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Study ID: 192024-092

Title: The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

SAP Date: October 29, 2018

1.0 TITLE PAGE

192024-092

THE EFFICACY AND SAFETY OF BIMATOPROST SR IN PATIENTS WITH OPEN-ANGLE GLAUCOMA OR OCULAR HYPERTENSION

STATISTICAL ANALYSIS PLAN Amendment 1 - Clinical Study Report

Final: 29OCT2018

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2.1 LIST OF TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
AS-OCT	anterior segment optical coherence tomography
BCVA	best corrected visual acuity
BID	twice daily dosing
CCT	central corneal thickness
eCRF	electronic case report form
FDA	Food and Drug Administration
ITT	intent to treat
IOP	intraocular pressure
LOCF	last observation carried forward
MCMC	Markov chain Monte Carlo
MD	mean deviation
MI	multiple imputation
MMRM	mixed-effects model for repeated measures
OAG	open-angle glaucoma
OHT	ocular hypertension
OCT	optical coherence tomography
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SITA	Swedish Interactive Thresholding Algorithm
SOC	system organ class

SR	sustained release
TEAE	treatment-emergent adverse event
US	United States

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 for Study 192024-092. Specifications of tables, figures, and data listings are contained in a separate document.

Study 192024-092 is a Phase 3, multicenter, randomized, masked, parallel-group comparison, active-controlled, repeat administration study in patients at least 18 years of age who have been diagnosed with open-angle glaucoma (OAG) or ocular hypertension (OHT).

The length of the study will be approximately 22 months for each patient, consisting of screening of up to 28 days before washout, washout period of up to 42 days before initial administration of study medication, 52-week treatment period, plus 8 months extended follow-up. Signed informed consent from the patient or the patient's legally authorized representative will be obtained before any study-related procedures are begun. All patients who provide informed consent will be assigned a subject number. Patients meeting all inclusion and no exclusion criteria will be randomized in a 1:1:1 ratio to receive 1 of 2 dose strengths of Bimatoprost SR treatment (Bimatoprost 10 µg or 15 µg plus vehicle twice daily [BID] eye drops) or control treatment (Sham administration procedure plus timolol BID eye drops) in the study eye on Day 1. The randomization will be further stratified by baseline study eye Hour 0 IOP (≤ 25 mm Hg or > 25 mm Hg). Patients who have not received nonstudy IOP-lowering medication in both eyes will receive a repeat administration of Bimatoprost sustained release (SR) or control treatment in the study eye at the Week 16 and Week 32 visits.

All patients will be masked to their treatment group. Treatment groups are shown as follows:

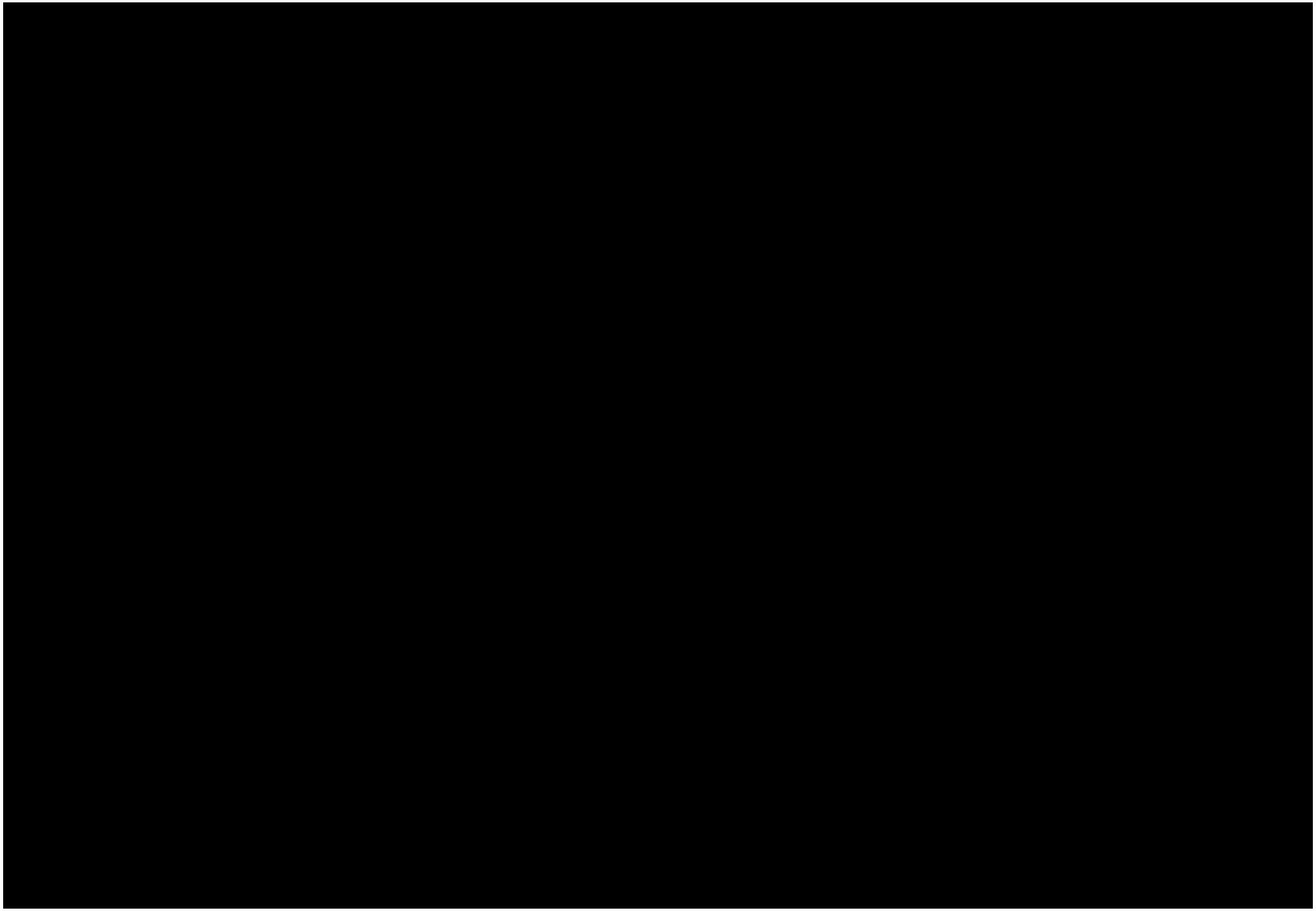
Treatment	Study Eye Treatment	Fellow Eye Treatment
Bimatoprost SR 10 µg	Dose strength: 10 µg Eye drops: Vehicle BID	Sham administration procedure Eye drops: Timolol BID
Bimatoprost SR 15 µg	Dose strength: 15 µg Eye drops: Vehicle BID	Sham administration procedure Eye drops: Timolol BID
Control	Sham administration procedure Eye drops: Timolol BID	Sham administration procedure Eye drops: Timolol BID

BID = twice daily

Three database locks are planned. The first database lock will take place after all patients have completed or prematurely discontinued before the Week 12 visit (defined as Week 12 Lock). Similarly, the database will be locked after all patients have completed or prematurely discontinued before Week 52 (defined as Week 52 Lock) and Month 20/Exit (defined as Final Lock). To avoid potential data unmasking between locks and to protect trial integrity, study personnel who have been unmasked after each lock will no longer be involved directly in any ongoing study conduct. Another statistician, who is still masked to study treatment, will assume these responsibilities until the next lock. Unmasked data handling and appropriate data and results access will be specified prior to each lock.

The schedule of evaluations for Study 192024-092 is presented in Table 4-1 to Table 4-5 per protocol amendment 3.

