1.0 TITLE PAGE

STATISTICAL ANALYSIS PLAN- Amendment 1.1

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

Amendment 1.1: Mar 2022

Protocol Number:	192024-093
Development Phase:	Phase 3
Name of Investigational Product:	Bimatoprost sustained release (SR)
Study Statistician:	[redacted]

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ATC	anatomical therapeutic chemical
ANCOVA	analysis of covariance
BCVA	best-corrected visual acuity
Bim SR	Bimatoprost SR
CCT	central corneal thickness
CECD	corneal endothelial cell density
CI	confidence interval
CV	coefficient of variation
CV_{AVE}	coefficient of variation average
dB	decibels
DBL	database lock
ECD	endothelial cell density
eCRF	electronic case report form
HEX_{AVE}	pleomorphism average
IOP	intraocular pressure
ITT	intent-to-treat
KM	Kaplan-Meier
LOCF	last observations carried forward
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MD	mean defect
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MMRM	mixed effect model for repeated measurement
MNAR	missing not at random
NA	not applicable
OAG	open-angle glaucoma
OD	right eye
OHT	ocular hypertension
OS	left eye
OU	both eyes
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
SOC	system organ class
SR	sustained release
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 192024-093. Specifications of tables, figures, and data listings (TFLs) are contained in a separate document.

Study 192024-093 is a multicenter, paired-eye, randomized, efficacy evaluator-masked 26- 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).

The study duration is approximately 26 months, including screening period of up to 28 days before washout; a washout period of up to 56 days before initial study treatment; and 24 months of follow-up after the initial Bim SR and SLT administration. 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. 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 key changes made in study protocol amendments that would impact the analysis dataset are summarized in Table 4-1.

Table 4-1 Summary of Protocol Amendments with Revisions related to Statistical Analysis

Protocol Amendment	Summary
Amendment 3	• 2 Bim SR administrations given at Day 4 and Week 16. • Discontinuation of Bim SR 15 µg dose strength for newly enrolled patients under Amendment 3. • Bim SR 10 µg dose strength was started to treat newly enrolled patients. (Stage 1: Bim SR 15 µg with 2 administration cycles; Stage 2: Bim SR 10 µg with 2 administration cycles).
Amendment 6	• For patients who do not meet retreatment criteria at Week 16, the second administration of Bim SR 10 µg may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met. (Note that for all patients who were enrolled and reached the Week 16 visit prior to implementation of Amendment 6, retreatment with Bim SR was fixed at Week16).

To mask the patient to the treatment assigned to each eye, on Day 1 a Sham SLT procedure will be performed in the eye that will receive Bim SR administrations (hereafter referred to as the Bim SR eye). Similarly, a sham, needleless Bim SR administration (hereafter referred to as the Sham Bim SR administration and involves touching the eye at the area of insertion with a needleless applicator that does not deliver an implant into the anterior chamber) will be performed on the SLT-treated eye (hereafter referred to as the SLT eye) at the Bim SR administration visits.

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 at eye level by randomized treatment (Bim SR and SLT). Where appropriate, data summaries at patient level will be provided.

Table 4-2 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)[a]	Bim SR	Sham Bim SR

SLT = selective laser trabeculoplasty; SR = sustained release

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

Three database locks will be performed:
1) when all patients treated with Bim SR 10 µg have completed the Week 24 visit or have prematurely discontinued before the Week 24 visit (referred to as the primary DBL);
2) when all patients treated with Bim SR 10 µg have completed the Month 12 visit or have exited the study prior to Month 12 (referred to as the Month 12 DBL). To provide sufficient safety follow-up data after the repeat administrations, the second database lock will occur when all patients have completed a minimum of 3 months of follow-up after the second administration or reached Month 12 without the need for the second administration; and
3) when all patients treated with Bim SR 10 µg have completed the Month 24 visit or have prematurely discontinued before Month 24 (referred to as the final DBL).

Analyses will be performed on unmasked data after each lock. The analysis based on the primary database lock will be considered as the primary analysis of the study. The analysis plan will support each of DBLs, but some analyses will be reduced for the final DBL (e.g, the primary efficacy analysis will not be re-produced at the final DBL).

Additional unmasked analyses based on accumulated data may be conducted after the initial Week 24 DBL (primary DBL) to support health authority submissions (e.g, 120 Day Safety Update and responses to questions). These analyses will be consisted of available data that are deemed suitable for regulatory submissions, although may not be of the quality standard used for formal, prespecified database locks.

Schedule of visits and procedures to be performed on randomized patients are presented in Table 4-3 to Table 4-7.

Table 4-3 Administration Cycle 1 Schedule of Visits and Procedures: Screening through Day 2

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

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

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

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

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

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

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

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

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

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

[h] At selected sites/patients, additional IOP measurements will be performed at Hour 2 and Hour 8.

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

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

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

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

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

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

Visit	Bimatoprost SR Cycle 1 Day 1 Administration	Cycle 1 Day 2 Safety Visit	Cycle 1 Day 4 Phone Call[a]	Cycle 1 Week 2 Phone Call[a]	Week 4	Week 8	Week 12	Week 15[b]
Visit	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[c]		OU			OU	OU	OU	OU
Best-Corrected Visual Acuity[d]		OU			OU	OU	OU	OU
Intraocular Pressure H0	SC/T[e]	OU			OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)								
Macroscopic Iris Color Assessment					OU		OU	
Manifest Refraction[d]							OU	
Specular Microscopy					OU		OU	
Biomicroscopy[c]	SC/T[e]	OU			OU	OU	OU	OU
Intraocular Pressure H2 and H8 (selected sites/patients)[f]							OU[f]	
Gonioscopy/Angle Assessment					OU[g]	OU	OU[g]	OU
Pachymetry (may be done any time after gonioscopy)					OU		OU	
Pupil Dilation (may perform post-dilation eye exams in any order)							OU	
Dilated Ophthalmoscopy							OU	

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

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

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

[b] Patients who meet the retreatment criteria will receive Cycle 2 administration at Week 16 (Table 4-5). Patients who do not receive Cycle 2 administration at Week 16 will not attend the Cycle 2 Administration Day visit at Week 16, or the Day 2 Safety and Day 4 and Week 2 phone call visits (visits shaded in grey in Table 4-5). For these patients, the second administration of Bimatoprost SR may be performed at the investigator's discretion during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met.

