the analysis cycle, if (a) the patient is a study completer or (b) the patient received the subsequent study treatment (Bim SR).

The categories of premature discontinuation reasons and the number of patients who prematurely discontinued during the study will be summarized.

8.0 DEMOGRAPHICS AND OTHER BASELINE DATA

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

8.1 DEMOGRAPHICS

Demographic parameters including age, age group, race, race group, ethnicity, sex as well as baseline characteristics such as weight (kg) and height (cm) will be summarized descriptively. Patient's age at Baseline (years) will be presented in categories of less than 45 years; between 45 years and 65 years, inclusive; and greater than 65 years. In addition, race will be further grouped as White versus non-White and Hispanic versus non-Hispanic (Ethnicity).

8.2 BASELINE CHARACTERISTICS

Baseline characteristics for each eye will be descriptively summarized by treatment of the eye for the following categories: iris color, diagnosis of either OAG (primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT, baseline Hour 0 IOP ($\leq$ 25 mm Hg or > 25 mmHg), iridocorneal angle Shaffer grade, and central endothelial cell density, will be summarized descriptively by treatment group for the ITT population. Study eye iris color will be summarized by color for each of the following categories: monochromic, heterochromic peripupillary, and heterochromic diffuse.

8.3 MEDICAL AND SURGICAL HISTORY

Abnormalities in patients' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), 21.0 or newer. The number and percentage of patients with non-ophthalmic medical and surgical histories at the time of randomization will be summarized separately by system organ class (SOC) and preferred term (PT) for the ITT population. Ophthalmic medical and surgical histories associated with Bim SR eye and SLT eye at randomization will also be summarized separately for the Safety Population by SOC and PT.

8.4 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded using the current version of World Health Organization Drug Global Dictionary and anatomical therapeutic chemical (ATC) classification system.

Prior medications are defined as medications with administration date or start date before the date of randomization. Concomitant medications are defined as those medications with administration date or start date on or after the date of the initial treatment. If a medication started prior to the date of randomization and continued past the date of randomization, it will be considered ongoing at randomization (i.e., study start) and will be presented as both a prior medication and a concomitant medication.

8.4.1 General Medications

Prior and concomitant non-ocular medications will be summarized by drug class and preferred name in the ITT population.

8.4.2 Ocular Medications

Prior ocular medications, washout ocular medications, concomitant ocular medications, and non-study IOP lowering medications will be summarized by eye identified by randomized treatment, drug class, and preferred name separately. A non-study IOP-lowering medication will be defined by the information provided by the investigator on electronic case report form (eCRF).

9.0 STUDY DURATION

Patients' study duration will be summarized using descriptive statistics for each treatment group using safety population. Duration of time on study (days) for each patient will be calculated as the last visit date available or study exit date– Day 1 SLT administration date + 1.

10.0 EFFICACY ASSESSMENTS

The primary efficacy measurement is IOP at Hour 0, which will be measured in each eye using the Goldmann applanation tonometer. Two consecutive measurements will be taken for each eye. If the first 2 measurements differ by > 1 mm Hg, a third measurement will be taken. The IOP value for a given eye will be the median of all measurements, and this is consistent with the protocol IOP description in Study Protocol Section 6.1.1 (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). For consenting patients at selected sites, additional IOP data will be collected at Hour 2 and 8, and these data will be included in [redacted].

10.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy variable is Hour 0 IOP change from baseline (follow-up value minus baseline value, thus negative values reflect IOP reduction from baseline) assessed at Weeks 4, 12, and 24. Intraocular pressure values at Hour 0 at Baseline visit is considered as the baseline values.

Baseline and Weeks 4, 12 and 24 Hour 0 IOP measurements with their changes from baseline will be descriptively summarized.

Primary efficacy analysis will be performed for patients in the mITT population. The null and alternative hypotheses for the comparison between Bim SR treated eyes and SLT treated eyes at Weeks 4, 12, and 24 are:

- Null hypothesis: the difference in mean IOP change from baseline between the Bim SR and SLT eye (Bim SR minus SLT) is > 1.5 mmHg.
- Alternative hypothesis: the difference in mean IOP change from baseline between the Bim SR eye and SLT eye (Bim SR minus SLT) is ≤ 1.5 mmHg.

Hour 0 IOP change from baseline will be analyzed using a mixed effect model for repeated measurement (MMRM). The model will include Hour 0 IOP change from baseline as the response variable and treatment, visit, eye, baseline Hour 0 IOP, treatment-by-visit, treatment-by-baseline Hour 0 IOP, treatment-by-eye, visit-by-eye interactions as covariates. Unstructured covariance matrix for study visit and compound symmetry correlation for eyes will be used for repeated measures on the same patient. If the model fails to converge, alternative covariance structures may be used in the MMRM analysis. If the model fails to converge with alternative covariance structures, multiple imputation (MI) will be implemented before MMRM.

The mean difference in the Hour 0 IOP change from baseline between the Bim SR eyes and SLT eyes (Bim SR minus SLT) in the mITT population and the corresponding 95% confidence intervals (CI) will be constructed at each visit from MMRM analysis. The noninferiority comparison for Bim SR versus SLT at Weeks 4, 12, and 24 is the primary analysis. If the upper limit of the 95% CI is ≤ 1.5 mmHg at all 3 visits, Bim SR 15 µg statistical noninferiority to SLT is considered demonstrated.

For additional clinical consideration, Bim SR is considered clinically noninferior to SLT if the upper limit of the 95% CI is ≤ 1.0 mmHg at 2 out of the 3 visits of Weeks 4, 12, and 24.