Table 4-1 Screening through Treatment Day 1



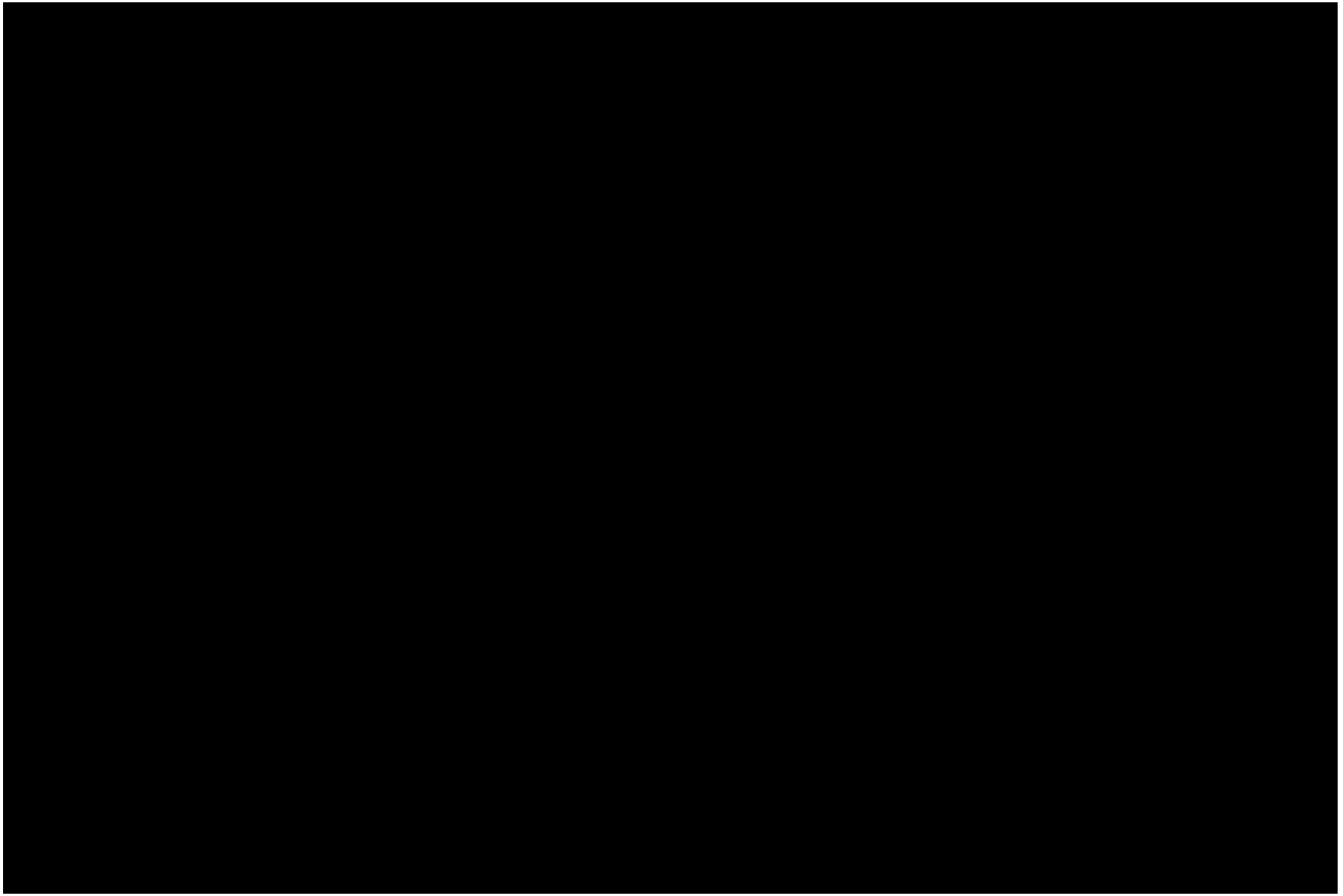
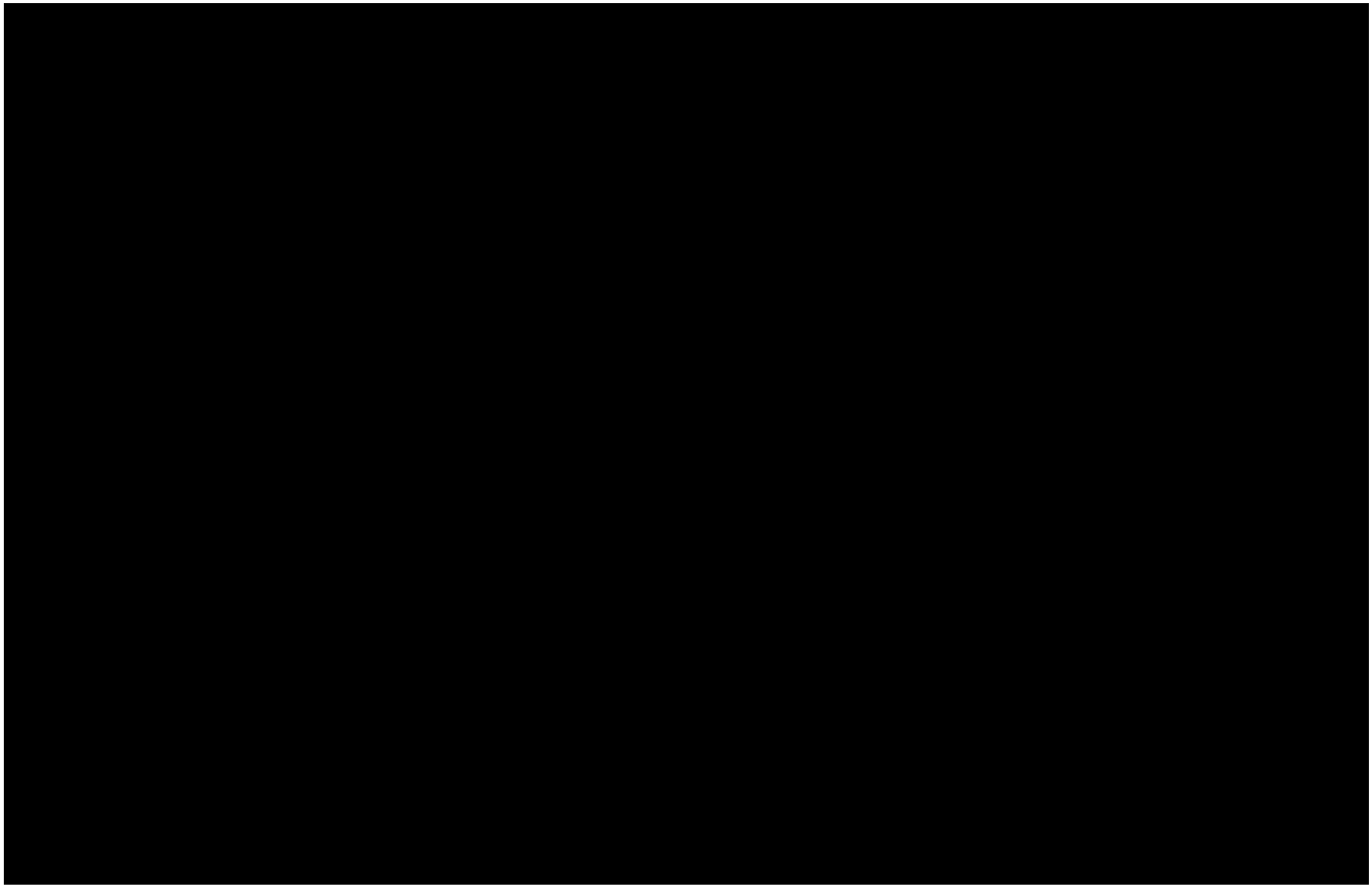


Table 4-2 Administration Cycle 1 Schedule of Visits and Procedures: Treatment Period Day 2 through Week 12

Table 4-3 Administration Cycle 2 Schedule of Visits and Procedures: Treatment Period Week 15 Through Week 28

Table 4-4 Administrtion Cycle 3 Schedule of Visits and Procedures: Treatment Period Week 31 Through Week 52



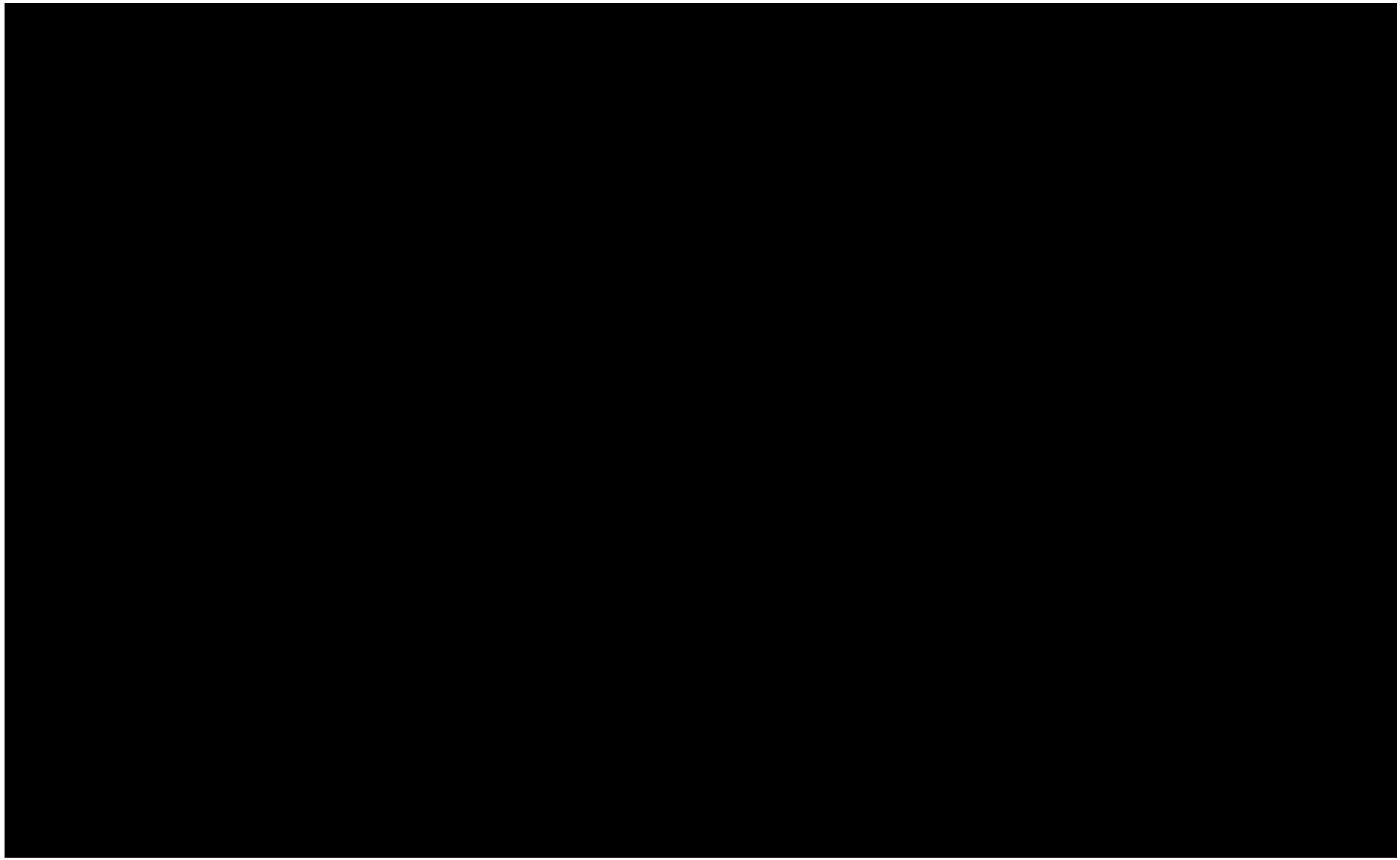
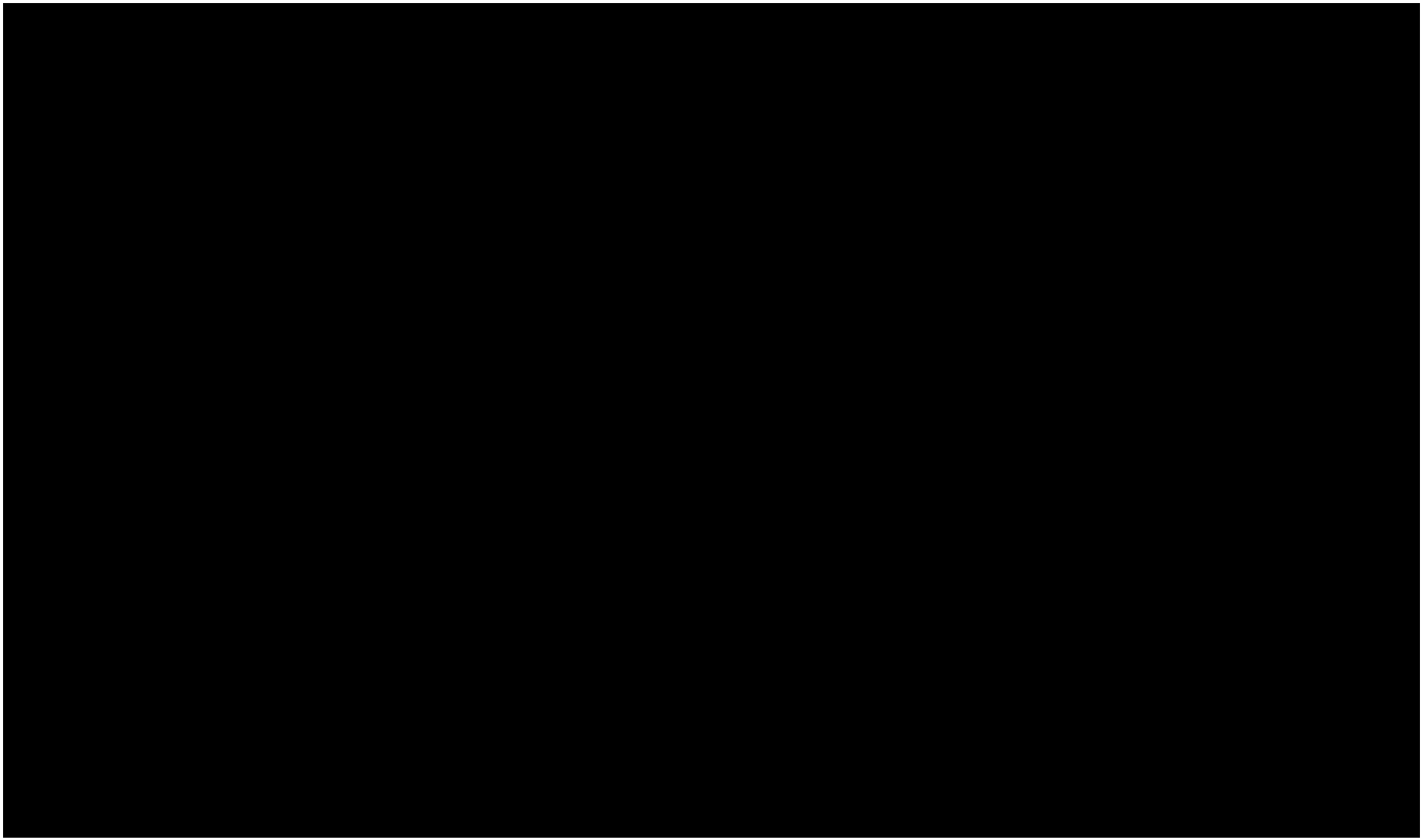


