

Title Page

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

Protocol Number: 1698-301-007
Amendment Number: 4

Product: Bimatoprost Sustained Release (SR)

Brief Protocol Title: Duration of effect of Bimatoprost SR in participants with open-angle glaucoma or ocular hypertension

Development Phase: 3b

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* For European Union countries: the sponsor is AbbVie Deutschland GmbH & Co. KG. The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	*Jan 2024*
Amendment 3	*Oct 2023*
Amendment 2	*Mar 2021*
Amendment 1	*Mar 2020*
Original Protocol	*Nov 2018*

Amendment 4 (Jan 2024)

This summary includes changes made to Protocol 1698-301-007 Amendment 3 (Oct 2023). Following is a summary of changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities Section 2.1 Study Rationale Section 2.2.4. Clinical Studies with Bimatoprost SR - Updated study status Section 2.3. Benefit/Risk Assessment Section 4.1 Overall Study design (including Table 4-1) Section 4.2 Scientific Rationale for Study Design Section 6.1 Study Intervention Administered (including Table 6-1) Section 6.4.1 Permitted Interventions Section 6.5 Dose Modification Section 8 Study Assessments and Procedures Section 10.8 Appendix 8 Study Schedule Supplement (subsections: 10.8.8 through 10.8.15)	After protocol Amendment 4 there will be no allowance for a third PRN administration. Deleted language for cycle 3 to allow up to 2 Bimatoprost SR PRN administrations in the study eye, at intervals of a minimum of 16 weeks after the previous Bimatoprost SR and removed no more than 2 in a 12-month period.	[redacted]
Section 1.1 Synopsis	Added a statement for Participants who received the third administration of Bimatoprost SR 10 µg implant (Cycle 3 Administration) prior to protocol Amendment 4 will continue in the study for at least 12 months after their last Bimatoprost SR administration in either eye.	This was implemented for monitoring of participant safety.

Section	Description of Change	Brief Rationale
Section 9.4.1 – Efficacy Analyses	Removed Kaplan-Meier analyses related to the third implant.	With the discontinuation of the third Bimatprost SR administration, this analysis is no longer relevant.

Amendment 3 (Oct 2023)

This summary includes changes made to Protocol 1698-301-007 Amendment 2 (Mar 2021). Following is a summary of changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Description of Change	Brief Rationale
Global	Changed "Allergan" to "AbbVie" where applicable	To update company name
Title Page	Updated emergency medical contact information	To update personnel change
Title page Section 4.4: Start of Study Definition Section 4.5: End of Study Definition Section 5.1.1: Inclusion Criteria at Study Entry Section 6.2: Preparation/Handling/Storage/Accountability Section 8.3.4: Regulatory Reporting Requirements for Serious Adverse Events Section 10.1.9: Publication Policy Section 10.1.10: Patients Confidentiality	EU-CTR related language was added	To align with EU-CTR requirements
Section 1.3: Schedule of Activities Section 7.2: Participant Discontinuation/Withdrawal from the Study Section 8.7: Optional Biomarker Research Endpoints Section 10.1.3: Informed Consent Process Section 10.8: Appendix 8: Study Schedule Supplement	Genetic sampling language was added (US sites only).	To evaluate study endpoints trends based on genetic variations amongst participants.
Section 1.3: Schedule of Activities Section 8.9.3: Patient Mobility/Postural Behavior Questionnaire Section 10.1.3: Informed Consent Process Section 10.8: Appendix 8: Study Schedule Supplement	Patient Mobility and Postural Behavior Questionnaire language was added (US sites only)	To evaluate physical activity for exploratory analysis.
Section 10.9: Appendix 9: Responsibilities of The Investigator	Investigator responsibilities were added.	To document investigator agreement to conduct study according to approved protocol

Amendment 2 (Mar 2021)

In accordance with criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, this amendment is considered to be substantial due to the significant impact on the safety of study participants.

Overall Rationale for the Amendment:

This summary includes changes made to Protocol 1698-301-007 Amendment 1 (Mar 2020).

Following is a summary of changes that were made to each section of the protocol, and a brief rationale for these changes.

Minor editorial and document formatting revisions have not been summarized.

Section No. and Name	Description of Change	Brief Rationale
Title page	Changed from: Allergan Ltd, 1st Floor, Marlow International, The Parkway, Marlow, Buckinghamshire, SL7 1YL, United Kingdom Changed to: Allergan Ltd. Ground Floor Marlow International, Parkway, Buckinghamshire SL7 1YL, United Kingdom	To provide the current name and legal registered address.
Title page	Addition of an emergency telephone number: +1 973-784-6402	To align with current Company processes across all study protocols.
Global changes	Retreatment with Bimatoprost SR will now be administered from Week 16 up to and including Month 36	To reflect the extended PRN treatment period and for clarification.
Synopsis (Number of participants) and 4.1 Overall design	Changed text underlined: In the study eye, participants will receive a 10 µg Bimatoprost SR implant on Day 1 Cycle 1 Administration and, if retreatment criteria are met, up to two additional Bimatoprost SR administrations (Cycle 2 Administration and Cycle 3 Administration) may be performed between 16 weeks after a previous Bimatoprost SR administration through completion of the PRN treatment period (up to and including the Month 36 visit from Day 1 Cycle 1 administration). In the fellow eye, participants will receive standard of care treatment for the duration of the study unless the fellow eye meets the treatment criteria for Fellow Eye Administration. From Week 16 through completion of the PRN treatment period, participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one week and three weeks after Cycle 2 Administration or Cycle 3 Administration. However, through the PRN treatment period, if the fellow eye meets treatment criteria outside of the suggested Cycle 2 or Cycle 3 Administration schedule of visits in the study eye, the fellow eye may receive a single administration of Bimatoprost SR, return for a Day 2 Safety Visit, a Week 4 follow up visit, and then return to the study eye schedule of visits as appropriate.	Sample size updated and PRN treatment period extended. See applicable sections of the protocol.

Section No. and Name	Description of Change	Brief Rationale
	Changed text underlined: Enrollment of up to approximately 490 participants in total is planned, with 62 already enrolled in the 15 µg group under the original protocol, and up to approximately 425 in total to be enrolled in the 10 µg group. Participants who prematurely discontinue from the study will not be replaced.	
Synopsis (Number of Sites)	Number of sites increased from 75 to 130 sites globally	To allow for recruitment of the increased number of participants planned for enrollment.
Synopsis (Treatment Groups and Study Duration) and 4.1 Overall design	Additional text: In order to provide adequate time to achieve a sufficient number of participants with multiple administrations of Bimatoprost SR, a minimum of 18 months and up to 36 months of PRN treatment period will be implemented in Amendment 2. For participants enrolled earlier in the study, the PRN treatment period may be up to 36 months depending on when the last patient reaches the end of their PRN treatment period. Changed from: The duration of the study for each participant is approximately 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, 18-month PRN treatment period, plus at least 12 months of extended follow up. Changed to: The duration of the study for each participant is at least 32 months, consisting of a screening period of up to 10 days before washout; a 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 patient 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 administration.	To reflect the extended PRN treatment period and for clarification.
1.2. Schema (Figure 1-1)	Study schema revised	To reflect the extended PRN treatment period and for clarification.
1.3. Schedule of Activities (SoA) (Table 1-1 and Table 1-2)	Additional ocular examination (non-contact) included (posterior segment imaging). Following 'Treatment Administration' (Table 1-1), a user experience questionnaire will be completed after each Bimatoprost SR administration.	For completeness.
1.3. Schedule of Activities (SoA) (Table 1-3)	Month 30 visit is no longer the Study Exit visit following the extension of the study for period of up to 48 months for each participant. Study Exit visit (Month 48) described in newly added table (see below). Additional ocular examination (non-contact) included at Baseline (posterior segment imaging)	To reflect the extended PRN treatment period and for clarification. Posterior segment imaging added for completeness.

