1 TITLE PAGE

1698-301-007

A Phase 3b Study to Evaluate the Duration of Effect of Bimatoprost SR in Participants with Open-Angle Glaucoma or Ocular Hypertension

STATISTICAL ANALYSIS PLAN - Clinical Study Report

Version 2.0: July 14, 2021

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3 LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CRF	case report form
FAS	full analysis set
IOP	intraocular pressure
OAG	open-angle glaucoma
OHT	ocular hypertension
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SOC	system organ class
SR	sustained release
TEAE	treatment-emergent adverse event

4 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 protocol amendment 2 of Study 1698-301-007 (version dated 26 Mar 2021). Specifications of tables, figures, and data listings are contained in a separate document. The SAP for health economics data will be prepared separately.

Study 1698-301-007 is a Phase 3b, multicenter, open label, study in participants at least 18 years of age with open-angle glaucoma (OAG) or ocular hypertension (OHT) who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy.

The length of this study will be at least 32 months consisting of a screening period of up to 10 days before washout, washout period of up to 56 days before the initial Bimatoprost SR administration, and a minimum 18-month PRN treatment period. However, for those enrolled earlier in the study, the PRN treatment period may be up to 36 months and the study duration may be up to 50 months, depending on when the last participant reaches the end of their minimum 18-month PRN treatment period. All participants will have at least 12 months of extended follow-up after their last Bimatoprost SR administration. Signed informed consent from the participant will be obtained before any study-related procedures are begun. Participants enrolled prior to amendment 1 and meeting the entry criteria were randomized in 1:1 ratio to receive either 10 µg or 15 µg Bimatoprost SR in the study eye and stratified by Baseline Hour 0 IOP (baseline study eye IOP $\leq$ 25 mm Hg or > 25 mm Hg). Mis-stratified participants, if any, will be analyzed based on the stratum to which the participants should have been randomized. All participants enrolled after amendment 1 will receive 10 µg Bimatoprost SR in the study eye and no randomization, masking, or stratification will be performed.

The dosing regimen and schedule for this study in the original protocol (Table 4-1) and post amendment 1 (Table 4-2) are as follows:

Table 4-1 Treatment Schedule by Eye In the Original Protocol

Treatment Visit	***Study Eye***	***Fellow Eye***
Bimatoprost SR Cycle 1 Administration	Bimatoprost SR 10 µg or 15 µg	Standard of Care or Same dose strength of Bimatoprost SR as the Study Eye[a] (10 µg or 15 µg)
Bimatoprost SR Cycle 2 Administration: Week 16 up to and including Month 18	Same dose strength of Bimatoprost SR as Cycle 1 (10 µg or 15 µg)	
Bimatoprost SR Cycle 3 Administration: at least 16 weeks after Cycle 2 Administration up to and including Month 18	Same dose strength of Bimatoprost SR as Cycle 1 and 2 (10 µg or 15 µg)	

a The fellow eye may receive only one single administration of Bimatoprost SR from Week 16 through completion of the Month 18 visit (Fellow Eye Administration).

Table 4-2 Treatment Schedule by Eye Post Amendment 1

Treatment Visit	***Study Eye***	***Fellow Eye***
Bimatoprost SR Cycle 1 Administration	Bimatoprost SR 10 µg	Standard of Care or Bimatoprost SR 10 µg
Bimatoprost SR Cycle 2 Administration: Week 16 up to and including Month 36	Bimatoprost SR 10 µg	
Bimatoprost SR Cycle 3 Administration: at least 16 weeks after Cycle 2 Administration up to and including Month 36	Bimatoprost SR 10 µg	

a The fellow eye may receive only one single administration of Bimatoprost SR from Week 16 through completion of the Month 36 visit (Fellow Eye Administration). Bimatoprost SR administration in the fellow eye must be separated by at least one week from administration in the study eye.

Please refer to section 1.3 of the protocol for the schedule of activities for the study.

5 OBJECTIVES

Objectives	Endpoints/Measures
• To evaluate the duration of IOP-lowering effect of Bimatoprost SR in participants with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).	• Duration of effect of Bimatoprost SR.
• To evaluate the safety of Bimatoprost SR in participants with OAG or OHT who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).	• Adverse events; visual fields; visual acuity; macroscopic bulbar conjunctival hyperemia; slit-lamp biomicroscopic assessments; dilated ophthalmoscopic assessments (including optic disc assessment); contact ultrasound pachymetry; gonioscopy; specular microscopy

6 PARTICIPANT POPULATIONS

The analysis sets will consist of each participant's eyes as individual experimental units (ie, Bimatoprost SR eye and fellow eye) for efficacy analyses and ocular safety analyses, and participants as experimental units for demographic and systemic safety variables.

6.1 Full Analysis Set

All study eyes that have received study treatment and have at least one postbaseline IOP assessment will contribute to the full analysis set (FAS), which will be used for efficacy analyses.

6.2 Safety Analysis Set

All participants who have received at least 1 dose of study treatment in either eye will contribute to the safety analysis set (SAS). All safety data collected from these participants will be included in the SAS.

7 PARTICIPANT DISPOSITION

The number of participants in the study populations (SAS and FAS) will be summarized by treatment group and overall.

The number and percentage of participants who complete the study and participants who prematurely discontinue the study will be presented for each treatment group for all screened participants. A participant is considered to have completed the study if he/she has completed 12 months of follow up after the PRN treatment period, or if the participant has early exited. Participants who receive nonstudy IOP-lowering treatment (rescue) in the Bimatoprost SR treated eye may early exit the study at least 12 months after the participant's last Bimatoprost SR administration, if the investigator deems the participant not appropriate for additional Bimatoprost SR retreatments in the study eye, and there are no safety concerns in the opinion of the investigator. Additionally, participants randomized to receive 15 μg Bimatoprost SR under the original protocol will be considered to have completed the study if he/she has completed at least 12 months of follow-up after the last Bimatoprost SR administration in either eye. The reasons for premature discontinuation from the study as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group and overall. For participants who prematurely discontinue due to adverse events (AEs), the reason will be further classified into ocular AE and non-ocular AE. All participants who prematurely discontinue from the study will be listed by discontinuation reason for all screened participants.