Sample SAS® code for primary analysis is shown as below:

```
proc mixed data=iop4;
     where avisitn >1;
     class subjid eye trt avisitn;
     model chg=trt avisitn eye base trt*avisitn
               trt*base trt*eye avisitn*eye/ddfm=kr;
     repeated avisitn*eye/type=un@cs subject=subjid rcorr;
     lsmeans trt*avisitn/diff;
run;
```

The definitions of variables are:
chg = Hour 0 IOP percentage change from baseline at the primary analysis time points of Week 4, Week 12, and Week 24
avisitn = Programming derived analysis visits at Week 4, Week 12, and Week 24
subjid = Subject ID
eye = Variable to indicate primary eye or contralateral eye
trt = Variable to indicate Bim SR treatment or SLT treatment
base = Baseline IOP

10.2 SECONDARY ANALYSIS

Superiority test of Bim SR 15 µg versus SLT

As the secondary efficacy analysis, a superiority test of Bim SR 15 µg versus SLT will be performed if noninferiority is demonstrated in the primary efficacy analysis. Superiority of Bim SR versus SLT is considered achieved if the upper limit of the 95% CI is < 0 mm Hg at Weeks 4, 12, and 24. The mITT population will be used.

Time to initial use of non-study IOP-lowering treatment (as determined by the investigator)

Time to the event of the initial use of non-study IOP-lowering treatment from the Date of the First Treatment will be estimated using Kaplan-Meier (KM) method with graphical displays.

Time to initial use of non-study IOP-lowering treatment = (Date of initial use of non-study IOP-lowering treatment – Date of the First Treatment) +1,

where the Date of the First Treatment for SLT is the SLT Treatment date (study Day 1), and the Date of First Treatment for Bim SR is Bim SR Cycle 1 Day 1 administration date (study Day 4).

Additionally, for Bim SR, the time to non-study IOP-lowering treatment from the second injection and the time to non-study IOP-lowering treatment from the third injection will be summarized:

Time to initial use of non-study IOP-lowering treatment from the second Bim SR implant = (Date of initial use of non-study IOP-lowering treatment after the second Bim SR implant – Date of the second Bim SR implant) +1

Time to initial use of non-study IOP-lowering treatment from the third Bim SR treatment = (Date of initial use of non-study IOP after the third Bim SR implant -lowering treatment – Date of the third Bim SR implant) +1

In the calculation of time to initial use of non-study IOP-lowering treatment, if a patient did not use any non-study IOP-lowering medications in an eye, then the event (initial use of non-study 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.

In the calculation for the time to the event of non-study IOP-lowering treatment from the second Bim SR implant, patients with at least two Bim SR implants will be used, and the event will be censored at the third Bim SR implant if the patients didn't use any non-study IOP-lowering medications up-to the third implant.

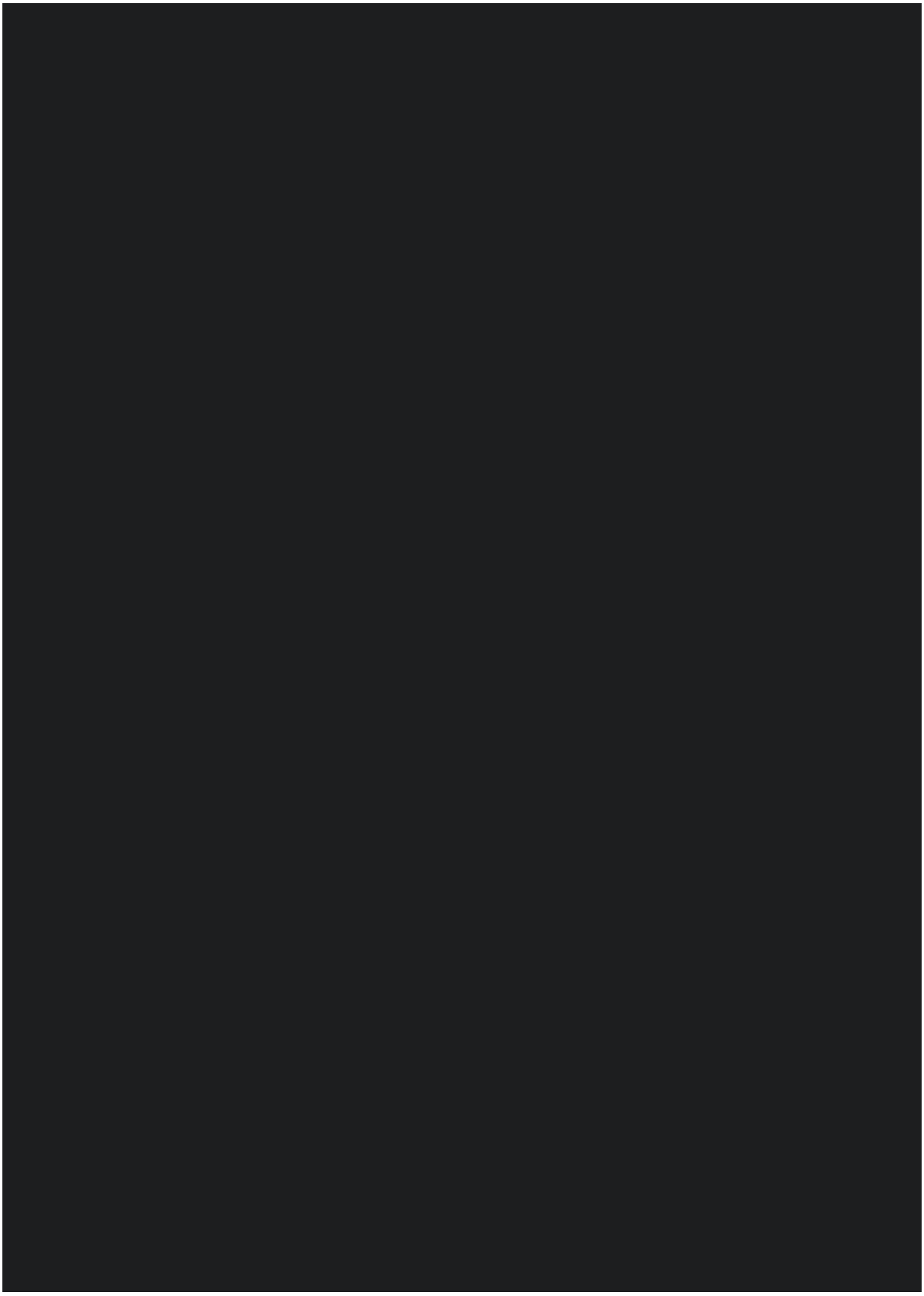
Percentage of Bim SR and SLT eyes achieving ≥ 20% reduction by visit

Number and percent of Bim SR and SLT eyes that have achieved a ≥ 20% reduction in IOP by each post-baseline visit in each eye will be summarized.