Table 4-5 Schedule of Visits and Procedures: Extended Follow Up Months 14, 16, 18, and 20



5.0 OBJECTIVES

The objective of this study is to evaluate the intraocular pressure (IOP)-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR in patients with OAG or OHT after initial and repeated administrations.

The clinical hypotheses are:

- At least 1 dose strength (10 µg or 15 µg) of Bimatoprost SR will have an IOP-lowering effect that is noninferior to that of topically administered timolol 0.5% (hereafter referred to as timolol) eye drops in patients with OAG or OHT following single and repeat administrations.

- Bimatoprost SR administered intracamerally in dose strengths of 10 µg or 15 µg will have an acceptable safety profile in patients with OAG or OHT following single and repeat administrations.

6.0 PATIENT POPULATIONS

6.1 INTENT-TO-TREAT POPULATION

The intent-to-treat (ITT) population will consist of all randomized patients.

6.2 SAFETY POPULATION

The safety population will consist of all patients who received at least 1 dose of study treatment.

6.3 PER-PROTOCOL POPULATIONS

The per-protocol (PP) population will consist of the subset of patients in the ITT population who had the primary efficacy variable measured. IOP measures deemed being influenced by other medications would be excluded from PP analysis. The PP population will be used to confirm the primary efficacy analyses. A separate document to define further criteria and details of data to be excluded from the PP analyses will be finalized prior to the Week 12 database lock.

6.4 DATA COLLECTED BUT NOT ANALYZED

Clinical lab test data and general (non-ophthalmic) physical examination will only be collected at screening and will not be analyzed.

Any other data collected, but not analyzed, will be described in the clinical study report.

7.0 PATIENT DISPOSITION

The number and percentage of patients in the 3 study populations (ITT, Safety, and PP) will be summarized by treatment group; the number of patients screened will be summarized overall only.

The number and percentage of patients who complete and the number and percentage of patients who prematurely discontinue will be presented for each treatment group and pooled across treatment groups for the ITT population by Cycle and for the entire study. The study completers will be defined as the patients who received at least 1 injection and complete the extended safety follow up visits. The completers for each cycle will be defined as the patients who received injection in the relevant cycle and completed the cycle by either receiving the following injection or completing the extended safety follow up visits. The reasons for premature discontinuation from each administration cycle and the entire study will be summarized (number and percentage) by treatment group for the ITT population. For patients who prematurely discontinue due to adverse events (AEs), the reason will be further classified into ocular AE and nonocular AE. All patients who prematurely discontinue during the study will be listed by discontinuation reason for the ITT population.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Continuous variables will be summarized by number of patients and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

Demographics

Demographic parameters including age, age group, race, race group, and sex; and baseline characteristics including weight (kg), and height (cm) will be summarized descriptively by treatment group for the ITT population. Patient's age (years) will be classified into 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 nonwhite.

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

Medical History and Ophthalmic History

Findings in patients' medical histories, and ophthalmic histories, will be coded using the Medical Dictionary for Regulatory Activities. The number and percentage of patients with abnormalities in medical histories (ophthalmic excluded) in each system organ class (SOC) and preferred term will be summarized by treatment group for the safety population.

Abnormalities in ophthalmic history in each system organ class and preferred term will be separately summarized as frequency count and percent by treatment group for study eye and pooled for fellow eye in the safety population.

Surgical and Ophthalmic surgical history will be presented in listings.

Prior and Concomitant Medications/Procedures

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment. If any medication is taken before the date of the first dose of study treatment and continues after initiation of study treatment, it will be considered as both a prior and concomitant medication.

Prior and concomitant medications will be separately summarized using the safety population for each treatment group as the number and percentage of patients under each indication preferred term (MedDRA) and unique base preferred name from the World Health Organization Drug Dictionary Enhanced (WHODDE).

Concurrent procedures will be provided in the listings.

Non-study IOP Lowering Medications/Procedures

A non-study IOP-lowering medication is defined as a medication for which the investigator specifically marked "Yes" to the question "Is this medication used as a non-study IOP-lowering medication?" on the concomitant medication electronic case report from (eCRF). A non-study IOP-lowering procedure is defined as a procedure for which the investigator specifically marked "Yes" to the question "Was this an IOP-lowering procedure?" on the concurrent procedure eCRF.

Other medications or procedures that could potentially reduce IOP but are not marked in the eCRF as non-study IOP-lowering medications/procedures will be listed in the separate document used to identify data excluded from the PP analysis.

Washout Ocular Medication

Similarly, washout ocular medications will be tabulated by treatment group for the study eye and pooled for the fellow eye.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Throughout the study, each patient will receive up to 3 administrations of Bimatoprost SR or Sham injection in each eye with a fixed interval of 16 weeks. The number and percent of patients receiving Bimatoprost SR or Sham treatment in the study eye during the study will be tabulated by the number of treatment administrations for each treatment group.

Each patient's study duration will be calculated as the number of days between the exit date and Day 1 Administration Day, inclusively (date of the exit - Day 1 Administration date + 1). Patients' study duration will be summarized using descriptive statistics for each treatment group.

10.0 EFFICACY ANALYSES

The primary efficacy variable for country/regions other than US will be time-matched IOP change from baseline in the study eye. The primary efficacy variable for the United States (US) Food and Drug Administration (FDA) (Division of Transplant and Ophthalmology Products) is IOP in the study eye (Section 10.3.1).

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

10.1 PRIMARY EFFICACY PARAMETER(S)

The primary efficacy measurement is IOP. IOP of each eye will be measured using the Goldmann applanation tonometer at Hours 0 (08:00 ± 1 hour) and 2 (2 hours after Hour 0 [± 30 minutes]) of each visit other than administration days. For each IOP assessment, two consecutive measurements will be taken for each eye. If these 2 measurements differ by > 1 mm Hg, a third measurement will be performed for the given eye. The IOP value for a given eye will be the median of all measurements.

Intraocular pressure values at Hours 0 and 2 of Baseline visit will be considered as the time-matched baseline values for the corresponding timepoints of follow-up visits (e.g., study eye IOP time-matched change from baseline at Hour 0 of Week 12 will be calculated as: study eye IOP at Hour 0 of Week 12 – study eye IOP at Hour 0 of Baseline).

To avoid confounding of efficacy data, IOP values obtained after initiating the use of non-study IOP-lowering medication or procedure in an eye 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.

10.1.1 Primary Efficacy Analysis

The primary efficacy variable is the study eye time-matched IOP change from baseline at each hour evaluated (Hours 0 and 2). Mean IOP change from baseline will be compared between each Bimatoprost SR dose strength and the timolol group for each evaluation hour using the ITT population. The comparisons at Week 12 will be considered the primary analysis.

The null and alternative hypotheses for the comparison between a given Bimatoprost SR dose strength and timolol at each evaluation hour of Week 12 are:

- Null hypothesis: the difference in mean IOP change from baseline between the given Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) is > 1.5 mm Hg.

- Alternative hypothesis: the difference (Bimatoprost SR minus timolol) in mean IOP change from baseline between the given Bimatoprost SR dose strength and timolol is ≤ 1.5 mm Hg.

Intraocular pressure change from baseline will be analyzed using a mixed-effects model with repeated measures (MMRM). The model will include IOP time-matched change from baseline as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint-by-baseline time-matched IOP interaction. Unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance matrix fails to converge, multiple imputation (MI) will be implemented before MMRM.

Mis-stratified subjects, if any, will be analyzed based on the stratum to which the subjects should have been randomized.

Within the framework of this model, the mean difference between each Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) and the corresponding 2-sided 95% confidence interval will be provided for each hour (Hours 0 and 2) at each visit. The formal noninferiority test will be performed at each evaluation hour of Week 12 for each Bimatoprost SR dose strength versus timolol using a noninferiority margin of 1.5 mm Hg.

Assume SAS variables:

A pseudo SAS code to perform the analysis could be as below:

[redacted]

A gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level for each hour at Week 12, testing Bimatoprost SR 15 µg against timolol first and followed by the comparison between Bimatoprost SR 10 µg and timolol. The test of Bimatoprost SR 10 µg versus timolol is valid only if the noninferiority of Bimatoprost SR 15 µg to timolol is demonstrated. Bimatoprost SR 15 µg (or 10 µg) will be declared noninferior to timolol if the upper limit of the 95% confidence interval is ≤ 1.5 mm Hg for both Hours 0 and 2 at Week 12.

The following sensitivity analyses will be performed for the primary efficacy variable.

1. PP population analysis – The analysis outlined for primary efficacy analysis will be repeated on the PP population.

2. Time-matched last observation carried forward (LOCF) analysis – Missing value will be imputed by time-matched LOCF method. At each visit/hour, treatment difference and its 95% confidence interval will be based on least square means by using an Analysis of Covariance (ANCOVA) model with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate.