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group of <45, 45 – 65, >65; race; race group of white and non-white; ethnicity; sex), baseline characteristics (weight and height) will be summarized descriptively by treatment group and overall for the FAS population. Continuous variables will be summarized by number of participants, mean, SD, median, 1st and 3rd quartiles, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Other disease characteristics, including diagnosis of either OAG (primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT, baseline Hour 0 IOP (≤ 25 mm Hg or > 25 mmHg), baseline central endothelial cell density based on automated analysis , baseline Shaffer grade, and lens status, will be summarized descriptively by treatment group for the study eye and overall for the FAS population. Additionally, a descriptive summary of diagnosis of OAG and OHT, baseline Hour 0 IOP, baseline central endothelial cell density based on automated analysis, baseline Shaffer grade, and lens status will be provided for the fellow eye treated with Bimatoprost SR (10 µg or 15 µg).

The reason participants are not adequately managed with topical IOP medications will be summarized descriptively by treatment group for the study eye and all fellow eyes.

Abnormalities in participants' medical and surgical histories, and ophthalmic histories, will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA), version 24.0 or newer. The number and percentage of participants with abnormalities in medical and surgical histories (ophthalmic excluded) in each SOC and PT will be summarized by treatment group and overall for the safety population.

Abnormalities in ophthalmic and surgical history in each SOC and PT will be separately summarized as frequency count and percent by the treatment group for study eye and fellow eye treated with Bimatoprost SR (10 µg or 15 µg) as well as pooled for all fellow eyes in the safety population.

Prior medication is defined as any medication taken before the date of the first dose of study treatment in the study eye or in fellow eye never treated with Bimatoprost SR or prior to a fellow eye being treated with Bimatoprost SR. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of study treatment in the study eye or after a fellow eye is treated with Bimatoprost SR.

Both prior and concomitant medications will be coded by drug name and therapeutic class. Ocular and non-ocular prior and concomitant medications will be summarized by the number and percentage of participants in each treatment group and overall for the safety population. The number and percentage of eyes receiving IOP lowering medications used at screening (if "IOP Lowering medication used at the time of study entry/Screening" option is selected on the medication CRF) will be summarized by treatment group in the study eye and overall for the safety population. Additionally, the number and percentage of eyes receiving washout ocular medications will be summarized by treatment group in the study eye and pooled for fellow eyes. Also, standard of care medications for fellow eyes prior to being treated with

Bimatoprost SR will be summarized by the number and percentages in each treatment group. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class.

The WHODrug B2 Enhanced 201703 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Rescue treatment is defined as any non-study IOP lowering treatment in the eye treated with Bimatoprost SR. Number and percentage of eyes that received rescue treatment will be summarized overall and by cycle by treatment group in the study eye. Number and percentage of eyes that received permanent rescue treatment ("Permanent Rescue" was marked for the question "What was the purpose of the IOP medication?" on the prior and concomitant medications eCRF or "Non Study IOP Lowering/Rescue" was marked for the question "What was the purpose of the IOP lowering procedure?" on the concurrent procedure eCRF) will be summarized overall and by cycle by treatment group in the study eye. Similar descriptive summary will be presented for intermittent rescue medication ("Intermittent Rescue" was marked for the question "What was the purpose of the IOP medication?" on the prior and concomitant medications eCRF) used in the study eye treated with Bimatoprost SR 10 μg. Additionally, any rescue treatments given to the fellow eye after being treated with Bimatoprost SR will be summarized by treatment group (10 μg or 15 μg). Rescue treatments will be listed for the study eye and fellow eye treated with Bimatoprost SR, separately.

Additionally, duration of intermittent rescue after the first Bimatoprost SR administration but prior to the second administration in the study eye will be summarized. Duration will be calculated as the number of days between the first intermittent rescue medication start date and last intermittent rescue medication stop date, inclusively (start date of first intermittent rescue medication – stop date of last intermittent rescue medication + 1). The duration will be summarized descriptively for the study eyes treated with Bimatoprost SR 10 μg.

Duration of first intermittent rescue after the second administration but prior to the third administration in the study eye will also be summarized. Duration will be calculated as the number of days between the first intermittent rescue medication start date after second administration and last intermittent rescue medication stop date, inclusively (start date of the first intermittent rescue medication after second administration – stop date of the last intermittent rescue medication + 1). The duration will be summarized descriptively for the study eyes treated with Bimatoprost SR 10 μg.

9 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 Extent of Exposure

For the participants who received Bimatoprost SR treatment, the number and percentage of participants receiving Bimatoprost SR retreatment will be tabulated by the number of retreatment administrations and treatment group in the study eye. Additionally, the number and percentage of participants who were treated with Bimatoprost SR in the fellow eye will be tabulated by treatment received.

Each participant's study duration will be calculated as the number of days between the exit date (from the Disposition CRF) and Cycle 1 administration date in the study eye, inclusively (date of the exit - Cycle 1 administration date + 1). If the date of exit is missing, then the date of last visit will be used to calculate study duration. Participants' study duration will be summarized using descriptive statistics by the number of administrations and treatment group in the study eye.

10 EFFICACY ANALYSES

All efficacy analyses will be based on the FAS, unless stated otherwise. When applicable, all statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects and all confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

10.1 Efficacy Parameters

The duration of effect for Bimatoprost SR will be evaluated by the below time to event efficacy endpoint, which is the primary endpoint for efficacy:

- Time to second administration of Bimatoprost SR or first rescue treatment after the first administration in the study eye.

The empirical survival function will be estimated for each treatment group using the Kaplan-Meier (KM) method and the corresponding KM curves and survival probabilities with 95% CI will be presented. The derivation of the variables used in the KM analyses are described below.