IOP changes from baseline in raw IOP at Weeks 8, 15, and 20

Week 8, 15 and 20 raw IOP values and their changes from baseline will be descriptively summarized for Bim SR eye and SLT eye at each timepoint.

10.3 OTHER EFFICACY ANALYSES



10.4 SENSITIVITY ANALYSES

As part of the sensitivity analyses, the mean difference and 95% CI in the IOP change from baseline between the Bim SR eyes and SLT eyes (Bim SR minus SLT) will be constructed for each analysis visit for the Per Protocol (PP) population using the same MMRM model as the one used in the primary analysis.

To simplify the interpretation of treatment effect, and to allow flexible adjustment for baseline effect and the between-eye correlation across different visits, the following MMRM model will be used in sensitivity analysis using mITT population: (1) the MMRM model will include Hour 0 IOP change from baseline as the response variable and treatment, visit, eye, baseline Hour 0 IOP, treatment-by-visit, visit-by-baseline Hour 0 IOP, and visit-by-eye interactions as covariates; (2) an unstructured covariance matrix (6×6 matrix) will be used for measurements across 3 primary visits (Weeks 4, 12, and 24) and 2 eyes for the same patients. The same MMRM model will be used in the tipping-point sensitivity analysis described in the later part of the section.
Sample SAS® code for the sensitivity analysis is shown as below:

```
proc mixed data=iop4;
     where avisitn >1;
     class subjid eye trt avisitn repid;
     model chg=trt avisitn eye base trt*avisitn
               avisitn*base avisitn*eye/ddfm=kr;
     repeated repid/type=un subject=subjid rcorr;
     lsmeans trt*avisitn/diff;
run;
```

The definitions of variables are:
chg = Hour 0 IOP percentage change from baseline at the primary analysis time points of Week 4, Week 12, and Week 24
avisitn = Programming derived analysis visits at Week 4, Week 12, and Week 24
subjid = Subject ID
eye = Variable to indicate primary eye or contralateral eye
trt = Variable to indicate Bim SR treatment or SLT treatment
base = Baseline IOP
repid=Variable created to identify the repeated measures cross each eye and each visit within a given subject for the unstructured covariance matrix (6 × 6).

Additionally, ANCOVA including within-subject correlation at each visit will be conducted using the observed values of ITT population, where IOP measurements obtained after initiating the use of non-study IOP-lowering medication will be set to missing. At each visit, the model for IOP change from baseline is specified as: IOP Change from Baseline = Treatment + Eye + Baseline IOP, where Eye is primary eye or contralateral eye. A compound symmetric covariance matrix will be used for between eye correlation.

The tipping-point sensitivity analysis will also be used to assess the robustness of the analysis results. A multiple imputation (MI) will be performed to the missing data as the first step; then different shifts using various assumptions on the missing IOP CFB will be applied to the imputed missing values in Bim SR treated eyes separately (note: shift will not be applied to SLT treated eyes); finally MMRM analyses will be conducted based on the imputed data with shifts and the corresponding tipping region of the shifts will be used to evaluate the robustness of the noninferiority conclusion.

In the MI procedures, a two-step method will be used to impute the missing values at Weeks 4, 8, 12, 15, 20, and 24 for each eye. During Step 1, missing intermittent data will be imputed to obtain a monotone missing pattern and during Step 2 linear regression will be used to impute the remaining missing values. Note that baseline IOP values associated with each eye must not be missing in any of the patients; otherwise they will be excluded from this analysis. At least twenty-five (25) sets of imputed datasets will be created using SAS proc MI procedure. A sample code is shown below for Hour 0 IOP measurements associated with each eye:

```
proc mi data=iop nimpute=25 seed=123451 out=_miint;
   var baseline week4_hr0 week8_hr0 week12_hr0 week15_hr0 week20_hr0 week24_hr0;
 by treatment;
 mcmc chain=single impute=monotone;
run;

proc mi data=_miint nimpute=1 seed=123457 out=mifull;
 class race_group sex lens;
 var race_group sex lens age baseline week4_hr0 week8_hr0 week12_hr0 week15_hr0 week20_hr0
week24_hr0;
 monotone regression (week4= race_group sex lens age baseline/details);
 monotone regression (week8= race_group sex lens age baseline week4/details);
 monotone regression (week12= race_group sex lens age baseline week4 week8/details);
 monotone regression (week15= race_group sex lens age baseline week4 week8 week12/details);
 monotone regression (week20= race_group sex lens age baseline week4 week8 week12 week15/details);
 monotone regression (week24= race_group sex lens age baseline week4 week8 week12 week15
week20/details);
by _imputation_ treatment;
run;
```

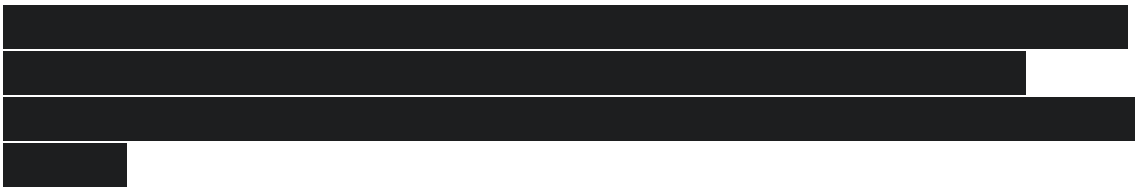
MMRM method will be used to analyze each imputation dataset obtained from the above. PROC MIANALYZE will then be used to pool the analyses results across the imputation datasets and produce final parameter estimates.

Additional sensitivity analyses may be conducted to further evaluate the robustness of primary analysis results.