Section No. and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) (Table 1-4)	Newly added table: Schedule of Visits and Procedures: Month 32 through Month 48	To reflect the extended PRN treatment period and for clarification.
1.3. Schedule of Activities (SoA) (Table 1-5 and Table 1-6)	Following 'Treatment Administration' (Table 1-5 and Table 1-6), a user experience questionnaire will be completed after each Bimatoprost SR administration.	For completeness.
2.2.4. Clinical Studies with Bimatoprost SR	Additional text: A Phase 3b study (Study 1698-304-007 [NCT04285580], initiated in 2020) is also in progress. This multicenter, open-label study evaluates the 24-hour IOP lowering effect of Bimatoprost SR 10 µg.	For completeness.
4.2 Scientific Rationale for Study Design	Changed from: This Phase 3b study is designed to mimic clinical practice and collect information on the duration of effect of PRN administration of Bimatoprost SR. Because OAG is a bilateral disease, this study is also investigating the safety of the Bimatoprost SR implant when additionally administered to the fellow eye. Changed to (text underlined): This Phase 3b study is designed to mimic clinical practice and collect information on the duration of effect of PRN administration of Bimatoprost SR. As the retreatment rate will vary in a real-world setting, a flexible duration for the PRN treatment period and increased sample size will be implemented in Amendment 2. These changes will provide the adequate time and sample size needed to achieve a sufficient number of participants with multiple administrations of Bimatoprost SR. Because OAG is a bilateral disease, this study is also investigating the safety of the Bimatoprost SR implant when additionally administered to the fellow eye. Changed from: The duration of the study for each participant is approximately 32 months, with an 18-month retreatment period. Data available from the Phase 1/2 Study 192024-041D suggest that the IOP-lowering effect provided by the Generation 2 Bimatoprost SR implant (currently used in ongoing Phase 3 studies) is closely aligned with that of topical LUMIGAN administration up to Week 12/Week 16. Therefore, the study duration allows for up to 3 Bimatoprost SR PRN administrations in the study eye, at intervals of a minimum of 16 weeks after the last previous Bimatoprost SR administration.	To reflect the extended PRN treatment period and for clarification.

Section No. and Name	Description of Change	Brief Rationale
	Changed to (text underlined): All enrolled participants will have a minimum of 18-month PRN treatment period and all patients will have at least 12 months follow up after the last administration. Therefore, the duration of the study for each participant is at least 32 months, consisting of a screening period of up to 10 days before washout; a washout period of up to 56 days before the initial Bimatoprost SR administration, and a minimum 18 month PRN treatment period. Data available from the Phase 1/2 Study 192024-041D suggest that the IOP-lowering effect provided by the Generation 2 Bimatoprost SR implant (currently used in ongoing Phase 3 studies) is closely aligned with that of topical LUMIGAN administration up to Week 12/ Week 16. Therefore, the study duration allows for up to 3 Bimatoprost SR PRN administrations in the study eye, at intervals of a minimum of 16 weeks after the previous Bimatoprost SR administration and no more than 2 in a 12 month period.	
4.4. End of Study Definition	Changed from: A participant is considered to have completed the study if he/she has completed all visits of the study to Month 30, 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 there are no safety concerns in the opinion of the investigator. With implementation of Amendment 1, participants enrolled to 15 µg Bimatoprost SR under the original protocol will be followed for safety purposes for at least 12 months after the last administration of Bimatoprost in either eye. All other participants will exit at the Month 30/Study Exit visit. At the Month 30/Study Exit visit, if the investigator determines any safety concerns warrant participant follow up, the participant may be followed post exit until safety concerns are resolved based on the investigator's discretion. Changed to (text underlined): 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. With implementation of Amendment 1, participants enrolled to 15 µg Bimatoprost SR under the original protocol will be followed for safety purposes for at least 12 months after the last administration of Bimatoprost in either eye. When participants early exit or discontinue prior to the Month 48/Study Exit visit, the site should complete all procedures for the Month 48/Study Exit visit at the participant's last visit. At the	To reflect the extended PRN treatment period and for clarification.

Section No. and Name	Description of Change	Brief Rationale
	Month 48/Study Exit visit, if the investigator determines any safety concerns warrant participant follow up, the participant may be followed post exit until safety concerns are resolved based on the investigator's discretion.	
5.1.1. Inclusion Criteria at Study Entry (Criterion 6.06)	Changed from: a minimum endothelial cell density of 1800 cells/mm^2 in the **study eye** by automated analysis Changed to: a minimum endothelial cell density of 2000 cells/mm^2 in the **study eye** by automated analysis	Participant safety.
5.2.1. Exclusion Criteria at Study Entry (Criterion 1.04)	Additional text: Note: the investigator should consider a participant's overall health condition, including COVID-19 infection. This should include assessing if the patient is suspected of; quarantined for; or diagnosed with active COVID-19 infection, and whether or not the participant has any symptoms	Participant safety.
5.2.1. Exclusion Criteria at Study Entry (Criterion 1.06)	Changed from: Concurrent enrollment in another Allergan Bimatoprost SR study; or previous enrollment in which an implant was received. Participants enrolled in the 192024-091/092 studies who were randomized to the control treatment and never received an implant may be considered for enrollment at the investigator's discretion. Changed to: Previous use of commercially available Bimatoprost SR in the study eye; concurrent enrollment in another Allergan Bimatoprost SR study; or previous enrollment in which a Bimatoprost SR implant was received in the study eye. Note: Participants with an eye previously treated with Bimatoprost SR or participants previously enrolled in Bimatoprost SR studies 192024-091/-092, and -041D who have an eye that was not treated with Bimatoprost SR in that study may be enrolled, provided that the eye that did not receive Bimatoprost SR meets entry criteria for this study.	Participant safety and to prevent confounding of study results.
5.2.2. Exclusion Criteria for Fellow Eye Administration	Changed from: Note: participants do not need to meet Fellow Eye Administration criteria to qualify for study entry. Fellow Eye Administration criteria are only for fellow eyes that are being considered for Bimatoprost SR administration. Changed to: Note: participants do not need to meet Fellow Eye Administration criteria to qualify for study entry. Fellow Eye Administration criteria are only for fellow eyes that are being considered for Bimatoprost SR administration which is in addition to all study entry criteria required for that eye.	For clarification.
5.2.2. Exclusion Criteria for Fellow Eye Administration (Criterion 1.20)	Addition of a new criterion: Previous administration of Bimatoprost SR (including commercially available Bimatoprost SR) in the **fellow eye**	Participant safety and to prevent confounding of study results.
6.1.2.3. Administration Technique	Additional text: A user experience questionnaire will be completed after each Bimatoprost SR administration.	For completeness.