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

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

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

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

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

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

[i] [redacted]

Table 4-5 Administration Cycle 2 Schedule of Visits and Procedures: Week 16 through Week 31

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

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

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

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

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

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

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

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

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

[g] For all patients, IOP measurements will be performed at Hour 0 [8:00 AM ± 1 hour]. At selected sites in consenting patients, additional IOP measurements will be performed at Hour 2 (Hour 0 + 2 hours [± 30 minutes]) and Hour 8 (Hour 0 + 8 hours [± 30 minutes]).

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

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

[redacted]

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

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

Visits	Week 36	Week 40	Week 44	Week 47	Week 52
Visit Windows	±4 days	±4 days	±4 days	±4 days	±4 days
Optic Disc Examination		OU			OU

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

a [redacted] See Procedure Manual for details.

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

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

d [redacted] See Procedure Manual for details.

e [redacted] See Procedure Manual for details.

Table 4-7 Schedule of Visits and Procedures: Month 13 through Month 24/Exit

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

Visits	Month 13[a]	Month 14	Month 15[a]	Month 16	Month 18	Month 20	Month 22[a]	Month 24/Exit
Visit Windows	±4 days	±4 days	±4 days	±4 days	±7 days	±7 days	±7 days	±7 days
Optic Disc Examination				OU		OU		OU
Contact Interactive Response System[g]								X

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

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

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

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

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

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

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

[g] Contact at Month 24/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).

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

6.2 PER-PROTOCOL POPULATION

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

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:

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

A separate document will be prepared to describe the data exclusion criteria and algorithm for PP analysis. Additional considerations for PP exclusion from the IOP analysis may include situations where out of time window for Hour 0 IOP data; concomitant medication (or procedure) that potentially affects IOP data but is not identified as a non-study IOP lowering medication (or procedure) in the eCRF; or, implant removal, etc.

All patients with data excluded from the PP analysis will be identified and finalized prior to the primary 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 study treatment (regardless of whether it was the randomized 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. If a patient received both SLT and Bim SR in the same eye, safety assessment for this 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, Safety, and PP) will be summarized for the overall study. The numbers and percentages of patients randomized by country 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 as defined in Figure 11-1, with categories of premature discontinuation reasons included.

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).

8.0 DEMOGRAPHICS AND OTHER BASELINE DATA

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

8.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic parameters (including age, age group, race, race group, ethnicity, sex) and baseline characteristics (weight [kg], height [cm], and iris color) 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). The iris color will be summarized by color for each of the following categories: monochromic, heterochromic peripupillary, and heterochromic diffuse. In addition, the reason for not being adequately managed with topical IOP-lowering medications (memory loss, physical inability to administer medication, tolerability, and other) will be summarized at patient level.

8.2 BASELINE DISEASE CHARACTERISTICS

Baseline disease characteristics for each eye will be descriptively summarized by treatment of the eye for the following variables for the ITT population: diagnosis of either Open-Angle Glaucoma (OAG); primary, pseudoexfoliation , pigmentary, or Ocular Hypertension (OHT), baseline Hour 0 IOP (≤ 25 mm Hg or > 25 mmHg), iridocorneal angle Shaffer grade, and central endothelial cell density.

8.3 MEDICAL AND SURGICAL HISTORY

Abnormalities in patients' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), 23.1 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 the Bim SR eye and/or SLT eye at randomization will also be summarized separately for the ITT population by SOC and PT

8.4 PRIOR AND CONCOMITANT MEDICATIONS

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

Prior medications are defined as medications taken before the date of the first administration of study treatment. Concomitant medications are defined as those medications taken on or after the date of the first administration of study treatment. If a medication is taken before the date of the first administration of study treatment and continues after initiation of study treatment, it will be considered as both a prior medication and 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 for the ITT population. 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 days from the SLT administration date to the last visit date as shown below.

- Study duration = 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 diurnal IOP analyses.

Unless specified otherwise, the IOP measurements obtained after initiating the use of non-study IOP-lowering treatment (medications or procedures or both) in an eye will be excluded from the efficacy analysis.

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.

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

Primary efficacy analysis will be performed for patients treated with Bim SR 10 µg in the ITT population. The null and alternative hypotheses for the comparisons of IOP-lowering effect between Bim SR 10 µg and SLT at Weeks 4, 12, and 24 are:

- Null hypothesis: the difference in mean IOP change from baseline between the Bim SR 10 µg and SLT (Bim SR 10 µg minus SLT) is > 1.5 mmHg.
- Alternative hypothesis: the difference in mean IOP change from baseline between the Bim SR 10 µg and SLT (Bim SR 10 µg 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, visit-by-baseline Hour 0 IOP, visit-by-eye interactions as fixed effects. Unstructured covariance matrix for study visits and eyes will be used for repeated measures on the same patient. IOP measurements obtained after initiating the use of non-study IOP-lowering medication or procedure in an eye will be treated as missing. This will correspond to the hypothetical strategy defined in ICH E9 addendum (Section 18.0). If the model fails to converge, multiple imputation (MI) will be implemented for missing data before applying MMRM.

The mean difference in the Hour 0 IOP change from baseline between the Bim SR 10 µg and SLT (Bim SR 10 µg minus SLT) in the ITT population and the corresponding 95% confidence intervals (CI) will be constructed at each visit of Weeks 4, 12, and 24 from MMRM analysis. If the upper limit of the 95% CI is ≤ 1.5 mmHg at all 3 visits, the statistical noninferiority of Bim SR 10 µg to SLT is demonstrated.

For additional clinical consideration, Bim SR 10 µg 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.