11.0 SAFETY ANALYSES

All safety analyses will be performed using the Safety Population. As indicated in Section 6.5, safety data collected at Screening for eligibility assessment will not be analyzed.

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



Unless otherwise stated, the last non-missing safety assessment before the SLT treatment (Day 1) will be used as the baseline for all analyses of that safety parameter.

Analysis study periods are defined as follows:

- **During the study**: Date of SLT treatment through Week 52/Exit visit/last study visit available.
- **Analysis Cycle 1**: SLT Treatment date (Day 1) through the second Bim SR implant date – 1. If the second Bim SR implant was not given to a patient, all safety assessments through Week52/Exit visit/last study visit available will be included in analysis cycle1.
- **Analysis Cycle 2**: Second Bim SR implant date through the third Bim SR implant date – 1. If the third Bim SR implant was not given to a patient, all safety assessments through Week52/Exit visit/last study visit available will be included in analysis cycle 2.
- **Analysis Cycle 3**: Third Bim SR implant date through Week 52/Exit visit/last study visit available. Note that only Stage 1 patients were eligible to receive third Bim SR implant.

All summaries will be based on the first treatment received in each eye (Bim SR or SLT), except one patient who received both SLT and Bim SR in the same eye (Safety assessment will be summarized in Bim SR). For non-ocular safety measures, overall summaries will be presented. For ocular safety assessments, summaries will be presented for the periods of during the study, Analysis Cycle 1, Analysis Cycle 2, and Analysis Cycle 3 as shown in Figure 11-1 below.

Figure 11-1 Analysis Cycle Illustration

	Cycles for Safety Data Analyses	
Treatment	SLT eye	BIM SR eye
SLT	**Analysis Cycle 1**	**Analysis Cycle 1**
Bim SR 1st implant	**Analysis Cycle 1**	**Analysis Cycle 1**
Bim SR 2nd implant	**Analysis Cycle 2**	**Analysis Cycle 2**
Bim SR 3rd implant	**Analysis Cycle 3**	**Analysis Cycle 3**

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, version 21.0 or newer. An AE with the same PT may have two different worst severities associated with two eyes separately or could be associated with only one eye. For summary by severity of each PT, the highest severity will be counted for each eye separately. Therefore, the comparison of AE incidence rates will be conducted at the same treatment exposure across Bim SR eye and SLT eye.

An AE will be considered a treatment-emergent adverse event (TEAE) for the study treatment period if the AE meets one of the following criteria:

- The onset date is on or after the first study treatment date.
- The onset date is before the first study treatment date and either:
    - The severity of the event worsened on or after the first treatment date.
    - The event became serious on or after the first study treatment date.

An AE will be considered as a TEAE for a treatment cycle if the AE meets one of the following criteria:

- The onset date is on or after the treatment administration of the cycle but prior to the next cycle administration.
- The onset date is before the treatment administration of the cycle and either:
    - The severity of the event worsened on or after the treatment administration of the cycle.
    - The event became serious on or after the treatment administration of the cycle.

An ocular AE will be defined by the location information on the adverse event page in eCRF. Additionally, questions about adverse event relationships to study treatment and study procedure will be asked in eCRF, and the answers to these questions will be used together to derive the treatment related TEAE.

An overall summary of patient incidences of TEAEs will be presented by event type and event category (ocular or non-ocular). These summaries will include the following:

- All TEAE
- Treatment-related TEAE
- TEAE related to study procedure:
    - Related to study drug
    - Related to study drug administration procedure
    - Related to SLT laser
- All serious TEAE
- Treatment-related serious TEAE

- Serious TEAE related to study procedure:
  - Related to study drug
  - Related to study drug administration procedure
  - Related to SLT laser
- Any TEAE leading to Bim SR implant removal
- Any TEAE leading to study discontinuation

The following non-ocular adverse events will be summarized by SOC and PT:

- Any non-ocular TEAEs,
- Any treatment related non-ocular TEAEs,
- Any serious non-ocular TEAEs, and
- Any non-ocular TEAEs leading to study discontinuation.

Additionally, a summary by SOC, PT, and severity will be provided for non-ocular TEAEs.

For patient eye incidences of treatment emergent ocular adverse events, overall and by period summaries will be provided for the following categories:

- Any ocular TEAEs by SOC and PT
- 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 within two days of study treatment by SOC and PT

  i.e, Ocular TEAEs that occur within two days from the Bim SR treatment or Bim SR sham
- Any ocular TEAEs after two days of study treatment by SOC and PT

  i.e, Ocular TEAEs that occur after two days from the Bim SR treatment or Bim SR sham to next Bim SR treatment or Bim SR sham
- SLT procedure related ocular TEAEs by SOC and PT

  i.e, Ocular TEAEs that occur starting from Day 1, but before the first Bim SR treatment will be summarized.

- Any corneal TEAEs of interest by SOC and PT (Corneal AEs of interest will be identified separately prior to database lock.)
- Any anterior segment inflammation TEAEs of interest by SOC and PT (Anterior segment inflammation AEs will be identified separately prior to database lock.)

11.2 VITAL SIGNS

Vital signs (systolic and diastolic blood pressures [mmHg], pulse rate [bpm], and temperature [Celsius]) will be collected at baseline, but will not be analyzed.

11.3 OTHER SAFETY PARAMETERS

Blood and urine samples obtained for the analysis of blood chemistry, hematology, and urinalysis will be reviewed by the investigator or qualified site personnel for any adverse events. Any safety laboratory test results that represent adverse events will be reflected on adverse event eCRF page, and thus will be part of the suggested analyses of AEs. Therefore, laboratory data collected will not be analyzed.

11.3.1 Pregnancy

Pregnancy test results for female patients of childbearing potential will be collected, but will not be analyzed or listed.

11.3.2 Best Corrected Visual Acuity

Best-corrected visual acuity (BCVA) at an assessment timepoint 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 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:

$$\text{Line change} = 10\times[\log_{10}(d_{BL}/d_{PBL})]$$

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:

$$\text{Line change} = 10\times[\log_{10}(25/80)] = 10\times(-0.5) \text{ (rounded to nearest tenth)} = -5$$

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 best corrected visual acuity (BCVA) from baseline will be summarized for each eye with respect to number of line change categories by study period. Categories will be summarized as worsening VA of 2 lines or more, worsening of one line, no change, improvement of one line, and improvement of 2 lines or more.