Section No. and Name	Description of Change	Brief Rationale
6.4.2. Rescue Treatment	Additional text: For participants who need additional IOP lowering treatment but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12 month period, topical IOP-lowering medication (intermittent rescue) may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator).	Language added to align with updated study design.
6.4.3. Prohibited Interventions During the Study (Nonstudy IOP-lowering Treatments)	Additional text underlined: Nonstudy IOP-lowering Treatments Fellow eye: The fellow eyes of participants will receive standard of care for IOP lowering, provided, in the investigator's opinion there is no crossover effect to the study eye. Use of any concurrent nonstudy IOP-lowering treatment in the fellow eye with any known effect on study outcomes in the study eye (eg, crossover effect) is prohibited during the study. If applicable, upon the decision to administer Bimatoprost SR in the fellow eye, standard of care treatment will be stopped at least one day prior to Fellow Eye Administration and use of any topical ophthalmic medication containing an ocular antihypertensive is prohibited as concurrent therapy in the fellow eye, unless necessary for the safety of the participant due to inadequate control of IOP as determined by the investigator. Study eye: Prior to completion of the PRN treatment period, the investigator will be expected to attest to the need for additional nonstudy IOP-lowering (rescue) treatment in the study eye for safety reasons. Note: for participants who need additional IOP lowering treatment but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12-month period, topical IOP-lowering medication (intermittent rescue) may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator). After all retreatment requirements have been met, if the decision to administer Bimatoprost SR in the study eye is made, topical IOP-lowering medications shall be stopped at least one day prior to Bimatoprost SR administration. Contact Lenses Use of soft contact lenses within 3 days and/or use of rigid gas permeable or hard contact lenses within 1 week prior to a scheduled study visit or any Administration Day, and/or use of contact lenses of any kind within 1 week following any Bimatoprost SR administration in the eye receiving administration is prohibited.	Participant safety, to prevent confounding of study results, and align with updated study design.

Section No. and Name	Description of Change	Brief Rationale
	Other Treatments The following medications (or classes of medications) and treatment procedures are not permitted as concurrent therapy during the study through completion of the PRN treatment period or 12 months after the last Bimatoprost SR administration, whichever is longer, unless the participant has already been treated with rescue IOP-lowering medication in the Bimatoprost SR treated eye(s): • Subconjunctival, sub-Tenon's, intravitreal, or other ophthalmic injections of any medications in bimatoprost SR treated eye(s).	
6.5. Dose Modification (Retreatment Criteria)	Changed/additional text underlined: **Retreatment Criteria** Participants may receive up to two additional administrations of Bimatoprost SR in the study eye through completion of the PRN treatment period, if they meet the following criteria: • There is a clinically meaningful increase in IOP (eg, < 20% change from baseline IOP) in the study eye confirmed at a subsequent visit (scheduled or unscheduled) not on the same visit day; and/or, in the investigator's opinion, there are clinical signs or symptoms of disease worsening (eg, disc hemorrhage, worsened visual field). • Each previously administered implant is < 25% of the original size • Retreatments may not occur less than 16 weeks after a previous Bimatoprost SR administration and no more than 2 administrations in the study eye may occur in a 12-month period • The participant has not received any rescue treatment in the study eye o Note: For participants who need additional IOP lowering medication but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12-month period, topical IOP lowering medication (intermittent rescue) may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator). After all retreatment requirements have been met, if the decision to readminister Bimatoprost SR in the study eye is made, topical IOP-lowering medications shall be stopped at least one day prior to Bimatoprost SR administration • There is no evidence of any of the following: o Significant corneal findings related to presence of the implant (including corneal edema, peripherally adjacent to the implant location and/or central) at any visit	Participant safety and to prevent confounding of study results.

Section No. and Name	Description of Change	Brief Rationale
	○ Endothelial cell density less than 2000 cells/mm^2 by specular microscopy, by automated analysis, confirmed at 2 consecutive visits on separate days ○ Persistent and progressive corneal endothelial cell density decrease ≥ 15% from baseline confirmed at 2 consecutive visits on separate days (scheduled or unscheduled) ○ Remaining implant size or position from prior administration(s) that, based on the investigator's evaluation, precludes placement of another implant (eg, may cause chronic contact of the implants with the corneal endothelium) ○ Clinically significant intraocular inflammatory findings (eg, PAS, uveitis, iridocyclitis, macular edema, etc) at any visit. Note: mild intraocular inflammation related to the administration procedure itself that resolves rapidly (with or without NSAIDs or steroids) is not prohibitive • In the investigator's opinion, it is safe for the study eye to receive an additional administration of Bimatoprost SR Signs or symptoms will be documented in the eCRF.	
8. Study Assessments and Procedures	Global updates for the additional assessments and procedures consistent with the visits added and specified in Section 1 (Table 1-4).	For clarification.
8.2.5.3. Visual Field	Newly added content: Visual field data may also be submitted to an Allergan designated vendor for additional evaluation.	For additional analysis where appropriate.
8.2.5.4. Specular Microscopy	Newly added content: Specular microscopy images will also be submitted to a reading center for a centralized evaluation across sites.	For additional analysis where appropriate.
8.8.4. Posterior Segment Imaging	Newly added content: At selected sites only (those with qualified equipment), posterior segment imaging (eg, posterior segment optical coherence tomography [OCT]) may be performed using Allergan-approved instruments. See the Procedure Manual for details. The same instrument should be used throughout the study for a given participant. The participant's decision about whether to allow posterior segment imaging will not affect their eligibility for participation in the study.	For exploratory analysis.
8.9. Health Economics	Updated for the additional assessments and procedures consistent with the visits added and specified in Section 1 (Table 1-4).	To reflect the extended PRN treatment period and for clarification.

Section No. and Name	Description of Change	Brief Rationale
9.2. Sample Size Determination	Changed from: Prior to Amendment 1, similar assumptions were used for the 15 µg group, and approximately 50 participants were enrolled in the 15 µg group. Changed to: Prior to Amendment 1, similar assumptions were used for the 15 µg group, and 62 participants were enrolled in the 15 µg group. Newly added content: In order to assess participants 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 participants with multiple administrations of Bimatoprost SR.	Sample size updated.
9.3. Populations for Analyses	Changed from: The analysis populations will consist of participants as defined below: • The intent-to-treat (ITT) population includes all participants assigned to study treatment and will be used for all efficacy analyses. • The safety population includes all participants who receive at least 1 study treatment and will be used for all safety analyses. Changed to: The analysis sets will consist of experimental units as defined below: Note: The experimental unit will be participant eyes for efficacy analyses and ocular safety analyses and participant for systemic safety variables. • Full Analysis Set (FAS): All participants study eyes that have received study treatment with at least one postbaseline IOP assessments will contribute to the FAS which will be used for efficacy analyses. • Safety Analysis Set (SAS): All participants who have received at least 1 dose of study treatment in either eye will contribute to the SAS. All safety data collected from these participants will be included in the SAS.	For clarification.