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

```
proc mixed data=iop;
     where avisitn >1;
     class subjid eye trt avisitn;
     model chg=trt avisitn eye base trt*avisitn
               avisitn*base avisitn*eye/ddfm=kr;
```

```
     repeated avisitn*eye/type=un subject=subjid rcorr;
     lsmeans trt*avisitn/diff;
run;
```

The definitions of variables are:
`chg` = Hour 0 IOP change from baseline at the primary analysis time points of Week 4, Week 12, and Week 24
`avisitn` = 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

10.2.1 Superiority Test of Bim SR 10 µg versus SLT

As the secondary efficacy analysis, a superiority test of Bim SR 10 µg versus SLT will be performed if the statistical noninferiority is demonstrated in the primary efficacy analysis for the ITT population as the gatekeeping procedure to control overall type I error rate at the 0.05 level. Superiority of Bim SR 10 µg versus SLT is considered achieved if the upper limit of the 95% CI is < 0 mmHg at Weeks 4, 12, and 24.

10.2.2 Time to Initial Use of Non-study IOP-lowering Treatment

Time to the initial use of non-study IOP-lowering treatment from the Date of the First Treatment as defined below will be analyzed 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 (Day 1), and the Date of First Treatment for Bim SR 10 µg is Bim SR 10 µg administration date (Day 4).

Additionally, for Bim SR 10 µg, the time to non-study IOP-lowering treatment from the second injection will be summarized:

- Time to initial use of non-study IOP-lowering treatment from the second Bim SR 10 µg administration = (Date of initial use of non-study IOP-lowering treatment after the second Bim SR 10 µg implant – Date of the second Bim SR 10 µg administration) +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 treatment 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 10 µg administration, patients with at least two Bim SR 10 µg administrations will be used, and the event will be censored at the last available visit date or exit date if the patients did not use any non-study IOP-lowering treatment.

10.2.3 Percentage of Bim SR and SLT Eyes Achieving ≥ 20% Reduction by Visit

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

10.2.4 IOP Changes from Baseline at Weeks 8, 15, and 20

IOP values at Week 8, 15 and 20 and the changes from baseline will be descriptively summarized for Bim SR 10 µg and SLT at each timepoint for the ITT population.

10.3 OTHER EFFICACY ANALYSES

Other efficacy analyses comparing Bim SR 10 µg and SLT include:

- IOP change from baseline as time-weighted average through Week 24
- Post-baseline IOP as time-weighted average through Week 24
- Time to first achieving ≥ 20% IOP reduction
- Percentage of eyes achieving ≥ 15% and ≥ 30% reductions from baseline IOP by visit
- Diurnal IOP

Analyses will be performed for the ITT population. KM method will be used for time to event analysis.

For patients treated with Bim SR 15 µg, descriptive statistics for baseline and change from baseline IOP will be summarized for each eye (SLT and Bim SR 15 µg) and visits in the ITT population.

10.3.1 IOP Change from Baseline (and Post-baseline IOP) Time-weighted Average through Week 24

Time-weighted average change in IOP from baseline is calculated as described below:

Let $y_0, y_1, \ldots, y_n$ represent IOP measurements taken on calendar dates $d_0, d_1, \ldots, d_n$ respectively, where y_0 is the measurement taken on calendar date d_0, representing baseline IOP value, and let $\Delta y_i = y_i - y_0$, representing the change in IOP from baseline to date di for i=0, 1,…, n. Then the time-weighted average change, denoted by S1 is:

$$S1 = \frac{1}{(d_n - d_0)} \sum_{k=1}^{n} (\Delta y_k + \Delta y_{k-1}) \times \frac{(d_k - d_{k-1})}{2}$$

In this analysis, IOP measurements taken at Baseline (at d_0), Week 4, Week 8, Week 12, Week 15, Week 20, and Week 24 will be considered, thus n = 6. The analysis visit with missing value will be skipped from the calculation. S1 will be calculated for each patient and each eye by using the actual dates of the IOP measurements. The time-weighted average change from baseline will be summarized descriptively by Bim SR 10 µg eye and SLT eye. Similar equation will be applied for the time-weighted average post-baseline IOP.

10.3.2 Time to Onset of Effect (Time to First Achieving ≥ 20% IOP Reduction)

Percentage reduction in Hour 0 IOP from baseline will be calculated for all available post-baseline IOP measurement visits for each eye using the formula:

- Percentage Reduction = 100 x (Baseline IOP – Visit IOP)/Baseline IOP

Time in days to onset of effect will be calculated using the Date of First Treatment and the date of the earliest observation of ≥ 20% reduction in IOP using the formula:

- Time to onset of effect = (Date of the earliest observation of ≥ 20% reduction – Date of First Treatment) +1

where the Date of First Treatment for SLT is SLT treatment date (Day 1), and the Date of First Treatment for Bim SR 10 µg is the first administration date (Day 4).

For eyes that did not achieve ≥ 20% reduction in IOP at any post-baseline visit, 'Time to onset of effect' will be censored at the date of the latest IOP measurement. Due to large IOP drop on the day immediately after treatment, the IOP values within two days after SLT or Bim SR 10 µg treatment will not be considered for this analysis. Time to onset of effect associated with each eye will be analyzed using Kaplan-Meier method with graphical displays.

10.3.3 Percentage of Bim SR and SLT Eyes Achieving ≥ 15% and ≥ 30% Reductions in IOP by Visit

Number and percent of eyes that have achieved a ≥ 15% reduction in IOP will be summarized by visit and by treatment. Similar summaries for patients achieved ≥ 30% reductions in IOP will be provided.

10.3.4 Diurnal IOP Analyses

For consenting patients at selected sites, diurnal IOP measurements will be conducted at Hour 0, 2, and 8. The diurnal IOP measurements will be summarized by hour and by visit. Additionally, descriptive statistics for the mean IOP across Hours 0, 2, and 8 will be summarized by visit for patients who had least 2 IOP measurements available out of 3 timepoints. Similarly, descriptive statistics of the IOP range (max IOP – min IOP among three timepoints) will be summarized by visit.

10.3.5 Baseline Hour 0 IOP and Change from Baseline in Bim SR 15 µg

For patients treated with Bim SR 15 µg, descriptive statistics for baseline and change from baseline in Hour 0 IOP will be summarized for Bim SR 15 µg and SLT separately at each visit.