3. Multiple imputation implementation before performing ANCOVA analysis – Step 1: Intermittent missing values at each hour of Week 2, 6, and 12 will first be imputed by treatment group using Markov chain Monte Carlo (MCMC) method (defined as the MCMC step) with seed=79214203 resulting in data with a monotone pattern. Step 2: Multiple imputation by treatment group using linear regression with factors of demographics and baseline characteristics including but not limited to race group, sex, and lens status; and age, baseline IOP values at both Hour 0 and Hour 2 as covariates (defined as the regression step) will be applied to the data obtained from the MCMC step. The seed for the second multiple imputation step=63128917. Step 2 will immediately follow step 1 and the entire procedure will be repeated 25 times to provide reliable statistical inference (JW Graham, 2007).

   A typical SAS® code to perform the analysis could be as below:

10.2 SECONDARY EFFICACY PARAMETER(S)

The secondary efficacy variable is the study eye IOP at each hour evaluated.

10.2.1 Secondary Efficacy Analysis #1

The 2-sided 95% confidence interval for the mean difference in study eye time-matched IOP change from baseline between each Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) derived in the primary analysis will be used for secondary analysis of superiority comparison. If the upper 95% confidence limit is less than zero, the difference will be considered significant and in favor of the given Bimatoprost SR dose strength for the given timepoint.

Bimatoprost SR 15 µg (or 10 µg) will be considered superior to timolol if it demonstrates significant difference in favor of Bimatoprost SR 15 µg (or 10 µg) at each of the 6 timepoints within the 12-week period (Hours 0 and 2 at Weeks 2, 6, and 12).

10.2.2 Secondary Efficacy Analysis #2

Similarly, the superiority test of study eye IOP at each hour of a visit will be performed using the same MMRM model as described above in Section 10.1.1 with the response variable of study eye IOP.

Bimatoprost SR 15 µg (or 10 µg) will be considered superior to timolol if it demonstrates significant difference in favor of Bimatoprost SR 15 µg (or 10 µg) at each of the 6 timepoints within the 12-week period (Hours 0 and 2 at Weeks 2, 6, and 12).

10.3 EFFICACY ANALYSES FOR US FDA

10.3.1 Primary Efficacy Analysis for US FDA

For US FDA review, the primary efficacy variable will be the study eye IOP. The primary analysis will be based on Weeks 2, 6, and 12 using the ITT population. Mean IOP will be compared between each Bimatoprost SR dose strength and timolol for each hour (Hours 0 and 2) at Weeks 2, 6, and 12. Intraocular pressure measurements obtained after initiating the use of nonstudy IOP-lowering medication in an eye will be treated as missing for that eye.

The null and alternative hypotheses for the comparison between a given Bimatoprost SR dose strength and timolol for each hour at each visit are:

- The null hypothesis is that the difference in mean IOP between the given Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) is > 1.5 mm Hg.

- The alternative hypothesis is that the difference (Bimatoprost SR minus timolol) in mean IOP between the given Bimatoprost SR dose strength and timolol is ≤ 1.5 mm Hg.

Intraocular pressure will be analyzed using an MMRM approach based on the same MMRM model as described above with IOP as the response variable. The mean difference between each Bimatoprost SR dose strength and timolol and the corresponding 2-sided 95% confidence interval will be provided for each hour (Hours 0 and 2) and each visit (Weeks 2, 6, and 12).

A gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level. Bimatoprost SR 15 µg will be tested against timolol first at each timepoint (Hours 0 and 2 at Weeks 2, 6, and 12) and then followed by the comparison between

Bimatoprost SR 10 µg and timolol. The test for Bimatoprost SR 10 µg versus timolol for a given hour at a visit is valid only if the noninferiority of Bimatoprost SR 15 µg to timolol has been demonstrated for the given timepoint.

Bimatoprost SR 15 µg (or 10 µg) will be declared noninferior to timolol if the upper limit of the 95% confidence interval is ≤ 1.5 mm Hg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12). Each Bimatoprost SR dose strength that shows noninferiority to timolol will be declared clinically noninferior to timolol if the upper limit of the 95% confidence interval is ≤ 1.0 mm Hg for 3 or more timepoints.

Analysis will be repeated on PP population as a sensitivity analysis. The same analysis will also be repeated with missing values imputed by time-matched LOCF and multiple imputation as sensitivity analysis (similar to Section 10.1.1).

10.3.2 Secondary Efficacy Analysis for US FDA

For each Bimatoprost SR dose strength which demonstrates efficacy (clinical noninferiority) as described in the primary efficacy analyses for US FDA, the secondary efficacy analysis is to test the superiority of the Bimatoprost SR dose strength versus timolol.

For the superiority test of study eye IOP at each hour of a visit, the null hypothesis is that there is no difference between a given Bimatoprost SR dose strength and timolol. The alternative hypothesis is that there is a difference. The null hypothesis will be tested using the same MMRM model as described for the primary efficacy analysis for US FDA. A 2-sided 95% confidence interval for the mean difference in study eye IOP between each Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) will be provided. If the upper 95% confidence limit is less than zero, the difference will be considered significant and in favor of the given Bimatoprost SR dose strength for the given timepoint.

The following gatekeeping procedure will be applied to control the overall type I error rate at the 0.05 level for the US FDA primary and secondary hypotheses sequentially.

1. Bimatoprost SR 15 µg is noninferior to timolol at all six time points using a non-inferiority margin of 1.5 mmHg.

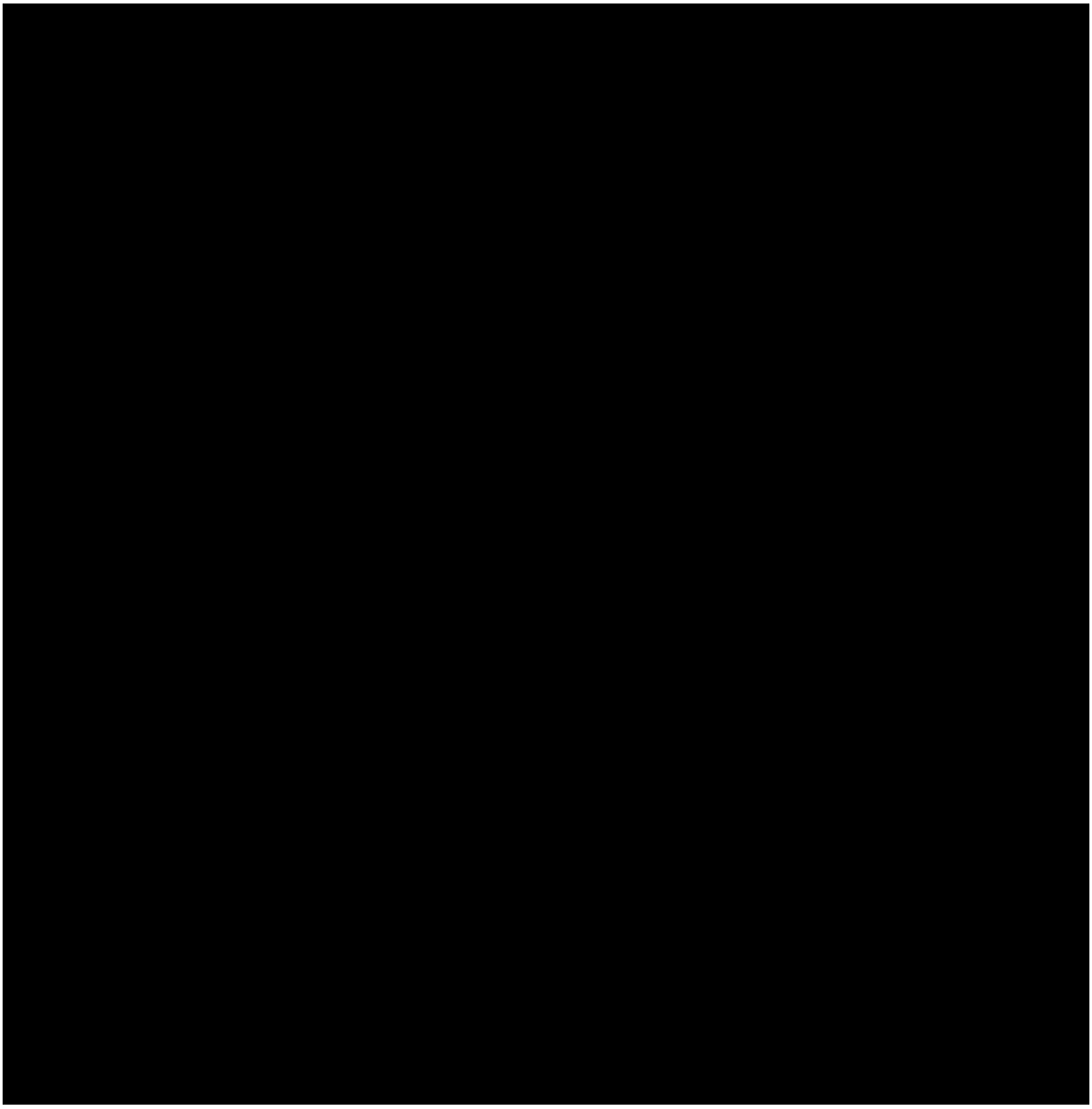
2. Bimatoprost SR 10 µg is noninferior to timolol at all six time points using a non-inferiority margin of 1.5 mmHg.