Section No. and Name	Description of Change	Brief Rationale
9.4.1.1. Analysis Endpoints	Changed from: The duration of effect of Bimatoprost SR will be evaluated by the below three key time to event efficacy variables: • Time to meeting retreatment criteria in the study eye for a second administration of Bimatoprost SR, • Time to second administration of Bimatoprost SR in the study eye, • Time to second administration of Bimatoprost SR or rescue treatment in the study eye. Changed to: The duration of effect of Bimatoprost SR will be evaluated by the below time to event efficacy variable which is the primary variable for efficacy: • Time to second administration of Bimatoprost SR or first rescue treatment after first administration in the study eye	Change incorporated to align with updated study design.
9.4.1.2. Efficacy Analyses	Changed from: For each of the three key time to event efficacy variables, the cumulative distribution function will be characterized by Kaplan-Meier curves by treatment group, and the corresponding life table with 95% CI for the survival probability will be presented. Changed to: For the time to event efficacy variable, the cumulative distribution function will be calculated by Kaplan-Meier method for each treatment group with the 95% CIs for the survival probability will be presented.	For clarification.
9.4.1.3. Other Analyses	Changed from: Other efficacy variables include: • The time to meeting retreatment criteria in the study eye for a third administration of Bimatoprost SR • Time to the third administration of Bimatoprost SR in the study eye • IOP raw values and change from baseline for study eye and for fellow eye treated with Bimatoprost SR The first two time to event variables will also be analyzed using Kaplan-Meier analysis by treatment group. IOP raw values and change from baseline will be summarized descriptively by treatment groups and visit. Changed to: Other efficacy variables include: • Time to second administration of Bimatoprost SR in the study eye regardless of intermittent rescue • Time to the third administration of Bimatoprost SR in the study eye after second administration regardless of intermittent rescue	Change incorporated to align with updated study design.

Section No. and Name	Description of Change	Brief Rationale
	• Time to third administration of Bimatoprost SR or first rescue treatment after second administration in the study eye • Time to first rescue treatment after third administration in the study eye • IOP raw values and change from baseline for study eye and for fellow eye treated with Bimatoprost SR. IOP raw values and change from baseline will be summarized descriptively by treatment groups and visit. To avoid confounding of efficacy data, IOP measurements obtained after initiating the use of nonstudy IOP-lowering treatment/rescue (medication[s] or procedure[s] or both) in the study eye will be excluded from efficacy analyses, unless otherwise specified.	
9.4.3 Ocular Safety Analyses	Additional text: Reading center as well as automated specular microscopy data will be used for endothelial cell density related safety analyses. Reading center data will be the primary source of safety analysis of specular microscopy data.	For clarification.
9.5. Interim Analyses	Additional text: Additional analyses may be performed with data from select US sites which evaluated the use of an alternate applicator in approximately 30 participants.	For completeness.
10.8. Appendix 8: Study Schedule Supplement	The Study Schedule Supplement has been updated to align with the changes made in Section 1.3 (Schedule of Activities).	To reflect the extended PRN treatment period and for clarification.

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1. Protocol Summary

1.1. Synopsis

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

Protocol Number: 1698-301-007

Amendment Number: 3

Brief Title: Duration of effect of Bimatoprost SR in participants with open-angle glaucoma or ocular hypertension

Study Phase: 3b

Study Rationale:

Study 1698-301-007 is a multicenter, open label, Phase 3b study to evaluate the duration of intraocular pressure (IOP)lowering effect and safety of up to two *pro re nata* (PRN) administrations of 10 µg Bimatoprost sustained release (SR) in the study eye of participants 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 (eg, due to intolerance or nonadherence). Participants who received the third administration of Bimatoprost SR 10 µg implant (Cycle 3 Administration) prior to protocol Amendment 4 will continue in the study for at least 12 months after their last Bimatoprost SR administration in either eye. Participants enrolled to receive 15 µg Bimatoprost SR under the original protocol will no longer receive any additional Bimatoprost SR administrations and will be followed for at least 12 months after the last administration of Bimatoprost SR in either eye.

The purpose of this study is to obtain data on as needed administration of Bimatoprost SR.

Objectives and Endpoints:

Objectives	Endpoints
• 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

Overall Study Design:

This is a multicenter, open label Phase 3b study 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).

In the study eye, participants will receive a 10 µg Bimatoprost SR implant on Day 1 Cycle 1 Administration and, if retreatment criteria are met, up to one additional Bimatoprost SR administration after protocol Amendment 4 (Cycle 2 Administration) may be performed between 16 weeks after the Cycle 1 Bimatoprost SR administration through completion of the PRN treatment period (up to and including the Month 36 visit from Day 1 Cycle 1 administration). After protocol Amendment 4 there will be no allowance for a third PRN administration; participants who entered Cycle 3 Administration prior to Amendment 4 will continue their participation in the study for at least 12 months after their last Bimatoprost SR administration in either eye. In the fellow eye, participants will receive standard of care treatment for the duration of the study unless the fellow eye meets the treatment criteria for Fellow Eye Administration. From Week 16 through completion of the PRN treatment period, participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one week and three weeks after Cycle 2 Administration. However, through the PRN treatment period, if the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, the fellow eye may receive a single administration of Bimatoprost SR, return for a Day 2 Safety Visit, a Week 4 follow up visit, and then return to the study eye schedule of visits as appropriate. Bimatoprost SR administration in the fellow eye must be separated by at least one week from administration in the study eye. Upon the decision to administer Bimatoprost SR in the fellow eye, standard of care treatment will be stopped at least one day prior to Fellow Eye Administration.

With implementation of Amendment 4, PRN Cycle 3 is no longer applicable for any eligible eye.

With implementation of Amendment 1, participants enrolled to receive 15 µg Bimatoprost SR under the original protocol will no longer receive any additional Bimatoprost SR administrations and will be followed for safety purposes for at least 12 months after the last administration of Bimatoprost SR in either eye. Although these participants will no longer receive additional retreatment, rescue IOP-lowering medication should only be initiated in the event that the study eye IOP does not meet or does not maintain IOP-lowering expectations (see Section 6.4.2 for details).

Number of Participants:

Enrollment of up to approximately 490 participants in total is planned, with 62 already enrolled in the 15 µg group under the original protocol, and up to approximately 425 in total to be enrolled in the 10 µg group. Participants who prematurely discontinue from the study will not be replaced.

Number of Sites:

Approximately 130 global sites

Treatment Groups and Study Duration:

In this open label study, participants will receive 10 µg Bimatoprost SR in the study eye.

In order to provide adequate time to achieve a sufficient number of participants with multiple administrations of Bimatoprost SR, a minimum of 18 months and up to 36 months of PRN treatment period will be implemented in Amendment 2.