10.4 SENSITIVITY ANALYSES

10.4.1 Per Protocol Analysis

As part of the sensitivity analyses, the mean difference and 95% CI in the IOP change from baseline between the Bim SR 10 µg and SLT (Bim SR 10 µg minus SLT) will be constructed for Week 4, 12, and 24 visits for the Per Protocol (PP) population using the same MMRM model as specified for the primary analysis.

10.4.2 Analysis of Covariance (ANCOVA)

Analysis of Covariance (ANCOVA) including within-patient correlation at each visit will be conducted for IOP change from baseline at Weeks 4, 12, and 24 in the ITT population. In this analysis, missing data will be imputed using the last observation carried forward. At each visit, the model for IOP change from baseline is specified as: IOP Change from Baseline = Treatment + Eye + Baseline IOP, where Eye is a primary eye or a contralateral eye. Unstructured covariance matrix will be used for between eye correlation.

10.4.3 Treatment Effect Regardless of Non-Study IOP Treatment Use

To evaluate the treatment effect regardless of whether there is any use of non-study IOP lowering treatment, the MMRM analysis for primary analysis in Section 10.1 will be performed in the ITT population using all available Hour 0 IOP data. In this analysis, data after the use of non-study IOP lowering treatment will not be excluded.

10.4.4 Tipping Point Analysis

A tipping-point analysis will be used to assess the robustness of the primary efficacy analysis with respect to possible deviations from missing at random (MAR) assumption in MMRM model. This analysis will evaluate the sensitivity of study results under the missing not at random (MNAR) assumption.

Tipping point analysis will be based on multiple imputed (MI) datasets for IOP data as described in Section 17.2 while applying a shift parameter to imputed IOP data for Bim SR 10 µg treated eyes. Specifically, missing IOP data will be calculated by adding a positive shift value to the imputed data to discount the treatment effect for Bim SR 10 µg. This shift will essentially make the IOP data higher than imputed for Bim SR 10 µg treated eyes. Note that there will be no shift applied to SLT treated eyes. With each shift, the MMRM analysis as specified for the primary efficacy will be performed based on the MI-based but shifted IOP data. SAS PROC MIANALYZE procedure will be used to aggregate the analysis results by using the parameter estimates from each imputed dataset.

Starting from a shift of 0 mmHg (ie, no shift), the above procedures will be repeated with incremental shift values of 1 mmHg. The shift values will be adjusted with unmasked data. The tipping point is reached when the analysis result being switched from positive (ie, Bim SR 10 µg is non-inferior to SLT) to negative (ie, Bim SR 10 µg is no longer non-inferior to SLT). The corresponding shift value is defined as the tipping point. If the IOP value at the tipping point is clinically implausible, the primary analysis results will be considered as robust.

The scientific plausibility, clinical relevance, as well as the interpretations of the different shift values will be discussed in the clinical study report.

10.4.5 Impact of Receiving the 2nd Bim SR After Week 16 and Prior to Week 24

Some patients may receive the second Bim SR 10 µg administration after Week 16 and prior to Week 24, thus the time interval between the second Bim SR 10 µg administration and the primary analysis endpoint at Week 24 will be shorter for these patients as compared with patients who received the second Bim SR 10 µg at Week 16. To evaluate any potential impact of this difference in timing of the second administration on Week 24 IOP data from these patients in the primary analysis, additional sensitivity analysis will be conducted by excluding the IOP data at Week 24 for these patients. More specifically, for patients who received flexible administration of the second Bim SR 10 µg beyond the Week 16 visit, the Week 24 IOP assessment will be excluded from the current sensitivity analysis if the second administration date is in the analysis windows for Week 20 or Week 24 and prior to the Week 24 IOP assessment. The MMRM model for the primary efficacy analysis as described in Section 10.1 will be used.

11.0 SAFETY ANALYSES

All safety analyses will be performed using the safety population. 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. As indicated in Section 6.4, safety data collected at Screening for eligibility assessment will not be analyzed.

All safety analyses described in the section 11.0 will be performed both Bim SR 10 µg and Bim SR 15 µg.

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.

Non-ocular safety analysis includes non-ocular adverse events (AEs), clinical laboratory results, vital signs (blood pressure, pulse rate and temperature), and pregnancy test results.

Safety analyses will be summarized by study periods. Analysis study periods are defined as follows:

- **During the study**: Date of SLT treatment through Month 24/Exit visit/last study visit available.
- **Analysis Cycle 1**: SLT Treatment date (Day 1) through the second Bim SR administration date – 1. If the second Bim SR administration was not given to a patient, all safety assessments through Month 24/Exit visit/last study visit available will be included in analysis cycle1.
- **Analysis Cycle 2**: Second Bim SR administration date through Month 24/Exit visit – 1.
- **Analysis Cycle 3**: Third Bim SR administration date through Month 24/Exit visit – 1, valid for only Bim SR 15 µg.

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

Figure 11-1 Analysis Cycle Illustration

	Cycles for Safety Data Analyses	
Treatment Schedule	SLT eye	BIM SR eye
Day 1, SLT administration	Analysis Cycle 1	Analysis Cycle 1
Day 4, Bim SR 1st administration	Analysis Cycle 1	Analysis Cycle 1
Week 16[a], Bim SR 2nd administration	Analysis Cycle 2	Analysis Cycle 2

Week 32[b], Bim SR 3rd administration	Analysis Cycle 3	Analysis Cycle 3

[a] The second administration of Bim SR 10 µg is performed at Week 16 for all patients who meet retreatment criteria. For those patients not meeting retreatment criteria at Week 16, the second administration may be performed during an unscheduled visit after Week 16 and prior to the Month 12 visit if the retreatment criteria are met.
[b] Analysis cycle 3 is valid only for Bim SR 15 µg.

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, version 22.0 or newer.

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.

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 TEAEs
    - Ocular
    - Non-ocular
- Treatment-related TEAEs:
    - Ocular
        - Related to study drug
        - Related to study drug administration procedure
        - Related to SLT laser
    - Non-ocular
- Treatment-related serious TEAEs:

  - Ocular
    - Related to study drug
    - Related to study drug administration procedure
    - Related to SLT laser
  - Non-ocular
- Any TEAEs leading to Bim SR implant removal
- Any TEAEs leading to study discontinuation
- Deaths

The following non-ocular TEAEs 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.