The variables associated with primary efficacy endpoint will be defined as the time from first administration of Bimatoprost SR in the study eye to the earliest of the following four events:

1. Participant receiving a second administration of Bimatoprost SR
2a. Participant receiving intermittent rescue medication
2b. Participant receiving permanent rescue treatment
3. Participant discontinuing the study
4. Participant completing the study

where, the start date of the first intermittent rescue medication after the first administration of Bimatoprost SR will be used as the date of intermittent rescue, i.e., 2a, for analysis. Additionally, the start date of the first permanent rescue treatment after the first administration of Bimatoprost SR will be used as the date of permanent rescue, i.e., 2b, for analysis. For 3) and 4) date on the Disposition CRF will be used.

The *primary efficacy endpoint* will take into consideration all second administrations of Bimatoprost SR or first use of any rescue treatments occurring after first administration. If the earliest occurrence is 1), 2a), or 2b) then the participant is considered having the event at the date of the second administration or date of the first rescue treatment (intermittent or permanent). However, if the earliest event is 3) or 4) then the participant is considered censored for this variable on the earliest date of the discontinuation or completion, respectively. If either 1), 2a), or 2b) occurs on the same day as 3) or 4) then the participant is considered having the event at the date of 1), 2a), or 2b).

10.2 Additional Efficacy parameters

Other efficacy variables include:

A. The time to second administration of Bimatoprost SR in the study eye regardless of intermittent rescue

B. The time to third administration of Bimatoprost SR in the study eye after second administration regardless of intermittent rescue

C. Time to the third administration of Bimatoprost SR or first rescue treatment after second administration in the study eye

D. Time to first rescue treatment after third administration in the study eye

E. IOP raw values and change from baseline for study eye and for fellow eye treated with Bimatoprost SR.

For the time to event variables, A through D, the empirical survival function will be estimated for each treatment group using the Kaplan-Meier (KM) method and the corresponding KM curves and survival probabilities with 95% CI will be presented. The second and third time to event variables will be assessed on participants who received at least two administrations of Bimatoprost SR in the study eye and the fourth time to event variable will be assessed on participants who received three administrations of Bimatoprost SR in the study eye.

The *additional efficacy endpoint A* will take into consideration all second administrations of Bimatoprost SR, including all study eyes that have received intermittent rescue treatment after the first administration but prior to second administration. Based on the variable definition in section 10.1, if the earliest occurrence is 1) compared to 2b), 3), and 4), then the participant is considered to have had the event at the date of the second administration. Additionally, if 2a) occurs prior to 1) then the participant is considered to have had the event at the date of the second administration. But if 2a) occurs without 1) occurring (i.e., if a participant receives intermittent rescue treatment and never received a second administration) then the participant is considered censored for this variable on the date of first intermittent rescue. If the earliest event is 2b), 3) or 4), then the participant is considered censored for this variable on the earliest date of permanent rescue, discontinuation, or study completion, respectively. If 1) occurs on the same day as 2a), 2b), 3), or 4), then the participant is considered to have had the event at the date of 1).

The variables associated with the additional endpoints B and C will be defined as the time from second administration of Bimatoprost SR in the study eye to the earliest of the following four events:

5. Participant receiving a third administration of Bimatoprost SR
6a. Participant receiving intermittent rescue medication
6b. Participant receiving permanent rescue treatment

7. Participant discontinuing the study
8. Participant completing the study

where, the start date of the first intermittent rescue medication after the first administration of Bimatoprost SR will be used as the date of intermittent rescue, i.e., 6a for analysis. Additionally, the start date of the first permanent rescue treatment after the first administration of Bimatoprost SR will be used as the date of permanent rescue, i.e., 6b, for analysis. For 7) and 8) date on the Disposition CRF will be used.

The *additional efficacy endpoint B* will take into consideration all third administrations of Bimatoprost SR, regardless of whether they have received intermittent rescue treatment after the second administration. If the earliest occurrence is 5) compared to 6b), 7), and 8), then the participant is considered to have had the event at the date of the third administration. Additionally, if 6a) occurs prior to 5), then the participant is considered to have had the event at the date of the third administration. But if 6a) occurs without 5) occurring (i.e., if a participant receives intermittent rescue treatment and never received a third administration) then the participant is considered censored for this variable on the date of first intermittent rescue. If the earliest event is 6b), 7) or 8), then the participant is considered censored for this variable on the earliest date of permanent rescue, discontinuation, or study completion, respectively. If 5) occurs on the same day as 6a), 6b), 7), or 8), then the participant is considered to have had the event at the date of 5).

The *additional efficacy endpoint C* will take into consideration all third administrations of Bimatoprost SR or first use of any rescue treatments occurring after second administration. If the earliest occurrence after second administration is 5), 6a), or 6b), then the participant is considered to have had the event at the date of the third administration or date of the first rescue treatment (intermittent or permanent). However, if the earliest occurrence after second administration is 7) or 8), then the participant is considered censored for this variable on the earliest date of discontinuation, or completion, respectively. If either 5), 6a), or 6b) occurs on the same day as 7) or 8), then the participant is considered to have had event at the date of 5), 6a), or 6b).

The *additional efficacy endpoint D* will take into consideration all rescue treatments occurring after third administration of Bimatoprost SR. If the earliest occurrence is 6a) or 6b), i.e., rescue treatment (intermittent or permanent), then the participant is considered to have had the event at the date of the first rescue treatment. However, if the earliest event is discontinuation from the study or study completion, then the participant is considered censored for this variable on the date of the discontinuation or completion, respectively. If 6a) or 6b) occurs on the same day as discontinuation or completion, then the participant is considered to have had the event at the date of 6a) or 6b).

All IOP measurements will be taken at approximately the same time of day for a given participant throughout the study whenever possible. Two consecutive measurements will be taken of each eye. If the first 2 measurements differ by > 1 mm Hg, a third measurement will be taken. If the first 2 measurements differ by ≤ 1 mm Hg, the IOP for the given eye will be the average of the 2 readings. If the difference between the first 2 measurements is > 1 mm Hg, the IOP for the given eye will be the median of the 3 readings. All Hour 0 IOP

examinations should be scheduled at 09:00 AM ± 1 hour. As scheduling permits, the participant should have approximately the same Hour 0 time of day throughout this study. The IOP value for a given eye will be the median of all measurements.