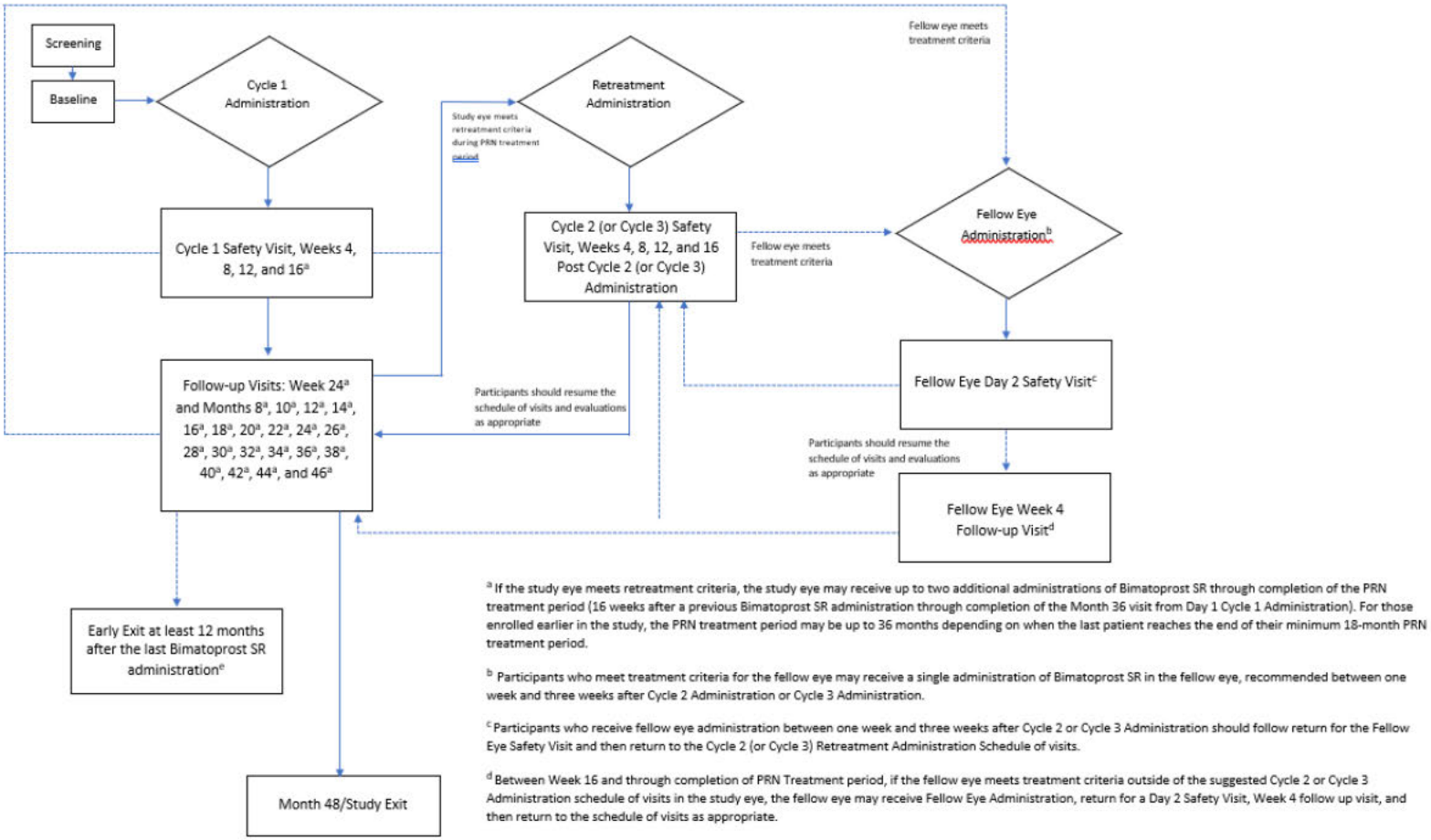
For participants enrolled earlier in the study, the PRN treatment period may be up to 36 months depending on when the last patient reaches the end of their PRN treatment period.

The duration of the study for each participant is at least 32 months, consisting of a screening period of up to 10 days before washout; a 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 patient 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 administration.

Data Monitoring Committee: No

1.2. Schema

Figure 1-1 Study Schema



[a] If the study eye meets retreatment criteria, the study eye may receive up to two additional administrations of Bimatoprost SR through completion of the PRN treatment period (16 weeks after a previous Bimatoprost SR administration through completion of the Month 36 visit from Day 1 Cycle 1 Administration). For those enrolled earlier in the study, the PRN treatment period may be up to 36 months depending on when the last patient reaches the end of their minimum 18-month PRN treatment period.

[b] Participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one week and three weeks after Cycle 2 Administration or Cycle 3 Administration.

[c] Participants who receive fellow eye administration between one week and three weeks after Cycle 2 or Cycle 3 Administration should follow return for the Fellow Eye Safety Visit and then return to the Cycle 2 (or Cycle 3) Retreatment Administration Schedule of visits.

[d] Between Week 16 and through completion of PRN Treatment period, if the fellow eye meets treatment criteria outside of the suggested Cycle 2 or Cycle 3 Administration schedule of visits in the study eye, the fellow eye may receive Fellow Eye Administration, return for a Day 2 Safety Visit, Week 4 follow up visit, and then return to the schedule of visits as appropriate.

[e] Participants who receive non-study IOP-lowering treatment (rescue) in Bimatoprost SR treated eye(s) may early exit the study at least 12 months after the participant's last Bimatoprost SR administration.

Note: Starting with Protocol Amendment 4, PRN Cycle 3 is no longer applicable for any eligible eye.

1.3. Schedule of Activities (SoA)

Table 1-1 Administration Cycle 1 Schedule of Visits and Procedures: Screening through Cycle 1 Week 16

Visit	Screening		Baseline[b]	Day 1 Cycle 1 Administration	Cycle 1 Day 2 Safety Visit	Week 4	Week 8	Week 12	Week 16[c]
Visit Windows	Up to 10 days		Up to 3 days			± 4 days	± 4 days	± 4 days	± 4 days
Informed Consent/Authorization	X	Washout[a] up to 56 days							
Demographic Data	X								
Medical/Ophthalmic History	X		X						
Adverse Events	X		X	X	X	X	X	X	X
Concomitant Medications/ Procedures	X		X	X	X	X	X	X	X
Physical Examination	X								
Vital Signs (at rest ≥ 5 minutes)	X		X	X	X	X	X	X	X
Pregnancy Test[d]			X						
Blood and Urine Sample Collection[e]	X								
Allergan Satisfaction with Treatment Experience Questionnaire: Baseline Module			X						
Allergan Satisfaction with Treatment Experience Questionnaire: Implant Module					X			X	
Treatment Satisfaction Questionnaire for Medication					X			X	
Ocular Examinations in bold should be performed in the order shown									
Pre-Hour 0 Exam (perform before Hour 0 IOP):									
Macroscopic Conjunctival Hyperemia Assessment	OU	Washout[a] up to 56 days	OU		OU	OU	OU	OU	OU
Manifest Refraction[f]	OU		OU						
Best-Corrected Visual Acuity	OU		OU		OU	OU	OU	OU	OU
Intraocular Pressure Measurement Hour 0	OU		OU		OU	OU	OU	OU	OU

Visit	Screening		Baseline[b]	Day 1 Cycle 1 Administration	Cycle 1 Day 2 Safety Visit	Week 4	Week 8	Week 12	Week 16[c]
Visit Windows	Up to 10 days		Up to 3 days			± 4 days	± 4 days	± 4 days	± 4 days
Non-contact Exams (may perform in any order at any time before gonioscopy)									
Visual Field[g]		Washout[a] up to 56	OU						
Specular Microscopy[h]	OU								OU
Anterior Segment Imaging (non-contact)[i]			OU						
Biomicroscopy	OU		OU		OU	OU	OU	OU	OU
Posterior Segment Imaging[m]			OU						
Gonioscopy/Angle Assessment	OU[j]	Washout[a] up to 56 days				OU[j]	OU	OU[j]	OU
Pachymetry: (may be done any time after gonioscopy)	OU								OU
Anterior Segment Imaging (contact)[i]			OU						
Pupil Dilation (may perform exams in any order)	OU		OU						
Dilated Ophthalmoscopy	OU		OU						
Optic Disc Examination	OU		OU						
Determination of Eligibility	X		X						
Contact Interactive Web Response System[k]	X		X	X					
Treatment Administration[l]				SE					
Optional Whole Blood DNA Sample (one time collection)				X[n]					
Patient Mobility and Postural Behavior Questionnaire (one time completion)				X[o]					