Ocular TEAEs will be summarized by analysis cycle and by treatment eye as described below:

- Any ocular TEAEs by 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 for the Bim SR eye and/or (Bim SR sham for the SLT eye)
- 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 for the Bim SR eye and/or (Bim SR sham for the SLT eye) to next Bim SR/ Sham Bim SR treatment (Bim SR sham for SLT eye)
- 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:

Line change = $10\times[\log_{10}(25/80)] = 10\times(-0.5)$ (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.

Summary statistics for the line change from baseline will be presented by visits in each of the following categories: worsening (< -2), no change (≥ -2 and ≤ 2), and improvement (> 2). The data for the largest line change from baseline across follow-up will be summarized for the entire study period (overall) and analysis cycle. The largest line change is defined as the greatest decrease from baseline in the number of lines read during the entire study period for overall summary or within analysis cycle for by-cycle summary.

11.3.3 Visual Field

Visual field examinations will be assessed by automated perimetry with either the Humphrey Field Analyzer (using a 24-2 full threshold or 24-2 [SITA] Standard program) or the Octopus Perimeter (using a G1 Dynamic or Normal strategy or 24-2 Dynamic or Normal strategy program) at Screening, Baseline, Week 24, Week 52, Month 18, and Month 24/Exit. The same machine type (Humphrey vs. Octopus) 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. Number and percentage of any post-baseline abnormal findings compared with baseline normal findings on visual field will be summarized by eye and by visit regardless of the machine type.

In addition, mean deviation or mean defect (MD) and change from baseline recorded in decibels (dB) 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. For patients, whose visual fields were assessed by one machine type as recorded, but there is a missing machine type at a post-baseline visit, the missing machine type will be assumed as the same machine type and the mean deviation or mean defect assessments will be derived.

11.3.4 Macroscopic Conjunctival Hyperemia

Severity assessment of hyperemia of each eye is performed at all scheduled visits except on any of the study treatment administration days using the following severity scale: 0 (None), +0.5 (Trace), +1 (Mild), +2 (Moderate), +3 (Severe) or ‘Not Evaluable’.

The frequency distribution for the severity grade at each scheduled visit will be summarized by eyes. In addition, patients who had at least 2-grade increase from baseline in severity (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) will also be summarized for each eye by visits and analysis cycle. If the severity grade during an analysis cycle decreases from baseline, it will be considered as 'no increase'.

11.3.5 Specular Microscopy

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, Week 52, Month 16, Month 20, and Month 24/Exit. Baseline endothelial cell density (measured at Screening), raw values, and change from baseline as well as percent changes from baseline will be summarized descriptively by visit and analysis cycle for each eye.

The number and percentage of patients will be tabulated by various thresholds (including but not limited to endothelial cell count change; e.g, >=10% gain, >=10% loss, >=15% loss, etc.) for the percent change from baseline at each visit and at the last visit (i.e., last visit assessment). Overall summary during the entire study and within analysis cycle will be summarized based on the greatest decrease from baseline.

Kaplan-Meier Analysis for Time to ECL Event

To further investigate the endothelial cell loss (ECL), time to event analyses will be performed on the ECL event using Kaplan-Meier (KM) method with graphical displays. The ECL event is defined as post-baseline percent loss in central corneal endothelial cell density (CECD) meeting a specified threshold. The analyses of ECL events will be performed for threshold values of ≥15% and ≥20%. For each threshold value, *First Observed* ECL and *First Confirmed* ECL are defined as following:

1. First *Observed* ECL: The first *observed* ECL meeting the threshold is considered the initial ECL event.
2. First *Confirmed* ECL:

   The first *confirmed* ECL event is defined as the first of two ECLs meeting the same threshold at two consecutive visits (scheduled or unscheduled) with CECD assessment done on different days.
   - ✓ For discontinued or completed patients, if the first ECL event meeting the threshold occurs at the patient's final CECD assessment before discontinuing/exiting the study, the loss will be counted as a confirmed loss at that date.
   - ✓ For analyses performed prior to the final database lock, if a patient is continuing in the study and the first ECL meeting the threshold occurs at the

most recent CECD assessment visit before data cutoff, the loss will NOT be counted as a confirmed loss.

The KM analyses will be performed for each of the first *confirmed* ECL and the first *observed* ECL. Compelling evidence of intra-eye variability of CECD has been observed in global, well-controlled, randomized, multicenter studies despite methodological measures in place to control for CECD variability. Therefore, the key analysis for Time to ECL Event will based on the confirmed ECL values. For each analysis, Time (days) is calculated as follows:

- Time to the First *Confirmed* ECL event = (Date of the First *Confirmed* ECL event – Date of the First Study Treatment) + 1,
- Time to the First *Observed* ECL event = (Date of the First *Observed* ECL event – Date of the First Study Treatment) + 1,

where the Date of First Study Treatment is the first date of Bimatoprost SR 10 µg or SLT administration. For eyes that did not have any observed ECL events, time to the first ECL event will be right-censored at the last available CECD assessment date.

For each scheduled visit, the tabulation will display the number of eyes at risk, cumulative number of eyes with events, and the cumulative probability of event and the associated 95% confidence interval.

Exposure Adjusted Analysis for ECL Rate

Additionally, to take into account the differences in follow up time, an exposure-adjusted analysis for ECL rate over the entire study period will be performed by treatment for Bimatoprost SR 10 µg and SLT treated eyes. Exposure time will be calculated for each treated eye. For eyes that experienced an ECL event during the study, exposure time is the number of days from the first study treatment administration to the date when the first ECL event occurred. For eyes without an ECL event, exposure time is the number of days from the first study treatment administration to the last assessment for CECD. Exposure time in person-years is calculated as (exposure time in days)/365.25. Exposure adjusted ECL rate will be calculated per 100 person-years as:

- 100 ×(number of eyes that experienced the ECL event)/total exposure time in person-years for the treatment group.

Listings for patients with ≥20% 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 and analysis cycle for each eye.