For *additional efficacy endpoint E*, IOP raw values and change from baseline will be summarized descriptively for overall and each treatment cycle by treatment group in study eye and pooled for fellow eye never treated with Bimatoprost SR or before it is treated with Bimatoprost SR. Additionally, a separate analysis will be presented for the fellow eye treated with Bimatoprost SR (10 µg or 15 µg). Baseline IOP for study eye and fellow eyes never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR is the IOP value at Hour 0 at Baseline visit. If IOP is missing at the Baseline visit then baseline is the last nonmissing assessment prior to the first dose of the study treatment. Baseline IOP for fellow eyes treated with Bimatoprost is the last nonmissing assessment at a scheduled visit prior to the fellow eye being treated with Bimatoprost SR.

To avoid confounding of efficacy data, IOP values obtained after initiating the use of rescue treatment (medication or procedure) in an eye treated with Bimatoprost SR will be excluded from the calculation of the summary statistics and the statistical analyses for that eye but raw values will be presented in the listings.

11 SAFETY ANALYSES

The safety analysis will be performed using SAS. General safety parameters will include AEs, clinical laboratory assessments and vital signs. Ocular safety parameters will include visual fields, BCVA, conjunctival hyperemia, biomicroscopy, dilated ophthalmoscopy (including optic disc assessment), pachymetry, gonioscopy, and specular microscopy. Unless otherwise stated, all safety assessments will be tabulated for overall and each treatment cycle by treatment group in the study eye and pooled for fellow eyes never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR. Additionally, a separate analysis will be presented for the fellow eye treated with Bimatoprost SR (10 μg or 15 μg).

Unless otherwise stated, the last nonmissing safety assessment prior to first dose of study treatment will be used as baseline for all analyses of that safety parameter in the study eye and fellow eye never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR. Unless otherwise stated, the last nonmissing assessment prior to the fellow eye being treated with Bimatoprost SR will be used as baseline for analyses of the fellow eyes treated with Bimatoprost SR.

11.1 Adverse Events

Adverse events will be coded by SOC and PT using the *Medical Dictionary for Regulatory Activities,* version 24.0 or newer.

Treatment-Emergent Adverse Events
An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of the study treatment. Per case report form instructions, a new AE record will be created with a new AE onset date for any AE that worsens. Therefore, TEAEs can simply be identified as those AEs with recorded onset date (and time, if known) on or after the date (and time, if known) of the first dose of study treatment. This definition of TEAE will be used for both study eye.

An AE will be considered as a TEAE for a treatment cycle if the AE onset date (and time, if known) is on or after the treatment administration date (and time) of the cycle but prior to the date (and time) of the next cycle administration. This definition of TEAE will be used for TEAE summary by cycle for the study eye.

An AE will be considered as a TEAE for an untreated fellow eye or prior to it being treated with Bimatoprost SR, if the onset date (and time, if known) of the AE occurring in the untreated fellow eye is on or after the date of the first dose of the study treatment in the study eye. An AE will be considered as a TEAE for fellow eye treated with Bimatoprost SR if the onset date (and time, if known) of the AE occurring in the fellow eye is on or after the date of the fellow eye being treated with Bimatoprost SR.

If more than 1 AE is coded to the same preferred term for the same participant/eye, the participant/eye will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

Adverse events will be classified into ocular AEs and nonocular AEs. An ocular AE will be determined as indicated on the AE form of CRF, and thus are not limited to AEs with primary SOCs of eyes. Ocular AEs will be tabulated by the treatment group for the study eye and pooled for fellow eyes never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR as well as for the fellow eye after being treated with Bimatoprost SR (10 µg or 15 µg). Additionally, ocular TEAEs identified (onset or worsened) within 2 days of administration and identified beyond 2 days of administration of each cycle will be summarized by treatment group for the study eye and pooled for fellow eyes never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR as well as for the fellow eye after being treated with Bimatoprost SR (10 µg or 15 µg).

Nonocular AEs will be summarized on per-participant basis by the treatment group (10 µg or 15 µg). All AE analyses for the study eye will be presented by overall and by each cycle of Bimatoprost SR administration. For example, for the by cycle analyses, all AEs occurring on or after the second administration of Bimatoprost SR (i.e., Cycle 2) but before the third administration (i.e., Cycle 3) will be included in the AEs analyses for Cycle 2.

An AE will be considered a treatment-emergent SAE (TESAE) if it is a TEAE that additionally meets any SAE criteria.

Overall summary of TEAEs will be provided on a per-participant basis for categories of all TEAEs, treatment-related TEAEs, study procedure-related TEAEs, study drug-related TEAEs, serious TEAEs (TESAEs), study procedure-related TESAEs, study drug-related TESAEs deaths, TEAEs leading to study discontinuation, and TEAEs leading to implant removal. Each category (except deaths) will be further classified into ocular and non-ocular subcategories.

The number and percentage of participants reporting non-ocular TEAEs in each treatment group will be tabulated by SOC and PT and by SOC, PT, and severity for overall. Also, the number and percentage of participants reporting treatment-related (including study drug related or injection procedure related) non-ocular TEAEs in each group will be tabulated by SOC and PT for overall.

Similar analyses will be done for ocular TEAEs including 1) by SOC, PT, and severity; 2) treatment-related TEAEs by PT for each treatment group by study eye and pooled for fellow eye never treated with Bimatoprost SR or before it being treated with Bimatoprost SR. A separate summary of ocular TEAEs and ocular serious TEAEs will be presented for fellow eye treated with Bimatoprost SR (10 µg or 15 µg). Additionally, a separate summary for treatment-related ocular TEAEs will be provided for participants who received Bimatoprost SR treatment in both eyes.

A summary of nonocular serious TEAEs and nonocular TEAEs leading to study discontinuation will be presented by SOC and PT for overall by treatment group

(10 µg or 15 µg). A summary of ocular serious TEAEs and ocular TEAEs leading to study discontinuation will be presented by SOC and PT overall and by cycle by treatment group in the study eye and pooled for fellow eye never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR. A separate summary of ocular serious TEAEs and ocular TEAEs leading to study discontinuation will be provided for the fellow eye after being treated with Bimatoprost SR (10 µg or 15 µg).