Hour 0 = 09:00 ± 1 hour

a. Washout may begin after all screening procedures have been completed.
b. Baseline visit procedures can be performed over a 3-day period. Perform pupil dilation/diagnostic procedures after the completion of the IOP measurement or a different day. If, after initial washout, the investigator believes the IOP does not meet entry criteria due to inadequate washout and if time remains in the washout period, he/she may perform additional washout up to a total of 56 days.
c. Prior to Protocol Amendment 4, if the study eye meets retreatment criteria, study eye may receive up to two additional administrations of Bimatoprost SR beginning not less than 16 weeks after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period. Participants who meet retreatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye recommended between one and three weeks after Cycle 2 Administration or Cycle 3 Administration. Starting with Protocol Amendment 4, if study eye meets retreatment criteria, study eye may receive up to one additional administration of Bimatoprost SR beginning not less than 16 weeks after the Cycle 1 Bimatoprost SR administration and continuing through completion of the PRN treatment period. Table 1-5 Participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR Table 1-5. If the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, see Table 1-6.
d. In countries/institutions where required by local institution or health authority, a serum test may be done, with negative results for all tests confirmed prior to the time of Bimatoprost SR administration. Pregnancy testing at Baseline is required regardless.
e. Blood and urine samples are collected only at Screening unless a retest is necessary.
f. Manifest refraction will be used to provide a correction for best-corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.
g. For a given participant, the same test methodology must be used for all fields performed throughout the study.
h. For a given participant, the same specular microscope model and analysis methodology must be used throughout the study.
i. At selected sites/participants only, anterior segment imaging may be performed in both eyes of consenting participants using AbbVie approved non-contact or contact instruments. Sites using non-contact instruments should perform the assessment prior to gonioscopy with other non-contact exams, and sites using contact instruments should perform the assessment after gonioscopy. Assessment may be performed at any interim study visit at the discretion of the investigator.
j. At selected sites only, the examination will also include gonioscopic photographs in consenting participants.
k. Screening: participant #; Baseline: H0 IOP; Day 1 Cycle 1 Administration: Contact pretreatment for kit allocation (and posttreatment to confirm kit assignment, if applicable) (may be done at end of Baseline visit if needed).
l. A user experience questionnaire will be completed after each Bimatoprost SR administration. Video of the Bimatoprost SR administration procedure may be collected in consenting participants only.
m. At selected sites/participants only, posterior segment imaging (eg, posterior segment OCT) may be performed in both eyes of consenting participants using AbbVie approved instruments. For a given participant, the same instrument should be used throughout the study. Assessment may be performed at any interim study visit at the discretion of the investigator.
n. **US sites only**: Whole blood DNA sample is optional. This one-time sample may be collected at any post-Baseline study visit.
o. **US sites only**: Patient Mobility and Postural Behavior Questionnaire is a one-time questionnaire and can be completed at any post-Baseline study visit.

Table 1-2 Schedule of Visits and Procedures: Week 24 through Month 18

Visit	**Week 24[a]**	**Month 8[a]**	**Month 10[a]**	**Month 12[a]**	**Month 14[a]**	**Month 16[a]**	**Month 18[a]**
Visit Windows	± 4 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications/ Procedures	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X	X	X	X	X
Allergan Satisfaction with Treatment Experience Questionnaire: Implant Module		X		X		X	
Treatment Satisfaction Questionnaire for Medication		X					
Ocular Examinations in bold should be performed in the order shown							
Pre-Hour 0 Exam (perform before Hour 0 IOP):							
Macroscopic Conjunctival Hyperemia Assessment	OU	OU	OU	OU	OU	OU	OU
Best-Corrected Visual Acuity	OU	OU	OU	OU	OU	OU	OU
Intraocular Pressure Measurement Hour 0	OU	OU	OU	OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)							
Visual Field[b]	OU			OU			OU
Manifest Refraction[c]				OU			
Specular Microscopy[d]		OU		OU		OU	
Anterior Segment Imaging (non-contact)[e]	OU			OU			OU
Biomicroscopy	OU	OU	OU	OU	OU	OU	OU
Posterior Segment Imaging[g]	OU			OU			OU
Gonioscopy/Angle Assessment	OU[f]	OU	OU[f]	OU	OU[f]	OU	OU[f]
Pachymetry: (may be done any time after gonioscopy)		OU		OU		OU	
Anterior Segment Imaging (contact)[e]	OU			OU			OU
Pupil Dilation (may perform exams in any order)				OU			
Dilated Ophthalmoscopy				OU			
Optic Disc Examination				OU			

Visit	Week 24[a]	Month 8[a]	Month 10[a]	Month 12[a]	Month 14[a]	Month 16[a]	Month 18[a]
Visit Windows	± 4 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Optional Whole Blood DNA Sample (one time collection)	X[h]						
Patient Mobility and Postural Behavior Questionnaire (one time completion)	X[i]						

Hour 0 = 09:00 ± 1 hour

a. Prior to Protocol Amendment 4, if the study eye meets retreatment criteria, study eye may receive up to two additional administrations of Bimatoprost SR beginning not less than 16 weeks after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period. Participants who meet retreatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye recommended between one and three weeks after Cycle 2 or Cycle 3. Starting with Protocol Amendment 4, if study eye meets retreatment criteria, study eye may receive up to one additional administration of Bimatoprost SR beginning not less than 16 weeks after the Cycle 1 Bimatoprost SR administration and continuing through completion of the PRN treatment period. If the participant meets these requirements, see Table 1-5. Participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one and three weeks after Cycle 2 Administration. If the participant meets fellow eye treatment criteria during the Cycle 2 Administration schedule of visits, see Table 1-5. If the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, see Table 1-6.
b. For a given participant, the same test methodology must be used for all fields performed throughout the study.
c. Manifest refraction will be used to provide a correction for best-corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.
d. For a given participant, the same specular microscope model and analysis methodology must be used throughout the study.
e. At selected sites/participants only, anterior segment imaging may be performed in both eyes of consenting participants using AbbVie approved non-contact or contact instruments. Sites using non-contact instruments should perform the assessment prior to gonioscopy with other non-contact exams, and sites using contact instruments should perform the assessment after gonioscopy. Assessment may be performed at any interim study visit at the discretion of the investigator.
f. At selected sites only, the examination will also include gonioscopic photographs in consenting participants.
g. At selected sites/participants only, posterior segment imaging (eg, posterior segment OCT) may be performed in both eyes of consenting participants using AbbVie approved instruments. For a given participant, the same instrument should be used throughout the study. Assessment may be performed at any interim study visit at the discretion of the investigator.
h. **US sites only**: Whole blood DNA sample is optional. This one-time sample may be collected at any post-Baseline study visit.
i. **US sites only**: Patient Mobility and Postural Behavior Questionnaire is a one-time questionnaire and can be completed at any post-Baseline study visit.