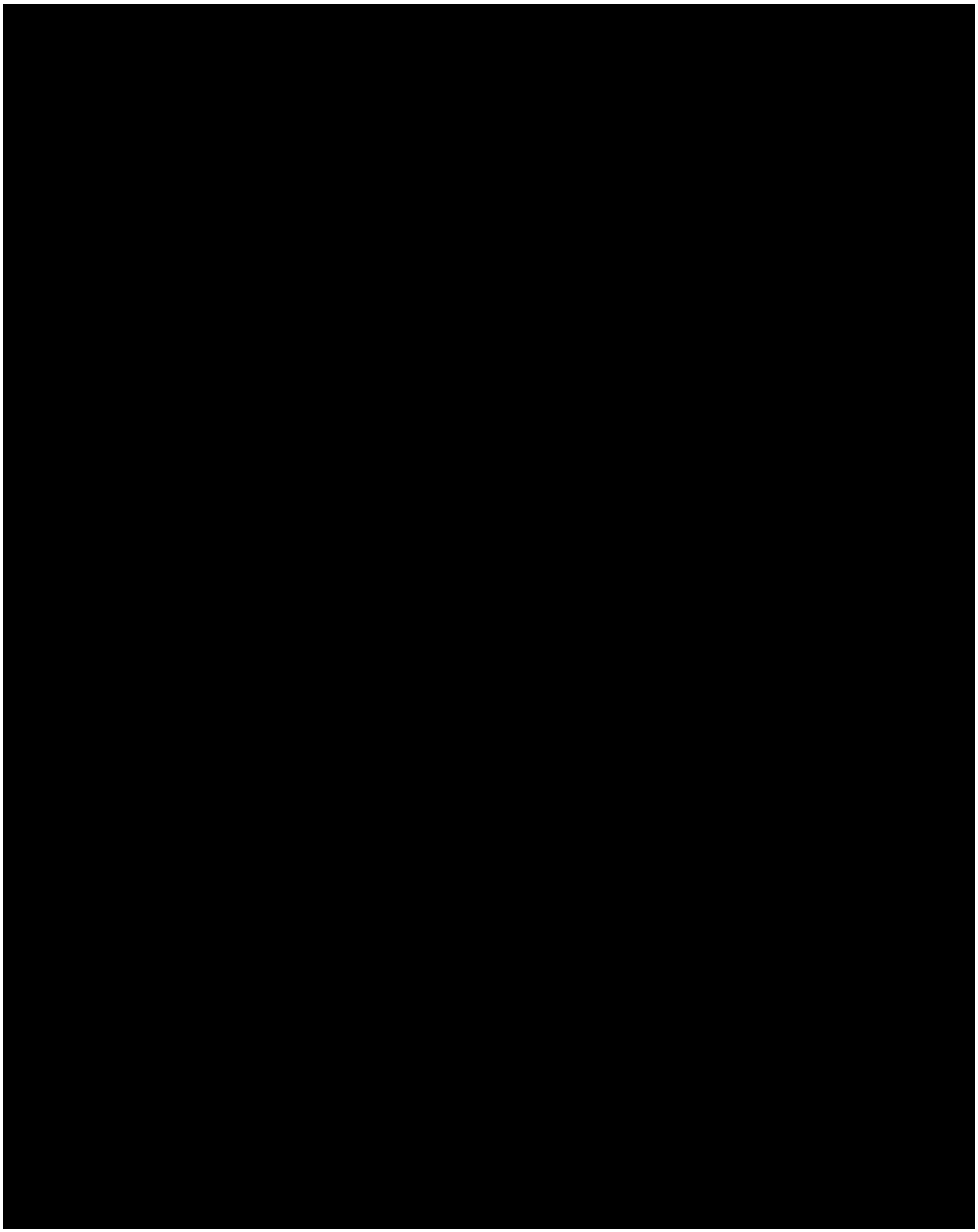
3. Bimatoprost SR 15 µg is superior to timolol at all 6 timepoints.

4. Bimatoprost SR 10 µg is superior to timolol at all 6 timepoints.

The above hypotheses will be tested in a sequential order. If at any step a test fails, the test procedure will stop and no further hypotheses will be tested. Following the above testing sequence, if Bimatoprost SR 10 µg demonstrates noninferiority to timolol at all six time points using a non-inferiority margin of 1.5 mm Hg, Bimatoprost SR 15 µg will be tested for superiority and considered statistically superior to timolol, if it shows statistically significant difference in favor of Bimatoprost SR 15 µg at all 6 time points (Hours 0 and 2 at Weeks 2, 6, and 12). A similar criterion for claiming superiority of Bimatoprost SR 10 µg over timolol will be employed.

10.4 ADDITIONAL EFFICACY PARAMETERS





11.0 SAFETY ANALYSES

The safety analysis will be performed using the safety population. The safety parameters will include the following nonocular safety parameters: nonocular AEs, clinical laboratory values, vital signs, and pregnancy; and ocular safety parameters: ocular AEs, implant/sham assessment, visual acuity, visual field examination, macroscopic iris color assessment, macroscopic conjunctival hyperemia assessment, Bimatoprost SR implant assessment, biomicroscopic examination, lens assessment, optic disc examination, dilated ophthalmoscopic examination, gonioscopy assessment, optical coherence tomography (OCT), specular microscopy, pachymetry, anterior segment optical coherence tomography (AS-OCT). Unless otherwise stated, the last nonmissing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, the 1st quartile and the 3rd quartile, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

For ocular safety assessments, analyses will be performed by treatment group for study eye and pooled for fellow eye based on the first actual treatment received in each eye. For nonocular safety measures, analyses will be performed on a patient basis for the treatment actually received.

For all safety by-cycle summary analyses, in order to compare cycles of similar duration, the data included in each cycle will be,

- Cycle 1 (16 weeks): data from the 1st injection to the 2nd injection date -1 or upper bound of week 15 visit window (section 16.1) if a patient didn't receive the 2nd injection;
- Cycle 2 (16 weeks): data from the 2nd injection to the 3rd injection date -1 or upper bound of week 31 visit window (section 16.1) if a patient didn't receive the 3rd injection;
- Cycle 3 (20 weeks): data from the 3rd injection to upper bound of week 52 visit window (section 16.1);
- Extended safety follow up: data after week 52 for patients with 3 injections and extended follow up.

11.1 ADVERSE EVENTS

Adverse events will be coded by SOC and preferred term using the Medical Dictionary for Regulatory Activities.

For a given AE and patient, if more than 1 severity grade is reported, the worst severity grade (the greater of the onset and maximum severity recorded on the electronic case report from [eCRF]), will be used for analysis.

Adverse events will be classified into ocular AEs and nonocular AEs. An ocular AE will be determined as indicated on the AE form of eCRF, and thus are not limited to AEs with primary SOCs of eyes. The treatment-related ocular AEs will be further broken down by either related to injection procedure or related to study drug as indicated on eCRF. Ocular AEs will be tabulated by treatment group for the study eye and pooled for the fellow eye, and nonocular AEs will be summarized by treatment group for patient. Analysis by cycle of treatment will also be performed.

Treatment-Emergent Adverse Events

An AE will be considered a treatment-emergent adverse event (TEAE) for the study treatment period if the AE meets 1 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 1 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.

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

The number and percentage of patients reporting TEAEs will be provided on a per-patient basis by 1) SOC and preferred term; 2) SOC, preferred term and severity in descending order of frequency for each treatment group.

The number and percentage of patients reporting nonocular TEAEs in each treatment group will be tabulated by SOC and preferred term. Also the number and percentage of patients reporting treatment-related (including study drug related or injection procedure related) nonocular TEAEs in each treatment group will be tabulated by SOC and preferred term.

Similar analyses will be done for ocular TEAEs including 1) by PT and severity; 2) treatment-related TEAEs by PT for each treatment group by study eye and fellow eye. In addition, similar analyses will be performed for ocular TEAEs by treatment cycle.

Within each treatment cycle, ocular TEAEs identified (onset or worsened) within 2 days of administration and identified more than 2 days of administration of each cycle will be summarized by each treatment group for study eye and pooled for fellow eye.

Serious TEAEs

Nonocular and ocular STEAEs will be summarized by preferred term and treatment group, respectively.

TEAEs Leading to Study Discontinuation

Nonocular TEAEs and ocular TEAEs leading to premature discontinuation of the study will be summarized by preferred term and treatment, respectively.

Similarly, ocular TEAEs leading to premature discontinuation will also be tabulated by treatment group by treatment cycle.

Ocular TEAEs Leading to Study Drug Discontinuation or Regimen Change

Ocular TEAEs leading to study drug discontinuation will be summarized by preferred term and treatment for the entire study period and also for each cycle. Ocular TEAEs leading to study drug discontinuation or regimen change are defined as the ocular TEAEs with action regarding study drug reported as “Discontinued” or “Regimen Changed” on the eCRF AE form.

Ocular TEAEs Leading to Implant Removal

Ocular TEAEs leading to implant removal will be summarized by preferred term and treatment for the entire study period and also for each cycle.

TEAEs of Special Interest
Corneal TEAEs and Anterior chamber inflammation TEAEs of interest will be summarized by preferred term and treatment group, respectively. Similar analyses will be done by treatment cycle. 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

Descriptive statistics for vital signs (systolic and diastolic blood pressures [mm Hg], pulse rate [bpm], and temperature [Celsius]) at baseline and changes from baseline values at each scheduled follow-up visit will be presented by treatment group.

11.3 OTHER SAFETY PARAMETERS

11.3.1 Implant/Sham Assessment (Postadministration Evaluation)

Implant/sham assessment after the administration of study treatment on each administration day will be summarized by treatment cycle. Number and percent of patient eyes (study eye) will be tabulated by treatment group (Bimatoprost 10 µg and Bimatoprost 15 µg) by the following categories:

- Implant visible in the anterior chamber after the injection
- Implant immediately release from the applicator needle
- Implant release from the applicator needle before the applicator was withdrawn from the eye
- Implant track back and remained attached to the corneal injection site (further classified the maneuvers performed to release the implant into 3 categories: tap on surface of cornea, use of Wilson Anterior Chamber Probe, and other)
- Wound leak with excessive loss in the anterior chamber volume
- Eye patched after injection procedure
- Anterior chamber formed before the patient was released

11.3.2 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 the 3 administration days. BCVA will be recorded in Snellen equivalent units. The line change from baseline at each follow-up evaluation will be calculated using the following formula:

$$\text{Line change} = 10 \times [\log10\ (20/d_{\text{follow-up}}) - \log10\ (20/d_{\text{baseline}})]$$

where d_{baseline} = denominator of the Snellen equivalent unit at baseline,
$d_{\text{follow-up}}$ = denominator of the Snellen equivalent unit at follow-up

The logarithmic values are to be rounded to the nearest tenth before calculation of the line change. A positive value indicates an improvement and a negative value indicates a worsening. 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 follow-up would be the following:

Line change = 10 x [log10(20/80) – log10 (20/25)] = 10 x (0.1 – 0.6) = -5

which represents a worsening of 5 lines in visual acuity.

The data for the worst line change from baseline across follow-up will be summarized by treatment group for study eye and pooled for fellow eye. The worst line change is defined as the greatest decrease from baseline in the number of lines read. Summary statistics of the worst line change will be presented in each of the following categories: worsening (< -2), no changes (≥-2 and ≤ 2), and improving (> 2). The number and percentage of patient eyes in each category will be presented. Similar analyses will be conducted by treatment cycle.

11.3.3 Visual Field

Visual field examinations will be assessed using automated perimetry (using either Humphrey 24-2 full threshold program or 24-2 Swedish Interactive Thresholding Algorithm [SITA] Standard, or Octopus G1 or 24-2 programs and Dynamic or Normal strategy) at screening, baseline, Week 28, Week 52, and Month 20/Exit. The same test methodology must be used throughout the entire study for a given patient. 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).