Ocular TEAEs leading to study drug withdrawal will be summarized by SOC and PT overall and by cycle by treatment group for study eye. A separate summary will be provided for the fellow eye treated with Bimatoprost SR (10 µg or 15 µg). Ocular TEAEs leading to study drug withdrawal are defined as the ocular TEAEs where action taken regarding study treatment is reported as "Drug Withdrawn" on the AE CRF.

Ocular TEAEs leading to implant removal will be summarized by SOC and PT overall and by cycle by treatment group for study eye. A separate summary will be provided for fellow eye treated with Bimatoprost SR (10 µg or 15 µg).

TEAEs of Special Interest

Corneal TEAEs and Anterior chamber inflammation TEAEs of interest will be summarized by SOC and PT for overall and each treatment cycle by treatment group for study eye and pooled for fellow eyes never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR. A separate summary will be provided for fellow eye after being treated with Bimatoprost SR (10 µg or 15 µg). The full list of corneal AEs and Anterior chamber inflammation AEs of interest will be provided prior to each database lock. Additional subcategory of TEAEs may be analyzed separately, such as for ocular TEAE associated with use of a prostaglandin analog (PGA), etc.

11.2 Vital Signs

No tables or listing will be provided for vital signs.

11.3 Macroscopic Conjunctival Hyperemia Assessment

Macroscopic conjunctival hyperemia assessment will be performed for each eye at all scheduled visits (except on any of the Bimatoprost SR administration days) using the following 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.

The number and percentage of treated eyes that had at least 2-grade severity grade increase (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) from the baseline will be tabulated. If the severity grade decreases from baseline, it will be considered as 'no increase'.

11.4 Best-corrected Visual Acuity

Best corrected visual acuity (BCVA) will be measured for both eyes using the logMar chart at all scheduled visits except on any of the Bimatoprost SR administration days. BCVA will be recorded in Snellen equivalent units. Baseline for BCVA is the last nonmissing safety assessment prior to first dose of study treatment will be used as baseline for all analyses of that safety parameter in the study eye and fellow eye never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR. Baseline BCVA for study eye and fellow eyes never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR is the BCVA value at Baseline visit. If BCVA is missing at the Baseline visit then baseline is the last nonmissing assessment prior to the first dose of the study treatment. Baseline BCVA for fellow eyes treated with Bimatoprost is the last nonmissing assessment at a scheduled visit prior to the fellow eye being treated with Bimatoprost SR. The line change from baseline at each follow-up evaluation will be calculated using the following formula:

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

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

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

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

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

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

11.5 Visual Field

Visual field examinations will be assessed using automated perimetry (using either Humphrey 24-2 full threshold program or 24-2 SITA Standard, or Octopus G1 or 24-2 and dynamic or normal strategy). The same test methodology must be used throughout the entire study for a given participant. Data will be reported as normal or abnormal and the mean deviation (MD) will also be recorded in decibels (dB). Visual field MD change from baseline will be calculated for each postbaseline visit and summarized with descriptive statistics by

machine type (Humphrey and Octopus respectively) and separately for participants with OAG in the study eye. If the machine type is different between baseline and post baseline visit, no change from baseline will be derived. For participants, 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.

Abnormal findings may include enlargement of blind spot, superior arcuate scotoma, interior arcuate scotoma, paracentral scotoma, nasal step, central scotoma, generalized depression, and temporal scotoma and other. A listing will be provided for participants with abnormal visual field finding(s).

The number and percentage of eyes with a normal examination value at baseline but became abnormal at any of the follow up visit will be tabulated based on the abnormal finding category. This analysis may also be conducted across all study visits.

11.6 Specular Microscopy

Central corneal endothelial cell density (CECD) average (cells/mm^2) will be assessed using specular microscopy performed on the central cornea of each eye. Reading center analysis as well as automated analysis will be performed; however, reading center data will be the primary source of safety analysis of specular microscopy data.

Raw values and change from baseline as well as percent change from baseline of endothelial cell density as assessed by reading center and automated analysis will be summarized descriptively by visit and for last visit for each eye.

The number and percentage of participants will be tabulated by various thresholds (including but not limited to endothelial cell loss) 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. The last visit of a participant for the primary and 12-month analysis is defined as the last assessment prior to the specific interim database lock. The last visit of a participant for final analysis is defined as the assessment at exit visit (i.e., the last assessment during the study). This summary will be provided on endothelial cell density as assessed by reading center analysis.

Listings for participants with 20% or more central corneal endothelia cell density (CECD) loss at any visit based on reading center analysis will be provided.

11.7 Biomicroscopy and Ophthalmoscopy

Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, cornea, anterior chamber (with Van Herick anterior chamber depth assessment at Screening only), iris/pupil, and lens (lens assessment is performed using the modified AREDS procedure and is collected on dilated

examination days through a dilated pupil, using the slit lamp biomicroscope). Dilated Ophthalmoscopy will include evaluation of the macula, vitreous, and retina.

All biomicroscopy and ophthalmoscopy examinations findings will be coded using MedDRA dictionary.

The number and percentage of eyes with biomicroscopy and ophthalmoscopy findings of at least 2-grade increase in severity (worsening, e.g., a change from 0 to 2 and above, or from 0.5 to 2 and above, or from 1 to 3 and above) from baseline for findings with a severity grade, or a status change from absence at baseline to presence at follow-up visit for not associated with a severity grade, at 1 or more postbaseline visits, will be tabulated by PT in descending order of incidence rate. The number and percentage of eyes with any clinically significant findings will be presented (as "Overall").

At follow-up visits, the lens opacity will be assessed only for eyes evaluated as phakic at baseline. The presence and severity of nuclear, cortical, and posterior subcapsular cataract lens opacities using a 3-point scale (absent, < standard photo #2, and ≥ standard photo #2) will be summarized. The lens status will be be summarized with frequency and percent as necessary.

11.8 Gonioscopy/Angle Assessment

Gonioscopy is performed to assess the inferior iridocorneal angle.