Table 1-3 Schedule of Visits and Procedures: Month 20 through Month 30

Visit	**Month 20[a]**	**Month 22[a]**	**Month 24[a]**	**Month 26[a]**	**Month 28[a]**	**Month 30[a]**
Visit Windows	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days
Adverse Events	X	X	X	X	X	X
Concomitant Medications/ Procedures	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X	X	X	X
Allergan Satisfaction with Treatment Experience Questionnaire: Implant Module	X		X		X	
Ocular Examinations in bold should be performed in the order shown						
Pre-Hour 0 Exam (perform before Hour 0 IOP):						
Macroscopic Conjunctival Hyperemia Assessment	OU	OU	OU	OU	OU	OU
Best-Corrected Visual Acuity	OU	OU	OU	OU	OU	OU
Intraocular Pressure Measurement Hour 0	OU	OU	OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)						
Visual Field[b]			OU			OU
Manifest Refraction[c]			OU			
Specular Microscopy[d]	OU		OU		OU	
Anterior Segment Imaging (non-contact)[e]			OU			OU
Biomicroscopy	OU	OU	OU	OU	OU	OU
Posterior Segment Imaging[g]			OU			OU
Gonioscopy/Angle Assessment	OU	OU[f]	OU	OU[f]	OU	OU[f]
Pachymetry: (may be done any time after gonioscopy)	OU		OU		OU	
Anterior Segment Imaging (contact)[e]			OU			OU
Pupil Dilation (may perform exams in any order)			OU			
Dilated Ophthalmoscopy			OU			
Optic Disc Examination			OU			
Optional Whole Blood DNA Sample (one time collection)	X[h]					
Patient Mobility and Postural Behavior Questionnaire (one time completion)	X[i]					

Hour 0 = 09:00 ± 1 hour

a. Prior to Protocol Amendment 4, if the study eye meets retreatment criterion, study eye may receive up to two additional administrations of Bimatoprost SR beginning not less than 16 weeks after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period. Participants who meet retreatment criterion for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye recommended between one and three weeks after Cycle 2 Administration or Cycle 3 Administration. Starting with Protocol Amendment 4, if study eye meets retreatment criteria, study eye may receive up to one additional administration of Bimatoprost SR beginning not less than 16 weeks after the Cycle 1 Bimatoprost SR administration and continuing through completion of the PRN treatment period. If the participant meets these requirements, see Table 1-5. Participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one and three weeks after Cycle 2 Administration. If the participant meets fellow eye treatment criteria during the Cycle 2 Administration schedule of visits, see Table 1-5. If the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, see Table 1-6.
b. For a given participant, the same test methodology must be used for all fields performed throughout the study.
c. Manifest refraction will be used to provide a correction for best-corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.
d. For a given participant, the same specular microscope model and analysis methodology must be used throughout the study.
e. At selected sites/participants only, anterior segment imaging may be performed in both eyes of consenting participants using AbbVie approved non-contact or contact instruments. Sites using non-contact instruments should perform the assessment prior to gonioscopy with other non-contact exams, and sites using contact instruments should perform the assessment after gonioscopy. Assessment may be performed at any interim study visit at the discretion of the investigator.
f. At selected sites only, the examination will also include gonioscopic photographs in consenting participants.
g. At selected sites/participants only, posterior segment imaging (eg, posterior segment OCT) may be performed in both eyes of consenting participants using AbbVie approved instruments. For a given participant, the same instrument should be used throughout the study. Assessment may be performed at any interim study visit at the discretion of the investigator.
h. **US sites only**: Whole blood DNA sample is optional. This one-time sample may be collected at any post-Baseline study visit.
i. **US sites only**: Patient Mobility and Postural Behavior Questionnaire is a one-time questionnaire and can be completed at any post-Baseline study visit.

Table 1-4 Schedule of Visits and Procedures: Month 32 through Month 48

Visit	Month 32[a]	Month 34[a]	Month 36[a]	Month 38	Month 40	Month 42	Month 44	Month 46	Month 48/ Study Exit[g]
Visit Windows	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medications/ Procedures	X	X	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X	X	X	X	X	X	X
Pregnancy Test									X
Allergan Satisfaction with Treatment Experience Questionnaire: Implant Module	X		X		X		X		X
Treatment Satisfaction Questionnaire for Medication									X
Ocular Examinations in bold should be performed in the order shown									
Pre-Hour 0 Exam (perform before Hour 0 IOP):									
Macroscopic Conjunctival Hyperemia Assessment	OU	OU	OU	OU	OU	OU	OU	OU	OU
Best-Corrected Visual Acuity	OU	OU	OU	OU	OU	OU	OU	OU	OU
Intraocular Pressure Measurement Hour 0	OU	OU	OU	OU	OU	OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)									
Visual Field[b]			OU			OU			OU
Manifest Refraction[c]			OU						OU
Specular Microscopy[d]	OU		OU		OU		OU		OU
Anterior Segment Imaging (non-contact)[e]			OU			OU			OU
Biomicroscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU
Posterior Segment Imaging[h]			OU			OU			OU
Gonioscopy/Angle Assessment	OU	OU[f]	OU	OU[f]	OU	OU[f]	OU	OU[f]	OU[f]
Pachymetry: (may be done any time after gonioscopy)	OU		OU		OU		OU		OU
Anterior Segment Imaging (contact)[e]			OU			OU			OU

Visit	Month 32[a]	Month 34[a]	Month 36[a]	Month 38	Month 40	Month 42	Month 44	Month 46	Month 48/ Study Exit[g]
Visit Windows	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days
Pupil Dilation (may perform post-dilation eye exams in any order)			OU						OU
Dilated Ophthalmoscopy			OU						OU
Optic Disc Examination			OU						OU
Optional Whole Blood DNA Sample (one time collection)	X[i]								
Patient Mobility and Postural Behavior Questionnaire (one time completion)	X[j]								

Hour 0 = 09:00 ± 1 hour

a. Prior to Protocol Amendment 4, if the study eye meets retreatment criterion, study eye may receive up to two additional administrations of Bimatoprost SR beginning not less than 16 weeks after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period. Participants who meet retreatment criterion for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye recommended between one and three weeks after Cycle 2 or Cycle 3Administration. Starting with Protocol Amendment 4, if study eye meets retreatment criteria, study eye may receive up to one additional administration of Bimatoprost SR beginning not less than 16 weeks after the Cycle 1 Bimatoprost SR administration and continuing through completion of the PRN treatment period. If the participant meets these requirements, see Table 1-5. Participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one and three weeks after Cycle 2 Administration. If the participant meets fellow eye treatment criteria during the Cycle 2 Administration schedule of visits, see Table 1-5. If the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, see Table 1-6.
b. For a given participant, the same test methodology must be used for all fields performed throughout the study.
c. Manifest refraction will be used to provide a correction for best-corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.
d. For a given participant, the same specular microscope model and analysis methodology must be used throughout the study.
e. At selected sites/participants only, anterior segment imaging may be performed in both eyes of consenting participants using AbbVie approved non-contact or contact instruments. Sites using non-contact instruments should perform the assessment prior to gonioscopy with other non-contact exams, and sites using contact instruments should perform the assessment after gonioscopy. Assessment may be performed at any interim study visit at the discretion of the investigator.
f. At selected sites only, the examination will also include gonioscopic photographs in consenting participants.
g. Participants who early exit or discontinue prior to the Month 48/Study Exit visit should complete all procedures for the Month 48/Study Exit visit at the participant's last visit.
h. At selected sites/participants only, posterior segment imaging (eg, posterior segment OCT) may be performed in both eyes of consenting participants using AbbVie approved instruments. For a given participant, the same instrument should be used throughout the study. Assessment may be performed at any interim study visit at the discretion of the investigator.
i. **US sites only**: Whole blood DNA sample is optional. This one-time sample may be collected at any post-Baseline study visit.
j. **US sites only**: Patient Mobility and Postural Behavior Questionnaire is a one-time questionnaire and can be completed at any post-Baseline study visit.