11.3.3 Visual Field

Visual field examinations will be assessed by automated perimetry with either Humphrey Field Analyzer (using 24-2 full threshold or 24-2 [SITA] Standard program) or Octopus Perimeter (using G1 Dynamic or Normal strategy or 24-2 Dynamic or Normal strategy program) at Screening, Baseline, Week 24, and Week 52/Exit by test methods. The same test methodology should be used throughout the entire study for a given patient. 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. 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 and 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 and machine type will not be imputed. For patients whose visual fields were assessed by one machine type as recorded, the mean deviation or mean defect assessments with missing machine type will be imputed as assessments by the corresponding unique machine type.

Any post-baseline abnormal findings on visual field will be summarized by eye using number and percentage format to calculate patient incidences overall and by analysis cycle.

11.3.4 Macroscopic Conjunctival Hyperemia

Severity assessment of hyperemia of both eyes is performed at Screening, Baseline, during Analysis Cycle 1 and during Analysis Cycle 2 for all patients and during Analysis Cycle 3. Conjunctival hyperemia severity in each eye is assessed as 0 (None), +0.5 (Trace), +1 (Mild), +2 (Moderate), +3 (Severe) or 'Not Evaluable'. These data will be summarized by eye using the worst severity of hyperemia observed by study period.

In addition, worst severity grade increase greater than 1 (worsening, i.e, 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 for each eye by study period. If the worst severity grade during a period is less severe compared to baseline, it will be considered as 'no increase'.

11.3.5 Specular Microscopy

Endothelial Cell Density: Endothelial cell density average (cells/mm^2) will be assessed using specular microscopy performed on the central cornea of each eye at Screening, Week 4, Week 12, Week 24, Week 40, and Week 52/Exit.

Endothelial cell density at baseline (Screening) and raw values and their changes from baseline will be summarized descriptively by visit for each eye.

In addition, the number and percentage of patient-eyes that showed following

- beyond 200 cells/mm^2 increase
- within 200 cells/mm^2 increase
- within 200 cells/mm^2 decrease
- $\geq$ 10% loss
- $\geq$ 20% loss
- $\geq$ 30% loss
- $\geq$ 40% loss
- $\geq$ 50% loss
- $\geq$ 10% and < 20% loss
- $\geq$ 20% and < 30% loss
- $\geq$ 30% and < 40% loss
- $\geq$ 40% and < 50% loss

in endothelial cell density change from baseline will be summarized by visit for each eye. Percent change from baseline is defined as: 100 × (At Visit ECD – Baseline ECD)/(Baseline ECD) where ECD = endothelial cell density. For the ECD decrease, the worst ECD assessment within the given analysis visit window (or analysis cycle) including unscheduled visits will be summarized by visit and by analysis cycle. For the ECD increase, the maximum ECD assessment will be summarized by visit and by

analysis cycle. Listings for patients with 20% or more central corneal endothelia cell density (CECD) loss at any visit will be provided.

Coefficient of Variation Average (CV_{AVE}): Coefficient of variation average of raw data and changes from baseline will be summarized descriptively by visit for each eye.

Pleomorphism Average (HEX_{AVE}): Pleomorphism average of raw data and their changes from baseline will be summarized descriptively by visit for each eye.

11.3.6 Pachymetry

Corneal thickness using ultrasound (contact) pachymetry is performed on the central cornea for each eye at Screening, Week 4, Week 12, Week 24, and Week 52/Exit visits. At each examination, 3 measurements of central corneal thickness (CCT) and associated standard deviation is 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 for each eye.

11.3.7 Biomicroscopy and Dilated Ophthalmoscopy

Biomicroscopy will be performed in each eye by slit-lamp examination at Screening, Baseline, and during Cycle 1, Cycle 2, Follow-up, and during Cycle 3 for Stage 1 patients.

At these exams, any findings noted on the following will be recorded for each eye on the eCRF as follows:

- Eyelids/Eyelid Margins/Lashes
  - Erythema
  - Edema
  - Other
- Conjunctiva (Bulbar or Palpebral)
  - Hyperemia
  - Edema
  - Subconjunctival Hemorrhage
  - Pterygium, encroaching on visual axis
  - Pterygium, not encroaching on visual axis
  - Other
- Cornea
  - Punctate Epithelial Staining
  - Infiltrates
  - Edema
  - Corneal Guttata
  - Endothelial Pigment

  - Keratic Precipitates
  - Neovascularization
  - Opacity(ies)
  - Stromal Haze
  - Other
- Anterior Chamber
  - Cells
  - Flare
  - Hypopyon
  - Hyphema
  - Other
- Iris/Pupil
  - Afferent Pupillary Defect (APD)
  - Posterior Synechiae
  - Transillumination Defect(s)
  - Pseudoexfoliative Material
  - Peripheral Iridectomy
  - Laser Peripheral Iridotomy
  - Other

Severity of findings in the categories of Eyelids/Eyelid Margins/Lashes, Conjunctiva (Bulbar or Palpebral) and Cornea will be recorded as +0.5 (Trace), +1 (Mild), +2 (Moderate), +3 (Severe) or Not Applicable. Severity of Anterior Chamber findings will be recorded as +0.5, +1, +2, +3, +4, or Not Applicable using the Standardization of the Uveitis Nomenclature (SUN) Working Group criteria. No severity grade will be assigned for Iris/Pupil findings, and only findings noted will be recorded.

Biomicroscopy findings will be coded using MedDRA. Number and percentage of patient eyes with findings showing more than one grade increase from baseline will be presented by coded PT (more than 1 severity grade increase means a change from 0 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 patient eyes with findings present at post-baseline which did not present at baseline will be summarized (i.e., findings not associated with a severity grade). The analysis results will be presented by study periods and analysis cycle.