For each cycle, the number and percentage of Bimatoprost SR eyes with no implant visible, with visible implants, and with implant size assessment will be tabulated for each visit. For Bimatoprost SR treated eyes with implant size data collected, implant size will be summarized based on the percentage category for each implant by cycle and visit. This data may also be summarized using graphical presentation based on the percentage category for each implant.

Also, the number and percentage of treated eyes who have implant(s) in contact with corneal endothelium at any visit within a cycle will be summarized by cycle.

11.9 Pachymetry

Corneal thickness using ultrasound (contact) pachymetry will be performed on the central cornea. At each examination, 3 measurements of central corneal thickness (CCT) and associated standard deviation will be reported for each eye, and the average of the 3 measurements will be calculated and used for analysis. CCT raw values and changes from baseline will be summarized descriptively.

11.10 Cup/Disc Ratio

The cup/disc ratio will be evaluated using a 0.0 to 1.0 scale for each eye at visits, with larger values indicating more advanced optic nerve damage, thus a reduction from baseline is a considered an improvement.

Change from baseline at each follow-up visit will be categorized as an improvement of 0.2 or more (≤ - 0.2), no change (> -0.2 to < 0.2), or a worsening of 0.2 or more (≥ 0.2). The number and percentage of eyes in each category will be provided.

11.11 Pregnancy Test

Positive pregnancy test results of females of childbearing potential will be presented in a data listing.

12 HEALTH OUTCOMES ANALYSES

Not applicable.

13 INTERIM ANALYSIS

At least one interim database lock may occur to support regulatory and marketing submissions. Additional analyses may be performed with data from select US sites that evaluated the use of an alternate applicator in approximately 30 participants.

14 DETERMINATION OF SAMPLE SIZE

Based on the Phase 1/2 study (192024-041D), approximately 70% of participants among Generation 2 10 μg implant did not require a second administration of Bimatoprost SR or rescue at 6 months, following a single administration of Bimatoprost SR. A more conservative assumption of 50% of participants having at least 6 months prior to meeting pre-specified criteria for a second administration is used for sample size calculation for this study. A sample size of 135 participants produces a two-sided 90% confidence interval, with a width no wider than 0.15 based on normal approximation with continuity correction. Prior to Amendment 1, similar assumptions were used for the 15 μg group, and 62 participants were enrolled in the 15 μg group. In order to assess eyes undergoing multiple administrations of Bimatoprost SR, up to approximately 425 participants will be enrolled and receive treatment with the 10 μg implant to achieve a sufficient number of eyes receiving multiple administrations of 10 ug Bimatoprost SR.

15 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.2 (or newer) of SAS.

16 DATA HANDLING CONVENTIONS

16.1 Visit Time Windows

Table 16-1 presents the visits assigned for by visit analyses of the efficacy and safety assessments of macroscopic conjunctival hyperemia, best-corrected visual acuity, biomicroscopy, and gonioscopy/angle for the study eye and fellow eye before it is treated with Bimatoprost SR (i.e., this table presents visits assigned for all assessment that occur every 2 months after 16 weeks of follow-up after every administration of Bimatoprost SR). The visits presented in Table 16-1 will also be used for analysis of the fellow eye after being treated with Bimatoprost SR; however, target day and analysis visit window will be computed using date of Bimatoprost SR administration to the fellow eye. The table also includes the corresponding range of treatment days (window) during which an actual visit may occur. All visits are indexed on the date of the first dose of the study treatment to the study eye (same date is used for both the study and fellow eye). Table 16-2 presents the visits assigned for by visit analyses of specular microscopy and pachymetry assessments which occur every 4 months. Table 16-3 presents the visits assigned for by visit analyses of visual field assessments which occur every 6 months. Table 16-4 presents the visits assigned for by visit analyses of cup/disc ratio assessments which occur every 12 months. Table 16-5 presents the visits assigned for by cycle analyses of efficacy and other safety assessments of the study eye.

Table 16-1 Visit Time Windows for By Visit Analysis for Assessments Occurring Every 2 Months

Derived Visit	***Target Day of the Visit*** [a]	***Analysis Visit Window***
Baseline	Day -3 to Day -1	
Randomization/ Administration/ Cycle 1 Day 1	Day 1	Day 1
Day 2	Day 2	Days [2, 14]
Week 4	Day 29	Days [15, 43]
Week 8	Day 57	Days [44, 71]
Week 12	Day 85	Days [72, 99]
Week 16	Day 113	Days [100, 151]
Week 24	Day 169	Days [152, 211]
Month 8	Day 241	Days [212, 271]
Month 10	Day 301	Days [272, 331]
Month 12	Day 361	Days [332, 391]
Month 14	Day 421	Days [392, 451]
Month 16	Day 481	Days [452, 511]
Month 18	Day 541	Days [512, 571]
Month 20	Day 601	Days [572, 631]

Table 16-1 Visit Time Windows for By Visit Analysis for Assessments Occurring Every 2 Months

Derived Visit	***Target Day of the Visit*** [a]	***Analysis Visit Window***
Month 22	Day 661	Days [632, 691]
Month 24	Day 721	Days [692, 751]
Month 26	Day 781	Days [752, 811]
Month 28	Day 841	Days [812, 871]
Month 30	Day 901	Days [872, 931]
Month 32	Day 961	Days [932, 991]
Month 34	Day 1021	Days [992, 1051]
Month 36	Day 1081	Days [1052, 1111]
Month 38	Day 1141	Days [1112, 1171]
Month 40	Day 1201	Days [1172, 1231]
Month 42	Day 1261	Days [1232, 1291]
Month 44	Day 1321	Days [1292, 1351]
Month 46	Day 1381	Days [1352, 1411]
Month 48	Day 1441	Days > 1411

a Relative to the date of the first dose of study treatment. Day 1 = the date of the first dose of study treatment. There is no Day 0 or Week 0.

Note: To derive analysis windows for fellow eye treated with Bimatoprost SR use the date of fellow eye dose administration. Use the same target day and window as in Table 16-1, except the last visit will be Month 44 and window for Month 44 will be >1291.