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

The number and percent of patient 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 for each treatment group by cycle and across all study visits.

11.3.4 Macroscopic Conjunctival Hyperemia Assessment

Macroscopic conjunctival hyperemia assessment will be performed for each eye at all scheduled visits except on any of the 3 administration days using the following scale: 0 = none, +0.5 = trace, +1 = mild, +2 = moderate, and +3 = severe. The frequency distribution for the severity grade at each scheduled visit will be summarized by treatment group for the study eye and pooled for the fellow eye.

To summarize findings from macroscopic conjunctival hyperemia assessment, a tabulation of the number and percentage of patient eyes who had more than 1 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 at any of the follow-up visits will be summarized. Similar analyses will be performed for each treatment cycle and may be provided for findings with other severity grade increase.

11.3.5 Biomicroscopy and Ophthalmoscopy

Biomicroscopy will be performed in each eye by slit-lamp examination at each scheduled visit. Dilated ophthalmoscopy (including vitreous, optic nerve, macula, and retina periphery) and lens status assessment will be performed for each eye at Screening, Baseline, Week 12, Week 28, Week 44, Week 52, and Month 20/Exit.

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

The number and percentage of patient eyes with biomicroscopy and ophthalmoscopy findings more than 1 severity grade increase (worsening, i.e., 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 findings under other pathology which is not associated with a severity grade, at 1 or more postbaseline visits, will be tabulated by preferred term in descending order of incidence rate. The number and percentage of eyes with any clinically significant findings will be presented (as “Overall”) by treatment group for study eye and pooled for fellow eye. Similar analyses will be performed for each treatment cycle and may be provided for findings with other severity grade increase.

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 by treatment group for study eye and pooled for fellow eye by visit. The lens status will be presented as data listings and may be summarized with frequency and percent as necessary.

11.3.6 Cup/Disc Ratio

The cup/disc ratio will be evaluated using a 0.0 to 1.0 scale for each eye at visits of Screening, Baseline, Week 12, Week 28, Week 44, Week 52, and Month 20/Exit.

Change from baseline at each follow-up visit will be categorized as an improvement of 0.2 or more (≤ - 0.2), no change - between 0.2 and -0.2 (> -0.2 to < 0.2), or a worsening of 0.2 or more (≥ 0.2). The number and percentage of patients in each category will be provided by treatment group for the study eye and pooled for the fellow eye.

11.3.7 Gonioscopy and Bimatoprost SR Implant Assessment

Gonioscopy will be performed to assess the iridocorneal (anterior chamber) angle for both eyes at visits as specified in the protocol. Patients presenting peripheral anterior synechiae on gonioscopy will be presented in listing.

The Bimatoprost SR implant assessment will be performed during gonioscopy examination. For patients who have implant size collected, implant size (percentage of the original material) will also be summarized based on the percentage category for each implant in the study eye by cycle and visit for bimatoprost treatment groups. The number and percentage of implants at each of 12 zones of implant location will be summarized by visit. Also, the number of patients who have implant(s) contact with corneal endothelium at any visit within a cycle will be summarized by cycle. Implant assessment will be presented as data listings for the location of implant (12 zones), status of contact with other implant(s), and status of contact with corneal endothelium.

11.3.8 Macroscopic Iris Color Assessment

Iris color will be assessed visually for each eye at Baseline, Week 12, Week 28, Week 44, Week 52, Month 16, and Month 20/Exit visits. Iris color change from baseline (No, Yes with Mild, Moderate and Severe) will be presented in listing and may be summarized as necessary.

11.3.9 Optical Coherence Tomography of the Macula

Optical coherence tomography (OCT) of the macula will be performed to assess macular edema in each eye at Screening, Week 52, and Month 20/Exit visits. Foveal central subfield (μm) from OCT data and change from baseline will be presented in listing and may be summarized as necessary.

11.3.10 Anterior Segment Optical Coherence Tomography (AS-OCT)

Anterior segment optical coherence tomography (AS-OCT) will be performed for both eyes at Screening for patients' iridocorneal angle eligibility before protocol amendment 2. The OCT images will be sent to a reading center to perform quantitative measurements of the patient inferior iridocorneal angle. If in the investigator's opinion the patient's angle size may have changed, an unscheduled AS-OCT may be performed prior to retreatment. Inferior angle measurements will be presented by data listing.

11.3.11 Pachymetry

Corneal thickness using ultrasound (contact) pachymetry will be performed on the central cornea for each eye at Screening, Week 12, Week 28, Week 44, Week 52, and Month 20/Exit. At each examination, 3 measurements of central corneal thickness (CCT) and associated standard deviation will be reported, and the average of the 3 measurements will be calculated and used for analysis. CCT baseline and changes from baseline will be summarized descriptively by treatment group for study eye and pooled for the fellow eye. In addition, CCT raw values will be summarized descriptively for each visit.

11.3.12 Specular Microscopy

Endothelial cell density will be assessed using specular microscopy performed on the central cornea for each eye at Screening, Week 12, Week 28, Week 44, Week 52, and Month 20/Exit. At each examination, average endothelial cell density for each eye will be reported by reading center and used for analysis.

Endothelial cell density baseline and changes from baseline, and raw values will be summarized descriptively by visit for each treatment group in study eyes and pooled for the fellow eyes.

In addition, the number and percentage of patient eyes who reported 1) within ±200 cells/mm^2 change; 2) ≥ 10% loss; 3) ≥ 20% loss; 4) ≥ 30% loss; 5) ≥ 40% loss; and 6) ≥ 50% loss in endothelial cell density will be summarized by visit for each treatment group in study eyes and pooled for fellow eyes respectively for each category.

Fellow eye-adjusted endothelial cell density changes from baseline and percent loss from baseline values in the study eye are defined below.

- Fellow eye-adjusted endothelial cell density change from baseline (CFB_ADJ) is defined as the difference in endothelial cell density change from baseline between the study eye and the fellow eye, and calculated as CFB_ADJ = CFB_SE - CFB_FE, where CFB_SE is endothelial cell density change from baseline in the study eye and CFB_FE is endothelial cell density changes from baseline in the fellow eye.
- Fellow eye-adjusted endothelial cell density percent loss from baseline (PLoss_ADJ) is defined as the difference in endothelial cell density percent loss from baseline between the study eye and the fellow eye, and calculated as PLoss_ADJ = PLoss_SE - PLoss_FE, where PLoss_SE is endothelial cell density percent loss from baseline in the study eye and PLoss_FE is endothelial cell density percent loss from baseline in the fellow eye.

Fellow eye-adjusted endothelial cell density will be summarized descriptively by visit for each treatment group, and the number of patients who reported changes within ± 200 cells/mm^2 will also be summarized.

Additionally, the number and percentage of patients who reported 1) $\geq$ 10% loss; 2) $\geq$ 20% loss; 3) $\geq$ 30% loss; 4) $\geq$ 40% loss; and 5) $\geq$ 50% loss in fellow eye-adjusted endothelial cell density percent loss will be summarized by visit for each treatment group for each category, respectively.

Coefficient of variation (COV) from specular microscopy baseline and changes from baseline, and raw values will be summarized descriptively by visit for each treatment group in study eyes and pooled for the fellow eyes. Fellow eye-adjusted COV will also be summarized descriptively by visit.

Similar analysis will be conducted on pleomorphism (HEX) from specular microscopy.

11.3.13 Pregnancy Test

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

11.4 SUBGROUP ANALYSES FOR SAFETY VARIABLES

Subgroup analyses for safety variables are not planned, but may be performed.

12.0 HEALTH OUTCOMES ANALYSES

Not applicable.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study. Each database lock will correspond to a milestone and statistical analysis will be provided when all randomized patients have either completed or exited from the targeted visit (Weeks 12, Week 52, and Month 20/Exit).

14.0 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy analysis of the IOP for US FDA review because the sample size based on the primary efficacy analysis for other regions is expected to be smaller.

The sample size is estimated based on a 2-sided t-test with $\alpha = 0.05$ at each timepoint and the assumption that the mean IOP difference between Bimatoprost SR 10 µg and timolol is -0.25 mm Hg (i.e., Bimatoprost SR 10 µg is 0.25 mm Hg better in IOP-lowering than timolol) at Weeks 2 and 6 and 0 mm Hg at Week 12, with a common SD of 4.0 mm Hg and a common within-subject correlation of 0.6. It is also assumed that the efficacy (IOP-lowering effect) of Bimatoprost SR 15 µg is better than that of Bimatoprost SR 10 µg by 0.25 mm Hg at each timepoint (Hours 0 and 2). These assumptions are based on the data obtained from the ongoing clinical study 192024-041D. Based on simulations, a sample size of 540 patients (180 per group) will provide approximately 95% and 81% power to show noninferiority of Bimatoprost SR 15 µg and Bimatoprost SR 10 µg, respectively, to timolol at all 6 scheduled timepoints based on a noninferiority margin of 1.5 mm Hg and at 3 or more timepoints based on an noninferiority margin of 1.0 mm Hg. Assuming a premature discontinuation rate of 10% within 12 weeks (before primary database lock), approximately 600 patients (200 per group) are to be enrolled into this study.

As part of ongoing centralized data monitoring of masked study data, some of the initial assumptions used for sample size calculation have been revisited. The rate of discontinued or rescued patients in the first 12 weeks is approximately 5%, which was less than the rate of 10% assumed at the study design phase. Furthermore, the masked common IOP variability (pooled standard deviation across treatments and timepoints) is approximately 3.8 mm Hg, which was also less than the assumed 4.0 mm Hg at the study design phase. With the updated assumption on the common IOP standard deviation of 3.8 mm Hg, a sample size of 486 patients (162 per group) would provide approximately 95.1% and 83.5% power to show NI of Bimatoprost SR 15 µg and Bimatoprost SR 10 µg, respectively, to timolol at all 6 scheduled timepoints based on an NI margin of 1.5 mm Hg; and at 3 or more timepoints based on an NI margin of 1.0 mm Hg. With the updated premature discontinuation or rescue rate of 5% within 12 weeks, approximately 510 patients (170 per group) are to be enrolled into this study.