Dilated ophthalmoscopy and lens status and opacity assessments will be performed in each eye at Screening, Baseline, Week 12, Week 24, Week 40, and Week 52/Exit. At ophthalmoscopy exams, any findings noted on the following areas will be recorded for each eye:

- Vitreous (each finding will be entered as free text field)
- Macula (Intraretinal Fluid or Other (other is entered as free-text))

- Retina Periphery (each finding will be entered as free text)
- Optic Nerve Exam – Cup/Disc Ratio Disc examination findings will be recorded under 2 sub-categories; Disk Hemorrhage, and Other Disc Pathology (other pathology is entered as a free text)

Dilated ophthalmoscopy findings will be coded using MedDRA. Similar analysis from Biomicroscopy will be performed for opthalmoscopy findings.

Optic Nerve cup/disc ratio is 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 by each post-Baseline assessment visit. Change from baseline at each follow-up visit (visit value – baseline values) will be categorized as an improvement of 0.2 or more (≤ - 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 (i.e., change ≥ 0.2). The number and percentage of patients in each category will be provided for each eye by assessment visit.

11.3.8 Lens Status and Opacification

Lens status and lens opacity assessments are performed through a dilated pupil in each eye at Screening, Baseline, Week 12, Week 24, Week 40, and Week 52/Exit. Lens status is assessed as phakic, pseudophakic, or aphakic and recorded on the eCRF.

Lens opacity is assessed by the Age-Related Eye Disease Study (AREDS) as:

- Nuclear cataract
- Cortical cataract
- Posterior subcapsular cataract
- Posterior capsular opacification with location central or peripheral
- Capsular bag not intact, due to central laser/surgical capsulotomy
- Capsular bag not intact, due to capsular tear with location central or peripheral
- Other

At post-Baseline visits, for eyes evaluated as phakic at Baseline, the severity of nuclear, cortical, and posterior subcapsular cataract lens opacities will be summarized (< standard photo #2, and ≥ standard photo #2) in number and percentage format by visit and eye.

11.3.9 Gonioscopy and Bim SR Implant Assessment

Gonioscopy is performed to assess the inferior iridocorneal angle and the Bim SR implant in study visits during Cycle 1 and Cycle 2 for all patients, and during Cycle 3. Patients presenting with peripheral anterior synechiae (PAS) on gonioscopy at any time during the study will be presented in a listing with the time period in which it occurred.

If an implant is visible, visible implant size is to be recorded on eCRF as a percentage of the original material (0-25, 26-50, 51-75, 76-100, 101-125, 126-150, 151-200, >200). Number and percentage of patients with any implant visible during the study will be summarized in a tabular format. In addition, number and percentage of implants visible will also be summarized during each study period for Bim SR eye further breaking down by the categorical percentage visible of each implant. Also, the number and percentage of patients who have any implant(s) in contact with corneal endothelium at any visit within a cycle will be summarized by analysis cycle. Implant assessment will be presented as data listings displaying the location of implant (12 zones), status of contact with other implant(s), and status of contact with corneal endothelium for each patient.

12.0 VISUAL FUNCTION QUESTIONNAIRE

National Eye Institute Visual Function Questionnaire responses collected at Baseline will not be summarized as part of this SAP.

13.0 INTERIM ANALYSES

No interim analysis is currently planned for the study.

Two database locks are planned for this study as described in Section 5.1:

1) When all patients have completed Week 24 visit or have prematurely discontinued before Week 24 visit (primary lock), and
2) When all patients have completed the Week 52 visit or exited the study.

The analysis results based on the first database lock is considered as the primary analysis. The analyses based on the second database lock will provide further efficacy and safety information. Two CSRs will be written, one following each lock.

14.0 DETERMINATION OF SAMPLE SIZE

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 Bim SR eyes and SLT eyes, and that change from baseline in IOP has a standard deviation of 4 mmHg. A sample size of 144 patients will provide approximately 98% power in showing noninferiority in 3 out of 3 timepoints with a noninferiority margin of 1.5 mmHg, and 90% power in showing noninferiority in 2 out of 3 timepoints with a noninferiority margin of 1.0 mmHg, assuming that both the between-eyes and the within-patient correlation coefficients are 0.5.

Assuming a premature discontinuation rate of 10%, approximately 160 patients are to be enrolled into this study.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.3 (or newer) of SAS software.

16.0 DATA HANDLING CONVENTIONS

16.1 EFFICACY DATA

As stated in protocol Section 5.9.1.5 Retreatment with Bim SR, when eye(s) received non-study IOP lowering medication or procedure, to avoid confounding of efficacy data, IOP measurements obtained after initiating the use of non-study IOP-lowering medication or procedure in an eye will be treated as missing for that eye.

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

16.2 VISIT TIME WINDOWS

Table 16-1, Table 16-2, and Table 16-3 present respectively, the analysis visits assigned for efficacy and safety assessments for patients who received only Cycle 1 implant, Cycles 1 and 2 implants and Cycles 1, 2, and 3 implants. If multiple assessments 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. Please be noted, IOP values will be measured for safety, and these safety IOP values should not be included in efficacy analysis of IOP. IOP values for safety are often recorded on unscheduled IOP eCRF page with assessment reason provided in free text, which cannot be programmed straightforwardly. For simplicity, an unscheduled IOP values in an analysis windows will not be used, unless the IOP value is the only one in the window.