Table 16-2 Visit Time Windows for By Visit Analysis for Assessments Occurring Every 4 Months

Derived Visit	***Target Day of the Visit*** [a]	***Analysis Visit Window***
Baseline	Day -3 to Day -1	
Randomization/ Administration/ Cycle 1 Day 1	Day 1	Day 1
Week 16	Day 113	Days [2, 181]
Month 8	Day 241	Days [182, 301]
Month 12	Day 361	Days [302, 421]
Month 16	Day 481	Days [422, 541]
Month 20	Day 601	Days [542, 661]
Month 24	Day 721	Days [662, 781]
Month 28	Day 841	Days [782, 901]
Month 32	Day 961	Days [902, 1021]
Month 36	Day 1081	Days [1022, 1141]
Month 40	Day 1201	Days [1142, 1261]
Month 44	Day 1321	Days [1262, 1381]
Month 48	Day 1441	Days > 1381

a Relative to the date of the first dose of study treatment. Day 1 = the date of the first dose of study treatment. There is no Day 0 or Week 0.

Note: To derive analysis windows for fellow eye treated with Bimatoprost SR use the date of fellow eye dose administration. Use the same target day and window as in Table 16-2, except the last visit will be Month 44 and window for Month 44 will be >1261.

Table 16-3 Visit Time Windows for By Visit Analysis for Assessments Occurring Every 6 Months

Derived Visit	***Target Day of the Visit*** [a]	***Analysis Visit Window***
Baseline	Day -3 to Day -1	
Randomization/ Administration/ Cycle 1 Day 1	Day 1	Day 1
Week 24	Day 169	Days [2, 271]
Month 12	Day 361	Days [272, 451]
Month 18	Day 541	Days [452, 631]
Month 24	Day 721	Days [632, 811]
Month 30	Day 901	Days [812, 991]
Month 36	Day 1081	Days [992, 1171]
Month 42	Day 1261	Days [1172, 1351]
Month 48	Day 1441	Days > 1351

a Relative to the date of the first dose of study treatment. Day 1 = the date of the first dose of study treatment. There is no Day 0 or Week 0.

Note: To derive analysis windows for fellow eye treated with Bimatoprost SR use the date of fellow eye dose administration. Use the same target day and window as in Table 16-3, except the last visit will be Month 42 and window for Month 42 will be >1171.

Table 16-4 Visit Time Windows for By Visit Analysis for Assessments Occurring Every 12 Months

Derived Visit	***Target Day of the Visit*** [a]	***Analysis Visit Window***
Baseline	Day -3 to Day -1	
Randomization/ Administration/ Cycle 1 Day 1	Day 1	Day 1
Month 12	Day 361	Days [2, 551]
Month 24	Day 731	Days [552, 911]
Month 36	Day 1081	Days [912, 1261]
Month 48	Day 1441	Days > 1261

a Relative to the date of the first dose of study treatment. Day 1 = the date of the first dose of study treatment. There is no Day 0 or Week 0.

Note: To derive analysis windows for fellow eye treated with Bimatoprost SR use the date of fellow eye dose administration. Use the same target day and window as in Table 16-4, except the last visit will be Month 36 and window for Month 36 will be >1261.

Table 16-5 Visit Time Windows for By Cycle Analyses

Derived Visit	*Target Day of the Visit*	*Analysis Visit Window*
Baseline	Day -3 to Day -1	
Cycle 1[a]		
Cycle 1 Day 1 Administration	Day 1	Day 1
Cycle 1 Day 2	Day 2	Days [2, 14]
Cycle 1 Week 4	Day 29	Days [15, 43]
Cycle 1 Week 8	Day 57	Days [44, 71]
Cycle 1 Week 12	Day 85	Days [72, 99]
Cycle 1 Week 16	Day 113	Days [100, 151]
Cycle 2[b]		
Cycle 2/Day 1 Administration	Day 1	Day 1
Cycle 2/Day 2	Day 2	Days [2, 16]
Cycle 2/Week 4	Day 29	Days [15, 43]
Cycle 2/Week 8	Day 57	Days [44, 71]
Cycle 2/Week 12	Day 85	Days [72, 99]
Cycle 2/Week 16	Day 113	Days [100, 151]
Cycle 3[c]		
Cycle 3/Day 1 Administration	Day 1	Day 1
Cycle 3/Day 2	Day 2	Days [2, 16]
Cycle 3/Week 4	Day 29	Days [15, 43]
Cycle 3/Week 8	Day 57	Days [44, 71]
Cycle 3/Week 12	Day 85	Days [72, 99]
Cycle 3/Week 16	Day 113	Days [100, 151]

a Relative to the date of Cycle 1 dose administration. The visits for Cycle 1 will continue all the way to Month 48. Use the same target day and window as in Table 16-1 for visits occurring every 2 months, use Table 16-2 for visits occurring every 4 months, use Table 16-3 for visits occurring every 6 months, and use Table 16-4 for visits occurring every 12 months.

b Relative to the date of Cycle 2 dose administration. Use the same target day and window as in Table 16-1 (except the last visit will be Month 44 and window for Cycle 2 Month 44 will be >1291) for visits occurring every 2 months, use Table 16-2 for visits occurring every 4 months (except the last visit will be Month 44 and window for Cycle 2 Month 44 will be >1261), use Table 16-3 for visits occurring every 6 months (except the last visit will be Month 42 and window for Cycle 2 Month 42 will be >1171), and use Table 16-4 for visits occurring every 12 months (except the last visit will be Month 36 and window for Cycle 2 Month 36 will be >911).

c Relative to the date of Cycle 3 dose administration. Use the same target day and window as in Table 16-1 (except the last visit will be Month 36 and window for Cycle 2 Month 42 will be >1051) for visits occurring every 2 months, use Table 16-2 for visits occurring every 4 months (except the last visit will be Month 36 and window for Cycle 2 Month 36 will be >1021), use Table 16-3 for visits occurring every 6 months (except the last visit will be Month 36 and window for Cycle 2 Month 36 will be >991), and use Table 16-4 for visits occurring every 12 months (except the last visit will be Month 36 and window for Cycle 2 Month 36 will be >911).