15.0 STATISTICAL SOFTWARE

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

16.0 DATA HANDLING CONVENTIONS

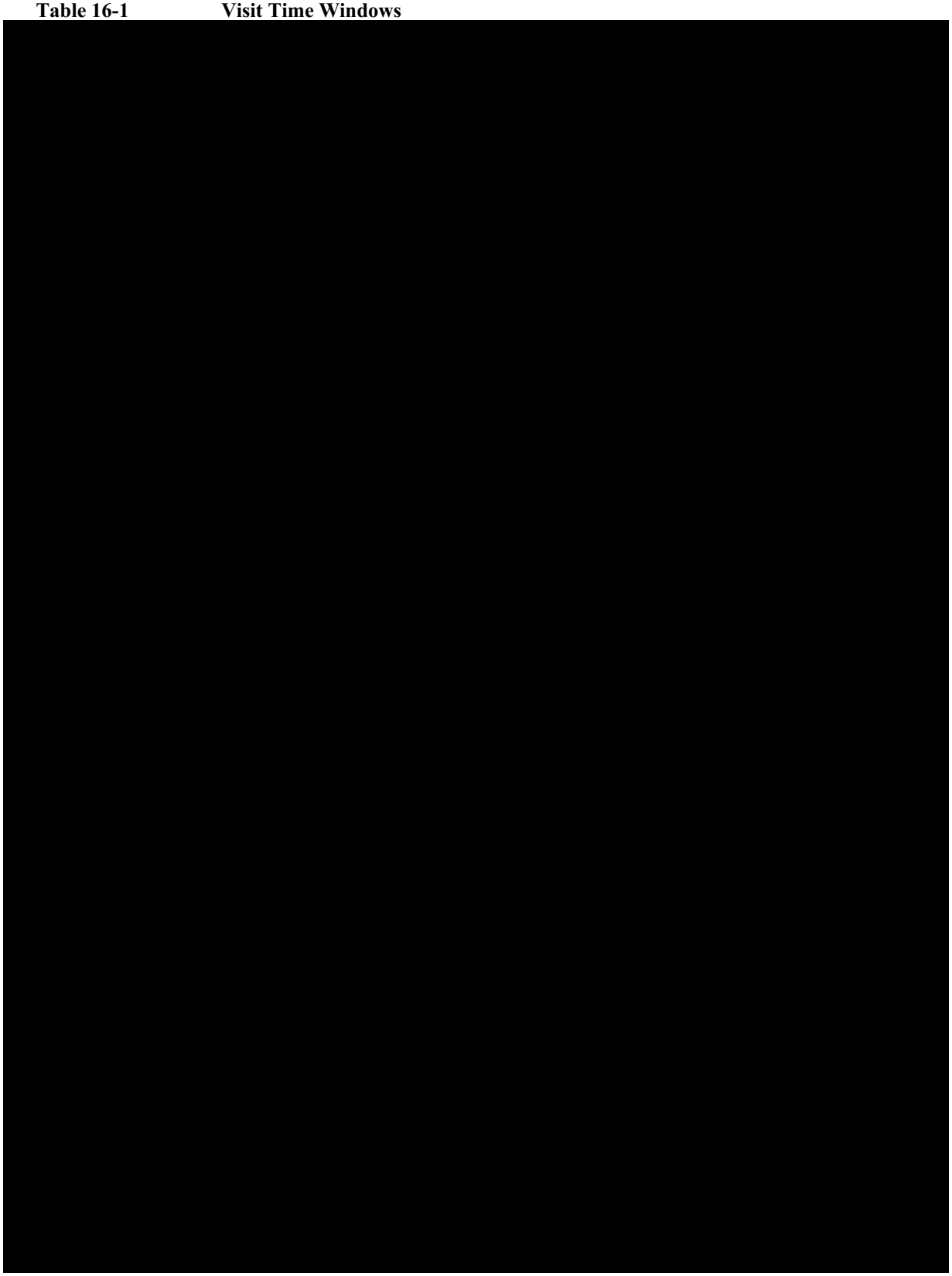
16.1 VISIT TIME WINDOWS

For all analyses, all follow-up visits or the exit visit will be reassigned with the visit number based on the study days according to the following windows in Table 16-1.

Table 16-1 Visit Time Windows

[redacted]

Table 16-1 Visit Time Windows



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.

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

No Applicable.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

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

16.4 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.

16.5 MISSING CAUSAL RELATIONSHIP TO STUDY TREATMENT 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.

16.6 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

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.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

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

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

16.7 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

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

16.7.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date unless the start date > 1 year is marked. 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. If in the cases that the start date > 1 year is marked, the same month and day of the first dose of study treatment and the previous year of the first dose of study treatment will be assigned to the missing fields.

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.

16.7.2 Incomplete Stop Date

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

Missing Month and Day

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

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

- If the year of the incomplete stop date is after the year of the study exit date, *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 study exit date, the day of the study exit date will be assigned to the missing day.

- If either the year of the incomplete stop date is before the year of the study exit 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 study exit 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 study exit date or if both years are the same but the month of the incomplete stop date is after the month of the study exit date, the first day of the month will be assigned to the missing day.

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Two additional terms the time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) and timepoint-by-baseline Hour 0 IOP interaction were added to the primary efficacy analysis model, but were not presented in protocol amendment 3, dated 5JUN2018.

18.0 REFERENCES

Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci 2007 Sep; 8(3):206-13.

19.0 AMENDMENTS

19.1 AMENDMENT 1

1. Updated visit schedule tables 4-1 to 4-5 per protocol amd 3.

2. In section 6.3, updated "The per-protocol (PP) population will consist of the subset of patients in the ITT population who had the primary efficacy variable measured. IOP measures deemed being influenced by other medications would be excluded from PP analysis. The PP population will be used to confirm the primary efficacy analyses.~~with no protocol deviations affecting the primary efficacy analyses and will be used to confirm the primary efficacy analyses.~~ A separate document to define further criteria and details of data to be excluded from the PP analyses ~~A list of patients excluded from the PP population will be finalized~~ prior to the Week 12 database lock."

3. In section 6.4, updated "Clinical lab test data and general (non-ophthalmic) physical examination will only be collected at screening and will not be analyzed."

4. In section 7.0, updated "The number and percentage of patients in the 3 study populations (ITT, Safety, and PP) will be summarized by treatment group ~~and study center~~; the number of patients screened will be summarized for overall only ~~by the study center~~."

5. In section 7.0, deleted "~~Patients screened but not randomized along with the associated reasons for failure to randomize will be tabulated overall for the all screened patients.~~"

6. In section 7.0, added the study and cycle completer definition "The study completers will be defined as the patients who received at least 1 injection and complete the extended safety follow up visits. The completers for each cycle will be defined as the patients who received injection in the relevant cycle and completed the cycle by either receiving the following injection or completing the extended safety follow up visits."

7. In section 8.0, updated "Prior and concomitant medications will be separately summarized using the safety population for each treatment group as the number and percentage of patients under each indication preferred term (MedDRA) and unique base preferred name from the World Health Organization Drug Dictionary Enhanced (WHODDE)."

8. In section 8.0, added the following:

   "Non-study IOP Lowering Medications/Procedures

   A non-study IOP-lowering medication is defined as a medication for which the investigator specifically marked "Yes" to the question "Is this medication used as a non-study IOP-lowering medication?" on the concomitant medication electronic case report from (eCRF). A non-study IOP-lowering procedure is defined as a procedure for which the investigator specifically marked "Yes" to the question "Was this an IOP-lowering procedure?" on the concurrent procedure eCRF.

   Other medications or procedures that could potentially reduce IOP but are not marked in the eCRF as non-study IOP-lowering medications/procedures will be listed in the separate document used to identify data excluded from the PP analysis."

9. In section 10.1, updated "To avoid confounding of efficacy data, IOP values obtained after initiating the use of non-study IOP-lowering medication or procedure in an eye 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."

10. In section 10.1.1, updated the primary efficacy analysis model, "The model will include IOP time-matched change from baseline as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors~~effects~~, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint-by-baseline time-matched IOP interaction."

11. In section 10.1.1, added "Mis-stratified subjects, if any, will be analyzed based on the stratum to which the subjects should have been randomized."

12. In section 10.1.1, updated pseudo SAS code for primary efficacy analysis.

13. In section 10.1.1, sensitivity analyses on primary efficacy variable were updated "At each visit/hour, treatment difference and its 95% confindence interval will be based on least square means by using an Analysis of Covariance (ANCOVA) model with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either ~~at~~ Hour 0 ~~and baseline IOP at~~ or Hour 2 according to the response variable) as a covariate~~s~~."

14. In section 10.1.1, sensitivity analyses on primary efficacy variable using MI were updated "Step 2: Multiple imputation by treatment group using linear regression with factors of demographics and baseline characteristics including but not limited to race group, sex, and lens status; and age, ~~IOP~~ baseline IOP values at both Hour 0 and Hour 2 as ~~a~~ covariates (defined as the regression step) will be applied to the data obtained from the MCMC step."

15. In section 10.1.1, updated pseudo SAS code for MI.

16. In section 10.2.1, deleted "~~For the superiority test of study eye time-matched IOP change from baseline at each hour of a visit, the null hypothesis is that there is no difference between a given Bimatoprost SR dose strength and timolol. The alternative hypothesis is that there is a difference. The null hypothesis will be tested using the same MMRM model as described for the primary efficacy analysis in Section 10.1.~~"

17. In section 10.2.1, updated "The ~~A~~ 2-sided 95% confidence interval for the mean difference in study eye time-matched IOP change from baseline between each Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) ~~will be provided~~ derived in the primary analysis will be used for secondary analysis of superiority comparison."

18. In section 10.3.2, deleted "~~The comparison will be made between each Bimatoprost SR dose strength and timolol for study eye IOP at each timepoint (Hours 0 and 2 at Weeks 2, 6, and 12) using the ITT population.~~"

19. In section 10.3.2, superiority claiming criterion for secondary efficacy analysis for US FDA is updated "Bimatoprost SR 15 µg will be tested for superiority and considered statistically superior to timolol, if it shows statistically significant difference in favor of Bimatoprost SR 15 µg at ~~3 or more~~ all 6 time points ~~and numerically better at the remaning time points of all scheduled timepoints~~ (Hours 0 and 2 at Weeks 2, 6, and 12)."

25. In section 11.0, updated "Continuous variables will be summarized by number of patients and mean, SD, median, the 1st quartile and the 3rd quartile, minimum, and maximum values."

26. In section 11.0, updated "For ocular safety assessments, analyses will be performed by treatment group for study eye and pooled for fellow eye based on the first actual treatment received in each eye. For nonocular safety measures, analyses will be performed on a patient basis for the treatment actually received."

27. In section 11.0, definition of cycle and safety follow up is added "For all cycle summary analyses, in order to compare cycles of similar duration, the data included in each cycle will be,

    - Cycle 1 (16 weeks): data from the 1st injection to the 2nd injection date -1 or upper bound of week 15 visit window (section 16.1) if a patient didn't receive the 2nd injection;

- Cycle 2 (16 weeks): data from the 2nd injection to the 3rd injection date -1 or upper bound of week 31 visit window (section 16.1) if a patient didn't receive the 3rd injection

- Cycle 3 (20 weeks): data from the 3rd injection to upper bound of week 52 visit window (section 16.1);

- Extended safety follow up: data after week 52 for patients with 3 injections and extended follow up."