Table 16-1 Visit Windows for Patients who only had Bim SR Cycle 1 Implant

Derived Visit	Target Visit Day	Visit Window
Baseline [a]	-1	≤ (SLT Date -1)
SLT/Sham SLT Administration Day 1	1	SLT Date
Bim SR Cycle 1 Day 1[b]	Bim SR Cycle 1 Day 1	Bim SR Cycle 1 Day 1
Bim SR Cycle 1 Day 2 [b]	Bim SR Cycle 1 Day 1 + 1	Bim SR Cycle 1 Day 1 + 1
Week 4/Cycle 1 Week 4 [b]	25	[Bim SR Cycle 1 Day 1+ 2, 38]
Week 8/Cycle 1 Week 8 [b]	53	[39, 66]
Week 12/Cycle 1 Week 12 [b]	81	[67, 91]
Week 15/Cycle 1 Week 15 [b]	102	[92, 105]
Week 16/Cycle 1 Week 16 [b]	109	[106, 122]
Week 20/Cycle 1 Week 20 [b]	137	[123, 150]
Week 24/Cycle 1 Week 24 [b]	165	[151, 178]
Week 28/Cycle 1 Week 28 [b]	193	[179, 203]
Week 31/Cycle 1 Week 31 [b]	214	[204, 217]
Week 32/Cycle 1 Week 32 [b]	221	[218, 234]
Week 36/Cycle 1 Week 36 [b]	249	[235, 262]
Week 40/Cycle 1 Week 40 [b]	277	[263, 290]
Week 44/Cycle 1 Week 44 [b]	305	[291, 315]
Week 47/Cycle 1 Week 47 [b]	326	[316, 343]
Week 52/Cycle 1 Week 52 [b]	361	>=344

[a] Relative to the date of the SLT treatment.

[b] Relative to the date of Bim SR 1st implant. If a patient did not receive the first Bim SR cycle, but treated in SLT at Day 1, Bim SR cycle 1 Day 1 will be determined as SLT+ 3 days.

Table 16-2 Visit windows for patients who only had Bim SR Cycles 1 and 2 implants

Derived Visit	Target Visit Day	Visit Window
Baseline [a]	-1	≤ (SLT Date -1)
SLT/Sham SLT Administration Day 1	1	SLT Date
Bim SR Cycle 1 Day 1[b]	Bim SR Cycle 1 Day 1	Bim SR Cycle 1 Day 1
Bim SR Cycle 1 Day 2[b]	Bim SR Cycle 1 Day 1 + 1	Bim SR Cycle 1 Day 1 + 1
Week 4/Cycle 1 Week 4[b]	25	[Bim SR Cycle 1 Day 1+ 2, 38]
Week 8/Cycle 1 Week 8[b]	53	[39, 66]
Week 12/Cycle 1 Week 12[b]	81	[67, 91]
Week 15/Cycle 1 Week 15[b]	102	[92, Bim SR Cycle 2 Day1-Bim SR Cycle 1 Day 1]
Week 16/Bim SR Cycle 2 Day 1[c]	1	Bim SR Cycle 2 Day 1
Cycle 2 Day 2[c]	2	Bim SR Cycle 2 Day 1 + 1
Week 20/Cycle 2 Week 4[c]	29	[Bim SR Cycle 2 Day 1+ 2, 42]
Week 24/Cycle 2 Week 8[c]	57	[43, 70]
Week 28/Cycle 2 Week 12[c]	85	[71, 95]
Week 31/Cycle 2 Week 15[c]	106	[96, 109]
Week 32/Cycle 2 Week 16[c]	113	[110, 126]
Week 36/Cycle 2 Week 20[c]	141	[127, 154]
Week 40/Cycle 2 Week 24[c]	169	[155, 182]
Week 44/Cycle 2 Week 28[c]	197	[183, 207]
Week 47/Cycle 2 Week 31[c]	218	[208, 235]
Week 52/Cycle 2 Week 36[c]	253	>=236

[a] Relative to the date of the SLT treatment.

[b] Relative to the date of Bim SR 1st implant. If a patient did not receive the first Bim SR cycle, but treated in SLT at Day 1, Bim SR cycle 1 Day 1 will be determined as SLT+ 3 days.

[c] Relative to the date of Bim SR 2rd implant.

Table 16-3 Visit windows for patients who had Bim SR Cycle 1, 2 and 3 implants

Derived Visit	Target Visit Day	Visit Window
Baseline [a]	-1	≤ (SLT Date -1)
SLT/Sham SLT Administration Day 1	1	SLT Date
Bim SR Cycle 1 Day 1[b]	Bim SR Cycle 1 Day 1	Bim SR Cycle 1 Day 1
Bim SR Cycle 1 Day 2[b]	Bim SR Cycle 1 Day 1 + 1	Bim SR Cycle 1 Day 1 + 1
Week 4/Cycle 1 Week 4[b]	25	[Bim SR Cycle 1 Day 1+ 2, 38]
Week 8/Cycle 1 Week 8[b]	53	[39, 66]
Week 12/Cycle 1 Week 12[b]	81	[67, 91]
Week 15/Cycle 1 Week 15[b]	102	[92, Bim SR Cycle 2 Day 1- Bim SR Cycle 1 Day 1]
Week 16/Bim SR Cycle 2 Day 1[c]	1	Bim SR Cycle 2 Day 1
Cycle 2 Day 2[c]	2	Bim SR Cycle 2 Day 1 + 1
Week 20/Cycle 2 Week 4[c]	29	[Bim SR Cycle 2 Day 1+ 2, 42]
Week 24/Cycle 2 Week 8[c]	57	[43, 70]
Week 28/Cycle 2 Week 12[c]	85	[71, 95]
Week 31/Cycle 2 Week 15[c]	106	[96, Bim SR Cycle 3 Day 1- Bim SR Cycle 2 Day1]
Week 32/Bim SR Cycle 3 Day 1[d]	1	Bim SR Cycle 3 Day 1
Cycle 3 Day 2[d]	2	Bim SR Cycle 3 Day 1 + 1
Week 36/Cycle 3 Week 4[d]	29	[Bim SR Cycle 3 Day 1+ 2, 42]
Week 40/Cycle 3 Week 8[d]	57	[43, 70]
Week 44/Cycle 3 Week 12[d]	85	[71, 95]
Week 47/Cycle 3 Week 15[d]	106	[96, 123]
Week 52/Cycle 3 Week 20[d]	141	>=124

[a] Relative to the date of the SLT treatment.

[b] Relative to the date of Bim SR 1st implant. If a patient did not receive the first Bim SR cycle, but treated in SLT at Day 1, Bim SR cycle 1 Day 1 will be determined as SLT+ 3 days.