Pleomorphism Average (HEX_{AVE}): Pleomorphism average of raw data and their changes from baseline will be summarized descriptively by visit and analysis cycle 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, Week 52, Month 16, Month 20, Month 24/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 and analysis cycle 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 post-baseline visits. Dilated ophthalmoscopy examination of the vitreous, macula, and retina periphery will be performed at the Screening, Baseline, Week 12, Week 24, Week 40, Week 52, Month 16, Month 20, Month 24/Exit visits.

All findings will be coded using the MedDRA dictionary.

The Number and percentage of patient eyes with findings at least 2-grade increase in severity from baseline, or a status change from absence at baseline to presence at follow-up visit for findings which is not associated with a severity grade, at 1 or more post-baseline visits, will be summarized by preferred term in descending order of incidence rate. For findings that are associated with a severity grade, at least 2-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.

11.3.8 Optic Disc Examination

Optic nerve cup/disc ratio will be evaluated using a 0.0 to 1.0 scale, with larger values indicating more advanced optic nerve damage, thus a reduction from baseline is a considered an improvement. Categorial changes in cup/disc ratio from baseline will be summarized for post-baseline visits. 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 ($>$ -0.2 to $<$ 0.2), or a worsening if the ratio increases by 0.2 or more (i.e., change $\geq$ 0.2). The number and percentage of patients in each category will be summarized by visit and analysis cycle.

11.3.9 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, Week 52, Month 16, Month 20, and Month 24/Exit. Lens status is assessed as phakic, pseudophakic, or aphakic and recorded on the eCRF.

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 analysis cycle.

11.3.10 Gonioscopy and Bim SR Implant Assessment

Gonioscopy is performed to assess the inferior iridocorneal angle and the Bim SR implant in all study visits except SLT and Bim SR administration days for all patients.

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.

12.0 SUBGROUP ANALYSES

Subgroup analyses will be conducted for patients who received the Bim SR 10 µg administration under the flexible dosing regimen as specified in the protocol amendment 6 regardless of the visit at which patients received the second Bim SR 10 µg administration. It will include patients enrolled under amendment 6 or patients reconsented to amendment 6 before receiving the second Bim SR 10 µg administration. Otherwise, patients will be classified in the fixed dosing regimen subgroup.

In addition, subgroup analysis by the disease diagnosis, open-angle glaucoma (OAG) or ocular hypertension (OHT) at screening, will be performed on IOP data.

12.1 IOP CHANGE FROM BASELINE

The primary efficacy analysis in Section 10.1 will be performed for the ITT and PP populations for the flexible administration regimen.

For the OAG and OHT subgroups, baseline IOP and IOP change from baseline will be summarized for the ITT population.

12.2 TIME TO SECOND BIM SR ADMINISTRATION

For patients who received 2 Bim SR 10 µg administrations under the flexible dosing regimen, the time from the first to the second administration will be analyzed using Kaplan-Meier (KM) method with graphical displays:

- Time to the second administration of Bim SR= (Date of the second administration of Bim SR 10 µg – Date of the First Bim SR 10 µg) +1.

In the calculation, if a patient did not receive the second Bim SR by Month 12 as specified in the study protocol, then the patient will be censored at Month 12 unless the patient withdrew early or received non-study IOP treatment prior to Month 12 visit which ever occurred first.

12.3 ECL ANALYSES BY FIXED AND FLEXIBLE ADMINISTRATION

Analyses of time to ECL events and exposure-adjusted ECL rate as well as the number and percentage of patients by various thresholds as described in Section 11.3.5 will be performed separately for the subgroups of patients treated under the fixed and flexible administration regimens.

12.4 OCULAR ADVERSE EVENT BY FIXED AND FLEXIBLE ADMINISTRATION

Overall and by-cycle ocular adverse event, corneal adverse events, and ocular adverse events leading to implant removal will be analyzed by flexible or fixed dosing regimen subgroup. Other ocular adverse events by the subgroup may be performed on as-needed basis.

13.0 VISUAL FUNCTION QUESTIONNAIRE

National Eye Institute Visual Function Questionnaire-25 responses collected at Baseline will not be summarized as part of this SAP.

14.0 INTERIM ANALYSES

No interim analysis is planned for the study. Three database locks are planned for this study as described in Section 4.0. The analysis results based on the first database lock is considered as the primary analysis. The analyses based on the Month 12 and/or final database locks will provide further efficacy and safety information. Three CSRs will be written, one following each lock.

15.0 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 10 µg eyes and SLT eyes, and that change from baseline in IOP has a standard deviation of 4 mmHg. A sample size of 144 patients with eyes treated with Bim SR 10 µg and SLT will provide approximately 98% power in showing noninferiority in 3 out of 3 timepoints with a noninferiority margin of 1.5 mm Hg, and 90% power in showing noninferiority in 2 out of 3 timepoints with a noninferiority margin of 1.0 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 and treated with Bim SR 10 µg. Additionally, there are 55 Bim SR 15 µg treated patients who were enrolled before implementation of Amendment 3 and treated with the 15 µg Bim SR dose strength.

16.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS software.

17.0 DATA HANDLING CONVENTIONS

17.1 EFFICACY DATA

As stated in protocol Section 4.5.2 Prohibited Medications/Treatments, eye(s) may receive 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 unless specified otherwise.

For sensitivity analyses, missing data will be imputed using the last observation carried forward (LOCF) and multiple imputation method as detailed in Section 17.2.

17.2 MISSING DATA HANDLING FOR SENSITIVITY ANALYSES

17.2.1 Last Observation Carried Forward (LOCF)

Last observations carried forward method will be used to impute missing IOP data up to Week 24. In this approach, IOP data after the rescue treatment will be replaced by LOCF.

17.2.2 Multiple Imputation

Multiple imputation will be utilized to impute missing IOP values. The primary efficacy variable is Hour 0 IOP change from baseline assessed at Weeks 4, 12, and 24. However, to gain additional imputation efficiency, multiple imputation with a 2-step approach will be used for imputing missing IOP at Weeks 4, 8, 12, 15, 20, and 24 separately for each treatment group. The first step of multiple imputation will use the Markov Chain Monte Carlo (MCMC) method to impute intermittent missing data to achieve a monotone missing pattern. The second step will be based on a linear regression to impute the missing data. 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. Covariates to be included in the regression will be baseline Hour 0 IOP, race, sex, lens status, and age. The planned number of MIs is 25 and a prespecified seed of "123451" will be used for MCMC and a seed of "123457" for the regression part.