28. In section 11.1, the overall summary of AEs was updated to "Overall summary of TEAEs will be provided on a per-patient basis for categories of all TEAEs, treatment-related TEAEs, injection procedure-related TEAEs, study drug-related TEAEs, serious ~~adverse events~~ TEAEs (STEAEs), deaths, and TEAEs leading to study discontinuation."

29. In section 11.1, TEAE summary table was updated to "the number and percentage of patients reporting TEAEs will be provided on a per-patient basis by 1) SOC and preferred term; 2) SOC, preferred term and severity in descending order of frequency for each treatment group."

30. In section 11.1, non-ocular TEAEs summary was updated to "The number and percentage of patients reporting nonocular TEAEs in each treatment group will be tabulated by ~~1) descending percentage in any group; 2)~~ by SOC~~,~~ and preferred term ~~and severity; and 3)~~. Also the number and percentage of patients reporting treatment-related ~~by causal relationship to the study treatment~~ (including study drug related or injection procedure related) nonocular TEAEs in each treatment group will be tabulated by SOC and preferred term. ~~If more than 1 nonocular AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.~~"

31. In section 11.1, ocular TEAEs summary was updated to "Similar analyses will be done for ocular TEAEs including 1) by PT and severity; 2) treatment-related TEAEs by PT for each treatment group by study eye and fellow eye. ~~Additionally, ocular TEAEs in each treatment group will also be tabulated by 1) by causal relationship to the study drug; 2) by causal relationship to injection procedure.~~"

32. In section 11.1, deleted "~~If more than 1 ocular AE is coded to the same preferred term for the same patient eye, the patient 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.~~"

33. In section 11.1, serious TEAEs summary was updated to "Nonocular and ocular STEAEs will be summarized by preferred term and treatment group, respectively."

34. In section 11.1, updated "Nonocular TEAEs and ocular TEAEs leading to premature discontinuation of the study will be summarized by preferred term and treatment, respectively. Similarly, ocular TEAEs leading to premature discontinuation will also be tabulated by treatment group by treatment cycle."

35. In section 11.1, added "Ocular TEAEs leading to study drug discontinuation will be summarized by preferred term and treatment for the entire study period and also for each cycle. Ocular TEAEs leading to study drug discontinuation or regimen change are defined as the ocular TEAEs with action regarding study drug reported as "Discontinued" or "Regimen Changed" on the eCRF AE form."

36. In section 11.1, updated "Ocular TEAEs leading to implant removal will be summarized by preferred term and treatment for the entire study period and also for each cycle."

37. In section 11.1, updated "Corneal TEAEs and Anterior chamber inflammation TEAEs will be summarized by preferred term and treatment group, respectively. Similar analyses will be done by treatment cycle. The full list of corneal AEs and Anterior chamber inflammation AEs 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."

38. In section 11.3.2, BCVA change from baseline analysis was updated to "Summary statistics of the worst line change will be presented in each of the following categories: worsening (< -2), no changes (≥-2 and ≤ 2), and improving (> 2).".

39. Deleted IOP section (originally section 11.3.4), all subsequent section numbers were updated.

40. In section 11.3.4, macroscopic conjunctival hyperemia assessment summary was updated "To summarize findings from macroscopic conjunctival hyperemia assessment, a tabulation of the number and percentage of patient eyes who had ~~at least 2~~ more than 1 severity grade ~~steps~~ increase (worsening, i.e, a change from 0 to ~~1~~ 2 and above, from 0.5 to 2 and above, or from 1 to 3 and above) from the baseline at any of the follow-up visits will be summarized."

41. In section 11.3.5, biomicroscopy and ophthalmoscopy findings summary was updated to "The number and percentage of patient eyes with biomicroscopy and ophthalmoscopy findings ~~at least 2~~ more than 1 severity grade ~~steps~~ increase (worsening, i.e, a change from 0 to ~~1~~ 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 findings under other pathology which is not associated with a severity grade, at 1 or more postbaseline visits, will be tabulated by preferred term in descending order of incidence rate."

42. In section 11.3.7, updated "For patients who have implant size collected, implant size (percentage of the original material) will also be ~~presented in listings and may be~~ summarized based on the percentage category for each implant in the study eye by cycle and visit for bimatoprost treatment groups. The number and percentage of implants at each of 12 zones of implant location will be summarized by visit. Also, the number of patients who have implant(s) contact with corneal endothelium at any visit within a cycle will be summarized by cycle."

43. In section 11.3.10, added "Anterior segment optical coherence tomography (AS-OCT) will be performed for both eyes at Screening for patients' iridocorneal angle eligibility before protocol amendment 2."

44. In section 11.3.12, endothelial cell density was updated to "Endothelial cell density baseline and changes from baseline, and raw values ~~number and percent of patient eyes reported at least 200 cells/mm^2 loss in endothelial cell density~~ will be summarized descriptively by ~~treatment group~~ visit for each treatment group in study eyes and pooled for the fellow eyes."

45. In section 11.3.12, updated "In addition, the number and percentage of patient eyes who reported 1) within ±200 cells/mm^2 change; 2) ≥ 10% loss; 3) ≥ 20% loss; 4) ≥ 30% loss; 5) ≥ 40% loss; and 6) ≥ 50% loss in endothelial cell density ~~raw values~~ will be summarized by visit for each treatment group in study eyes and pooled for fellow eyes respectively for each category."

46. In section 11.3.12, added "Fellow eye-adjusted endothelial cell density changes from baseline and percent loss from baseline values in the study eye are defined below.

    - Fellow eye-adjusted endothelial cell density change from baseline (CFB_ADJ) is defined as the difference in endothelial cell density change from baseline between the study eye and the fellow eye, and calculated as CFB_ADJ = CFB_SE - CFB_FE, where CFB_SE is endothelial cell density change from baseline in the study eye and CFB_FE is endothelial cell density changs from baseline in the fellow eye.

    - Fellow eye-adjusted endothelial cell density percent loss from baseline (PLoss_ADJ) is defined as the difference in endothelial cell density percent loss from baseline between the study eye and the fellow eye, and calculated as PLoss_ADJ = PLoss_SE - PLoss_FE, where PLoss_SE is endothelial cell density percent loss from baseline in the study eye and PLoss_FE is endothelial cell density percent loss from baseline in the fellow eye.

    Fellow eye-adjusted endothelial cell density change from baseline (CFB_ADJ) is defined as the difference in endothelial cell density change from baseline between the study eye and the fellow eye, and calculated as CFB_ADJ = CFB_SE - CFB_FE, where CFB_SE is endothelial cell density change from baseline in the study eye and

CFB_FE is endothelial cell density changs from baseline in the fellow eye.

Fellow eye-adjusted endothelial cell density will be summarized descriptively by visit for each treatment group, and the number of patients who reported changes within ±200 cells/mm2 will also be summarized.

Additionally, the number and percentage of patients who reported 1) ≥ 10% loss; 2) ≥ 20% loss; 3) ≥ 30% loss; 4) ≥ 40% loss; and 5) ≥ 50% loss in fellow eye-adjusted endothelial cell density percent loss will be summarized by visit for each treatment group for each category, respectively.

Coefficient of variantion (COV) from specular microscopy baseline and changes from baseline, and raw values will be summarized descriptively by visit for each treatment group in study eyes and pooled for the fellow eyes. Fellow eye-adjusted COV will also be summarized descriptively by visit.

Similar analysis will be conducted on pleomorphism (HEX) from specular microscopy."

47. In section 14.0, following protocol amendment 3, added "As part of ongoing centralized data monitoring of masked study data, some of the initial assumptions used for sample size calculation have been revisited. The rate of discontinued or rescued patients in the first 12 weeks is approximately 5%, which was less than the rate of 10% assumed at the study design phase. Furthermore, the masked common IOP variability (pooled standard deviation across treatments and timepoints) is approximately 3.8 mm Hg, which was also less than the assumed 4.0 mm Hg at the study design phase. With the updated assumption on the common IOP standard deviation of 3.8 mm Hg, a sample size of 486 patients (162 per group) would provide approximately 95.1% and 83.5% power to show NI of Bimatoprost SR 15 µg and Bimatoprost SR 10 µg, respectively, to timolol at all 6 scheduled timepoints based on an NI margin of 1.5 mm Hg; and at 3 or more timepoints based on an NI margin of 1.0 mm Hg. With the updated premature discontinuation or rescue rate of 5% within 12 weeks, approximately 510 patients (170 per group) are to be enrolled into this study.".

48. In section 16.1, some visit window names in table 16-1 were updated to "~~Extended~~ Cycle 1 Follow Up", "Month 20/~~Exit~~ Cycle 1 Month 20", "~~Extended~~ Cycle 2 Follow Up", "Month 20/~~Exit~~ Cycle 2 Month 16", "Month 20~~/Exit~~".

49. Deleted section 16.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT, and all following sections were re-numbered. "~~When the date of the last dose of study treatment is missing for a patient 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.~~"

50. In section 16.7.2, deleted "~~If the date of the last dose of study treatment is missing, impute it as described in Section 16.4.~~", updated "If the stop ~~day~~ date is marked as ongoing, the study exit date will be assigned to the missing fields.", and added "If the study exit date is not available, the last visit date will be used for imputation."

51. In section 16.7.2, updated the following,

    "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~~ study exit date, the month and day of the ~~last dose of study treatment~~ study exit date 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~~ study exit date, *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~~ study exit date, *January 1* will be assigned to the missing fields.

    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~~ study exit date, the day of the ~~last dose of study treatment~~ study exit date 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~~ study exit 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 last dose of study treatment~~ study exit date, the last day of the month will be assigned to the missing day.

52. In section 17.0, updated changes in this amendment to analyses specified in protocol, "~~There are no major changes to the analyses specified in protocol amendment 1, dated 11AUG2015.~~Two additional terms, the time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) and timepoint-by-baseline Hour 0 IOP interaction, were added to the primary efficacy analysis model, but were not presented in protocol amendment 3, dated 5JUN2018."

ALLERGAN

BIM SR study 192024-092 Statistical Analysis Plan Text_Amd 1

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
01-Nov-2018 16:57 GMT-07	[redacted]	Biostatistics Approval
01-Nov-2018 17:08 GMT-07		Clinical Development Approval
01-Nov-2018 18:35 GMT-07		Medical Monitor Approval
05-Nov-2018 11:50 GMT-08		Biostatistics Approval
05-Nov-2018 14:53 GMT-08		Management Approval