[c] Relative to the date of Bim SR 2rd implant.

d Relative to the date of Bim SR 3rd implant.

16.3 DERIVED VARIABLES

Not applicable.

16.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

For safety parameters, if a patient has repeated assessments before the SLT treatment, unless otherwise stated, the results from the latest non-missing assessment made prior to the SLT 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.

16.5 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.

16.6 MISSING CAUSAL RELATIONSHIP TO BIM SR IMPLANT 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.

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

Per database design, only the day part of an AE start or stop date could be set to 'unknown', month and year cannot be set to 'unknown'. If the day part is missing, it will be imputed as follows:

- If the month and year of the incomplete start date are the same as the month and year of the SLT Date or Bim SR Cycle 1 Date or Bim SR Cycle 2 Date or Bim SR Cycle 3 date, the day part of the earliest of the above matching dates will be used to impute the missing day.
- If either the year of the incomplete start date is before the year of the date of the SLT treatment or if both years are the same, but the month of the incomplete start date is before the month of the date of the SLT treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of SLT treatment or if both years are the same, but the month of the incomplete start date is after the month of the date of the SLT treatment, the first day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are the same as the month and year of the SLT Date or Bim SR Cycle 1 Date or Bim SR Cycle 2 Date or Bim SR Cycle 3 date, the day part of the latest of the above matching dates will be used to impute the missing day.
- If either the year of the incomplete stop date is before the year of the date of the SLT treatment or if both years are the same, but the month of the incomplete stop date is before the month of the date of the SLT treatment, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete stop date is after the year of the date of SLT treatment or if both years are the same, but the month of the incomplete stop date is after the month of the date of the SLT treatment, the last day of the month will be assigned to the missing day.

However, after the imputation if the stop date appears to be before the start date, start date will be set to stop date if the stop date was complete (non-missing) and stop date will be set to start date if the start date was complete (non-missing).

16.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including medications of interest, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. Per database design, year part of a medication start or stop date cannot be set to 'unknown' and if the medication started after informed consent form is signed, start date must be a complete date. If a medication stopped during the course of the study, then the medication stop date must be complete. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

16.8.1 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.

Missing month and day

- If the year of the incomplete start date is same as the year of the informed consent date, *January 1* will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the informed consent date, *December 31* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to rules described above.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the informed consent date, first day of the month will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the informed consent date or if both years are the same, but the month of the incomplete start date is before the month of the informed consent date, the last day of the month will be assigned to the missing day.

16.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be set equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the informed consent date, the month and day of the informed consent date will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of informed consent date, *December 31* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the rules described above.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the informed consent date, the day of the informed consent date will be assigned to the missing day.

- If either the year of the incomplete stop date is before the year of the date informed consent date or if both years are the same, but the month of the incomplete stop date is before the month of the informed consent date, the last day of the month will be assigned to the missing day

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

18.0 REFERENCES

None

19.0 AMENDMENTS

19.1 AMENDMENT 1

1. Provided the detail algorithm of mITT in Section 6.1 per protocol Amd 3.

    - If a patient had a missing Cycle 2 Day 1Bim SR administration date with study exit date after March 19, 2020 (IWRS deactivation date), unless the patient had AE leading to drug withdrawn or received a rescue medication before March 19, 2020 in planned Bim SR eye, then the patients will be excluded from the mITT.

2. In Section 6.3, caveat of treatment group assigned in safety population is added for patients who had two study treatments in the study eye.

    - However, one patient received both SLT and Bim SR in the study eye. Safety assessment for the patient will be summarized under the Bim SR treatment group.

3. In Section 7.0, definition of study and analysis cycle completers are updated to utilize eCRF disposition status since no eCRF from available to capture the safety follow-up completion.

4. In Section 10.3 [redacted]

5. In Section 10.4, additional sensitivity analysis is added.

    - To explore different covariates and covariance matrix in the primary analysis for the mITT population, the interaction of baseline IOP with visit will be used by replacing the interaction between treatment and baseline

IOP and the interaction between treatment and eye will be removed from the primary analysis model An unstructured covariance matrix (6×6 matrix) will be used for measurements across 3 primary visits (Weeks 4, 12, and 24) and between eye correlation.

6. In Section 11.0, definition of Bim SR cycle is updated to Analysis Cycle.

   - ~~SLT Cycle: SLT date through Cycle 1 Bim SR implant date -1~~
   - **Analysis ~~*Bim SR*~~ Cycle1**: ~~*Cycle 1 Bim SR implant*~~ SLT Treatment date (Day 1) through the second ~~*Cycle 2*~~ Bim SR implant date – 1. If the second Bim SR implant was not given to a patient, all safety assessments through Week52/Exit visit/last study visit available will be included in analysis cycle1.
   - **Analysis ~~*Bim SR*~~ Cycle 2**: Second ~~*Cycle 2*~~ Bim SR implant date through the third ~~*Cycle 3*~~ Bim SR implant date – 1. If the third Bim SR implant was not given to a patient, all safety assessments through Week52/Exit visit/last study visit available will be included in analysis cycle 2.
   - **Analysis ~~*Bim SR*~~ Cycle 3**: Third ~~*Cycle 3*~~ Bim SR implant date through Week 52/Exit visit/last study visit available. Note that only Stage 1 patients were eligible to receive third Bim SR implant.

7. In Section 11.1, analysis of SLT procedure related ocular TEAEs by SOC and PT is added.

8. In Section 16.1, delete the statement below since mITT is covered excluding patients who had one Bim SR implant. Details for mITT is described in Section 6.1.

   - ~~Additionally, for patients treated with Bim SR in Cycle 2, Week 24 data in primary analysis will be treated as missing if Bim SR treatment was not done in Cycle 2.~~

Electronic Signatures

User	Date	Justification
[redacted]	02-Oct-2020 23:27:42 (GMT)	Document Originator Approval
	02-Oct-2020 21:17:52 (GMT)	Subject Matter Expert Approval
	02-Oct-2020 23:24:21 (GMT)	Manager Approval
	02-Oct-2020 22:14:27 (GMT)	Subject Matter Expert Approval