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment + 1. If the assessment date is before the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment. Therefore, a negative day indicates a day before the start of the study treatment.

For IOP and BCVA, 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 a participant has 2 or more visits within the same window, the visit closest to the target day will be used in the analysis. If 2 visits are equidistant to the target day, the later visit will be used.

For all other assessments, if a participant has 2 or more visits (scheduled or unscheduled) within the same window, the visit closest to the target day will be used in the analysis. If 2 visits are equidistant to the target day, the later visit will be used.

16.2 Derived Variables

Not applicable.

16.3 Repeated or Unscheduled Assessments of Safety Parameters

For all safety assessments except BVCA, if a participant has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the first dose of the study treatment will be used as baseline in the study eye and fellow eyes never treated with Bimatoprost SR or prior to being treated with Bimatoprost SR. Baseline for the fellow eyes treated with Bimatoprost SR will be the last nonmissing assessment prior to the fellow eye being treated with Bimatoprost SR. Refer to section 11.4 for derivation of baseline assessments for BCVA. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all assessments will be presented in the data listings.

16.4 Missing Date of the Last Dose of Study Treatment

When the date of the last dose of study treatment is missing for a treated eye in the safety population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date in that eye.

16.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned.

The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.6 Missing Causal Relationship to study drug for Adverse Events

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

16.7 Missing Date Information for Adverse Events

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

- If the month and year of the incomplete start date are the same as the month and year of the Bimatoprost SR Cycle 1 Date, Bimatoprost SR Cycle 2 Date or Bimatoprost SR 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 Bimatoprost SR Cycle 1 Date or if both years are the same, but the month of the incomplete start date is before the month of the date of the Bimatoprost SR Cycle 1 Date, 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 the Bimatoprost SR Cycle 1 Date or if both years are the same, but the month of the incomplete start date is after the month of the date of the Bimatoprost SR Cycle 1 Date, 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 Bimatoprost SR Cycle 1 Date, Bimatoprost SR Cycle 2 Date, or Bimatoprost 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 Bimatoprost SR Cycle 1 Date or if both years are the same, but the month of the incomplete stop date is before the month of the date of the Bimatoprost SR Cycle 1 Date, 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 the Bimatoprost SR Cycle 1 Date or if both years are the same, but the month of the incomplete stop date is after the month of the date of the Bimatoprost SR Cycle 1 Date, the last day of the month will be assigned to the missing day.

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

16.8 Missing Date Information for Prior or Concomitant Medications

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

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 the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* 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 above procedure

MISSING DAY ONLY

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study 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 first dose of study 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 the first dose of study 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 first dose of study treatment, the first day of the month will be assigned to the missing day

INCOMPLETE STOP DATE

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

MISSING MONTH AND DAY

- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* 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 above procedure

MISSING DAY ONLY

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study 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 last dose of study 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 the last dose of study 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 last dose of study treatment, the first day of the month will be assigned to the missing day

17 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

The following are changes to version 1 of SAP:

1. In section 4, updated the study design based on protocol amendment 2.

2. In section 6, changed intent-to-treat population to full analysis set since the study has been changed to a single arm study with no randomization. Additionally, changed safety population to safety analysis set.

3. In section 7, updated definition of a participant who has completed the study based on protocol amendment 2 as well as the study populations for which the summary will be provided.

4. In section 8, changed analysis population from ITT to FAS, changed definitions or prior and concomitant medications, and added definitions of rescue treatment, permanent rescue treatment, and intermittent rescue medication. Additionally, added summaries for number and percent of participants receiving rescue treatments and types of permanent and intermittent rescue medications to study eye and all rescues medications for fellow eyes treated with Bimatoprost SR.

5. In section 9.1, added "if the date of exit is missing then the date of last visit will be used to calculate study duration" to the derivation of study duration.

6. In section 10, updated the analysis population from ITT to FAS.

7. In section 10.1, updated the endpoints based on protocol amendment 2.

8. In section 10.2, updated the endpoints based on protocol amendment 2. Additionally, added the definition of baseline IOP for study eye and fellow eye.

9. In section 11, updated the analysis population from safety population to SAS. Also, updated the baseline definition from "last safety assessment prior to randomization" to "last safety assessment prior to first dose of study treatment".

10. In section 11.1, added definition of TEAE for fellow eye, removed summary of TEAE by SOC, PT, and severity, and added summary of non-ocular TEAEs by SOC, PT, and severity.

11. In section 11.3, changed "more than 1" to "at least 2-grade".

12. In section 11.4, updated the formula for line change as well as the definition of baseline and worst line change to be consistent with other Bimatoprost SR studies.

13. In section 11.5, added clarification if the machine type is different or missing between visits.

14. In section 11.6, added "Reading center analysis as well as automated analysis will be performed; however, reading center data will be the primary source of safety analysis of specular microscopy data" to include analysis of specular microscopy assessment from reading center since reading center assessment was added in protocol amendment 2. Also, updated the summary to be consistent with other Bimatoprost SR studies.

15. In section 11.7, changed "more than 1" to "at least 2-grade".

16. In section 11.8, removed the listing for implant assessment.

17. In section 13, added interim lock to evaluate the use of an alternate applicator based on protocol amendment 2.

18. In section 14, updated sample size calculation based on protocol amendment 2.

19. In section 16.1, added footnotes to tables 16-1, 16-2, 16-3, and 16-4 regarding analysis window derivation for fellow eye treated with Bimatoprost SR. Updated the footnote in table 16-5 to add clarification regarding which tables to use for different assessments (based on the frequency of the assessments) and the window for the last visits in cycles 2 and 3. Additionally, added rules for deriving windows for IOP, BCVA, and other assessments as well as for when multiple visits (scheduled and/or unscheduled) are within the same window to be consistent with other Bimatoprost studies SR.

20. In section 16.3, added definition of baseline assessment for fellow eye.

21. In section 16.7, updated the algorithm for imputing partial AE start and stop dates to be consistent with other Bimatoprost SR studies.

18 REFERENCES

This section is not applicable.