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;
```

17.3 ANALYSIS WINDOWS

Table 17-1 provides an overview of efficacy and safety assessments with visit schedule and analysis window table for by-visit and by-cycle analysis.

Table 17-1 **Visit Schedule, Visit Windows and By-Cycle Analysis for Efficacy and Safety Assessments**

Efficacy/Safety Assessments	Visit Schedule	Visit Window for by-visit and Analysis Cycle Analysis
Hour 0 IOP	Baseline, Day 2, W4, W8, W12,W15, W20,W24,W28,W31,W36,W40,W44, W47,W52, M13, M14,M15,M16,M18, M20,M22, M24/EXIT	Table 17-2
Macroscopic conjunctival hyperemia	Baseline, Day2,W4,W8,W12,W15, W20,W24,W28,W31,W36,W40,W44,W47 ,W52,M13,M14,M15,M16,M18,M20,M22 , M24/EXIT	Table 17-2
BCVA	Baseline, Day 2, W4, W8, W12, W15, w20,W24,W28,W31,W36,W40,W44, W47,W52,M13,M14,M15,M16,M18,M20, M22,M24/EXIT	Table 17-2
Visual field	Baseline, W24,W52,M18,M24/exit	Table 17-4
Specular microscopy	Baseline, W4, W12, W24, W40, W52,M16,M20, M24/Exit	Table 17-3
Biomicroscopy	Baseline, Day2, W4, W8,W12,W15, W20,W24,W28,W31,W36,W40,W44, W47,W52, M13,M14,M15,M16,M18, M20,M22, M24/EXIT	Overall by-cycle summary
Gonioscopy/ Angle assessment	Baseline,W4(optional),W8,W12(optional), W15,W20,W24(optional),W28,W31,W36, W40,W44,W47,W52,M13,M14,M15,M16, M18,M20,M22,M24/EXIT	Table 17-2
Pachymetry	Baseline, W4, W12, W24, W40, W52, M16, M20, M24/EXIT	Table 17-3
Optic disc/ Ophthalmoscopy/ Lens assessment	Baseline, W12, W24, W40, W52, M16, M20, M24/EXIT	Table 17-3

Table 17-2 presents the visits assigned for by- visit and analysis cycle analyses of the efficacy (Hour 0 IOP), and safety assessments that occur every month (or 2 months after 1-year of follow-up after the first Bim SR administration), including of macroscopic conjunctival hyperemia, best-corrected visual acuity, biomicroscopy, and gonioscopy/angle assessment. Table 17-3 presents the visit assigned for by-visit and analysis cycle that occur every 3 or 4 months, including of specular microscopy, pachymetry and optic disc assessments which occur every 3 or 4 months. Table 17-4 presents the visits assigned for by-visit and analysis cycle analyses of visual filed, ophthalmoscopy, optic disc, and lens assessments which occur every 6 months.

If both scheduled and unscheduled visit occur within a single window, the scheduled visit will be used; and unscheduled visits will be used only if there are no scheduled values available in that window. If multiple visits are eligible for windowing within a single visit window, the scheduled visit closest to target day will be used in the analysis.

If 2 visits are equidistant to the target day, the later visit will be used.

Table 17-2 Visit Windows for By Visit Analysis for Assessments Occurring Every 4 weeks

Derived Visit	**Target Visit Day***	**Visit Window***
Baseline[a]	-1	≤ (SLT Date -1)
Analysis Cycle 1		
Cycle 1 SLT Day 1	1	SLT Date
Cycle 1 Bim SR Day 1[b]	Bim SR 1st administration, Day 1	Bim SR 1st administration, Day 1
Cycle 1 Bim SR Day 2 [b]	Bim SR 1st administration, Day 1 + 1	Bim SR 1st administration Day 1 + 1
Cycle 1 Week 4	25	[Bim SR 1st administration, Day 1+2, 38]
Cycle 1 Week 8	53	[39, 66]
Cycle 1 Week 12	81	[67, 91]
Cycle 1 Week 15	102	[92,119]
Cycle 1Week 20	137	[120, 150]
Cycle 1Week 24	165	[151, 178]
Cycle 1Week 28	193	[179, 203]
Cycle 1Week 31	214	[204, 231]
Cycle 1Week 36	249	[232, 262]
Cycle 1Week 40	277	[263, 290]
Cycle 1Week 44	305	[291, 315]
Cycle 1Week 47	326	[316, 343]
Cycle 1Week 52	361	[344,373]
Cycle 1 Month 13[c]	387	[374,401]
Cycle 1 Month 14	417	[402,431]
Cycle 1 Month 15[c]	447	[432,461]
Cycle 1 Month 16	477	[462,506]
Cycle 1 Month 18	537	[507,566]
Cycle 1 Month 20	597	[567,626]
Cycle 1 Month 22[c]	657	[627,686]
Cycle 1 Month 24	717	>686
Analysis Cycle 2[d]		
Cycle 2 Bim SR Day 1	1	Bim SR 2nd administration, Day 1
Cycle 2 Bim SR Day 2	2	Bim SR 2nd Administration Day 1 + 1
Cycle 2 Week 4	29	[Bim SR 2nd administration, Day 1+2, 42]
Cycle 2 Week 8	57	[43, 70]
Cycle 2 Week 12	85	[71, 98]
Cycle 2 Week 16	113	[99,126]
Cycle 2 Week 20	141	[127,154]
Cycle 2 Week 24	169	[155, 182]
Cycle 2 Week 28	197	[183,210]
Cycle 2 Week 32	225	[211, 238]
Cycle 2 Week 36	253	[239, 266]

Cycle 2 Week 40	281	[267, 294]
Cycle 2 Week 44	309	[295, 322]
Cycle 2 Week 48	337	[323,350]
Cycle 2 Week 52	365	[351, 377]
Cycle 2 Month 13	391	[378, 405]
Cycle 2 Month 14	421	[406,435]
Cycle 2 Month 15	451	[436,465]
Cycle 2 Month 16	481	[466,495]
Cycle 2 Month 17	511	[496, 525]
Cycle 2 Month 18	541	[526,555]
Cycle 2 Month 19	571	[556,585]
Cycle 2 Month 20	601	> 585
Analysis Cycle 3[e]		
Cycle 3 Bim SR Day 1	Bim SR 3rd administration, Day 1	Bim SR 3rd administration, Day 1
Cycle 3 Bim SR Day 2	Bim SR 3rd administration Day 1 + 1	Bim SR 3rd administration Day 1 + 1
Cycle 3 Week 4	29	[Bim SR 3rd administration, Day 1+2, 42]
Cycle 3 Week 8	57	[43, 70]
Cycle 3 Week 12	85	[71, 98]
Cycle 3 Week 16	113	[99,126]
Cycle 3 Week 20	141	[127,154]
Cycle 3 Week 24	169	[155, 182]
Cycle 3 Week 28	197	[183,210]
Cycle 3 Week 32	225	[211, 238]
Cycle 3 Week 36	253	[239, 266]
Cycle 3 Week 40	281	[267, 294]
Cycle 3 Week 44	309	[295, 322]
Cycle 3 Week 48	337	[323,350]
Cycle 3 Week 52	365	[351, 377]
Cycle 3 Month 13	391	[378, 405]
Cycle 3 Month 14	421	[406,435]
Cycle 3 Month 15	451	[436,465]
Cycle 3 Month 16	481	> 465

* Target days and window definitions from Week 4 and onward are based on the relative days from the date of the Bim SR administration for each cycle.

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

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

[c] Patients who received the second administration of Bim SR at W16 and patients who never received a second administration may skip the visits.

[d] Relative to the date of the second Bim SR administration.

[e] Relative to the date of the third Bim SR administration and valid for Bim SR 15 µg.

Table 17-3 Visit windows for By Visit and Analysis Cycle for Assessments Occurring Every 3- 4 Months

Derived Visit	Target Visit Day*	Visit Window*
Baseline [a]	-1	≤ (SLT Date -1)
Analysis Cycle 1		
Cycle 1 SLT Day 1	1	SLT Date
Cycle 1Bim SR 1st Day 1[b]	Bim SR 1st administration, Day 1	Bim SR 1st administration, Day 1
Cycle 1 Week 4[c]	25	[Bim SR 1st administration, Day 1+ 1, 52]
Cycle 1 Week 12	81	[53, 122]
Cycle 1 Week 24	165	[123, 220]
Cycle 1 Week 40	277	[221,318]
Cycle 1 Week 52	361	[319,418]
Cycle 1 Month 16	477	[419, 536]
Cycle 1 Month 20	597	[537, 656]
Cycle 1 Month 24	717	>656
Analysis Cycle 2[d]		
Cycle 2 Bim SR Day 1	1	Bim SR 2nd administration, Day 1
Cycle 2 Week 4	29	[Bim SR 2nd administration, Day 1+1, 42]
Cycle 2 Week 8	57	[43, 70]
Cycle 2 Week 12	85	[71, 98]
Cycle 2 Week 16	113	[99,126]
Analysis Cycle 3[e]		
Cycle 3 Bim SR Day 1	1	Bim SR 3rd administration, Day 1
Cycle 3 Week 4	29	[Bim SR 3rd administration, Day 1+1, 42]
Cycle 3 Week 8	57	[43, 70]
Cycle 3 Week 12	85	[71, 98]
Cycle 3 Week 16	113	[99,126]

* Target days and window definitions from Week 4 and onward are based on the relative days from the date of the Bim SR administration for each cycle.

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

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

[c] Optic disc assessment will not occur at Week 4. The lower bound of visit window at Week 12 will be Bim SR 1st administration, Day 1+2.

[d] Relative to the date of the second Bim SR administration. The visits for Cycle 2 will continue all the way to Month 20. Use the same target day and window as in Table 17-2.

[e] Relative to the date of the third Bim SR administration and valid for Bim SR 15 µg. The visits for Cycle 3 will continue all the way to Month 16. Use the same target day and window as in Table 17-2.

Table 17-4 Visit windows for By Visit Analysis for Assessments Occurring Every 6 Months

Derived Visit	Target Visit Day	Visit Window
Baseline [a]	-1	≤ (SLT Date -1)
SLT/Sham SLT Administration Day 1	1	SLT Date
Cycle 1Bim SR 1st Day 1[b]	Bim SR 1st administration, Day 1	Bim SR 1st administration, Day 1
Week 24	165	[Bim SR 1st administration, Day 1+1, 267]
Week 52	361	[268, 451]
Month 18	537	[448, 627]
Month 24	717	>627

[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, but treated in SLT at Day 1, Bim SR 1st administration, Day 1 will be determined as SLT+ 3 days.

17.4 DERIVED VARIABLES

Not applicable.

17.5 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.

17.6 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.

17.7 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.

17.8 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 Analysis Cycle 1 Date, Bim SR Analysis 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 Analysis Cycle 1 Date, Bim SR Analysis 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).

17.9 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.

17.9.1 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.

17.9.2 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

18.0 REFERENCES

[1] E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials; Guidance for Industry, by the Food and Drug Administration.

19.0 AMENDMENTS

19.1 AMENDMENT 1

1. In Section 10.4.5, clarified the planned analysis.
2. In Section 11.3.5, added new analyses for ECL events including Kaplan-Meier and exposure adjusted analysis for ECL rate.
3. In Section 12.0, added the subgroup analysis by the disease diagnosis, open-angle glaucoma (OAG) or ocular hypertension (OHT) as well as ocular AEs.
4. In Section 12.3, added new ECL analyses by fixed and flexible dosing subgroup.
5. In Section 12.4, added new ocular adverse events by fixed and flexible dosing subgroup.

19.2 AMENDMENT 1.1

1. In Section 4.0, added the clarification of the Month 12 DBL to include 3-month follow-up data after the second Bim SR administration.

2. In Section 10.1, added the clarification for the primary analysis model terms.

3. In Section 10.2.1, added the clarification for the superiority testing after meeting the statistical non-inferiority to control type I error.