Table 1-5 Schedule of Visits and Procedures: Retreatment Cycle 2 (or 3) Administration through Cycle 2 (or 3) Week 16 Visit

Visit	Cycle 2 (or 3)* Administration	Cycle 2 (or 3)* Day 2 Safety Visit	Cycle 2 (or 3) Day 7 FE Administration[a]	Cycle 2 (or 3) Day 8 FE Safety Visit[a]	Cycle 2 (or 3) Week 4	Cycle 2 (or 3) Week 8	Cycle 2 (or 3) Week 12	Cycle 2 (or 3) Week 16[b]
Visit Windows			+ 14 days	+14 days	±4 days	±4 days	±4 days	±4 days
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications/ Procedures	X	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X	X	X	X	X	X
Allergan Satisfaction with Treatment Experience Questionnaire: Implant Module		X		X				
Treatment Satisfaction Questionnaire for Medication		X		X				
Ocular Examinations in bold should be performed in the order shown								
Pre-Hour 0 Exam (perform before Hour 0 IOP):								
Macroscopic Conjunctival Hyperemia Assessment		OU		OU	OU	OU	OU	OU
Best-Corrected Visual Acuity		OU		OU	OU	OU	OU	OU
Intraocular Pressure Measurement Hour 0		OU		OU	OU	OU	OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)								
Specular Microscopy[c]	OU[d]							OU
Biomicroscopy		OU		OU	OU	OU	OU	OU
Gonioscopy/Angle Assessment					OU[e]	OU	OU[e]	OU
Pachymetry: (may be done any time after gonioscopy)								OU

Visit	Cycle 2 (or 3)* Administration	Cycle 2 (or 3)* Day 2 Safety Visit	Cycle 2 (or 3) Day 7 FE Administration[a]	Cycle 2 (or 3) Day 8 FE Safety Visit[a]	Cycle 2 (or 3) Week 4	Cycle 2 (or 3) Week 8	Cycle 2 (or 3) Week 12	Cycle 2 (or 3) Week 16[b]
Visit Windows			+ 14 days	+14 days	±4 days	±4 days	±4 days	±4 days
Contact Interactive Web Response System[f]	X		X					
Treatment Administration[g]	SE		FE					
Optional Whole Blood DNA Sample (one time collection)	X[h]							
Patient Mobility and Postural Behavior Questionnaire (one time completion)	X[i]							

Hour 0 = 09:00 ± 1 hour

* Starting with Protocol Amendment 4, PRN Cycle 3 is no longer applicable for any eligible eye.

a. Prior to Protocol Amendment 4, participants who meet retreatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye recommended between one and three weeks after Cycle 2 or Cycle 3 Administration. Starting with Protocol Amendment 4, participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one week and three weeks after Cycle 2 Administration. If the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, refer to Table 1-6.

b. Participants who receive retreatment should follow this schedule through 16 weeks (± 4 days) after Administration. After that, they should return to the schedule of visits in Table 1-2, Table 1-3, or Table 1-4 as appropriate. Prior to Protocol Amendment 4, Participants who received retreatment should follow this schedule through 16 weeks (± 4 days) after Cycle 2 or Cycle 3 Administration. Starting with Protocol Amendment 4, Participants who receive retreatment should follow this schedule through 16 weeks (± 4 days) after Cycle 2 Administration.

c. For a given participant, the same specular microscope model and analysis methodology must be used throughout the study.

d. Perform specular microscopy prior to Bimatoprost SR administration. Specular microscopy must be performed within the month prior to Bimatoprost SR administration and must be reviewed by the investigator for clearance prior to administration.

e. At selected sites only, the examination will also include gonioscopic photographs in consenting participants.

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

g. A user experience questionnaire will be completed after each Bimatoprost SR administration. Video of the Bimatoprost SR administration procedure may be collected in consenting participants only.

h. **US sites only**: Whole blood DNA sample is optional. This one-time sample may be collected at any post-Baseline study visit.

i. **US sites only**: Patient Mobility and Postural Behavior Questionnaire is a one-time questionnaire and can be completed at any post-Baseline study visit.

Table 1-6 Schedule of Visits and Procedures: Independent Fellow Eye Administration through Week 4 Visit

Visit	Fellow Eye Administration	Fellow Eye Day 2 Safety Visit	Week 4[a]
Visit Windows			± 4 days
Adverse Events	X	X	X
Concomitant Medications/ Procedures	X	X	X
Vital Signs (at rest ≥ 5 minutes)	X	X	X
Allergan Satisfaction with Treatment Experience Questionnaire: Implant Module		X	
Treatment Satisfaction Questionnaire for Medication		X	
Ocular Examinations in bold should be performed in the order shown			
Pre-Hour 0 Exam (perform before Hour 0 IOP):			
Macroscopic Conjunctival Hyperemia Assessment		OU	OU
Best-Corrected Visual Acuity		OU	OU
Intraocular Pressure Measurement Hour 0		OU	OU
Non-contact Exams (may perform in any order at any time before gonioscopy)			
Specular Microscopy[b]	OU[c]		
Biomicroscopy		OU	OU
Gonioscopy/Angle Assessment			OU[d]
Contact Interactive Web Response System[e]	X		
Treatment Administration[f]	FE		
Optional Whole Blood DNA Sample (one time collection)	X[g]		
Patient Mobility and Postural Behavior Questionnaire (one time completion)	X[h]		

Hour 0 = 09:00 ± 1 hour

a. Prior to Protocol Amendment 4, From Week 16 through completion of the PRN Treatment period, if the fellow eye meets treatment criteria outside of the suggested Cycle 2 or Cycle 3 Administration schedule of visits in the study eye, the fellow eye may receive a single administration, return for a Day 2 Safety Visit, Week 4 follow up visit, and then return to the schedule of visits. Starting with Protocol Amendment 4, from Week 16 through completion of the PRN Treatment period, if the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, the fellow eye may receive a single administration, return for a Day 2 Safety Visit, Week 4 follow up visit, and then return to the schedule of visits in Table 1-2, Table 1-3, or Table 1-4 as appropriate.
b. For a given participant, the same specular microscope model and analysis methodology must be used throughout the study.
c. Specular microscopy must be performed within the month prior to Bimatoprost SR administration and be reviewed by the investigator for clearance prior to administration.
d. At selected sites only, the examination will also include gonioscopic photographs in consenting participants.
e. Contact pretreatment for kit allocation (and posttreatment to confirm kit assignment, if applicable).
f. A user experience questionnaire will be completed after each Bimatoprost SR administration. Video of the Bimatoprost SR administration procedure may be collected in consenting participants only.
g. **US sites only**: Whole blood DNA sample is optional. This one-time sample may be collected at any post-Baseline study visit.
h. **US sites only**: Patient Mobility and Postural Behavior Questionnaire is a one-time questionnaire and can be completed at any post-Baseline study visit.

2. Introduction

In an effort to develop ocular antihypertensive therapies that do not require patient self-administration, an SR formulation of bimatoprost was developed at Allergan, Inc. (now an AbbVie company) Bimatoprost SR refers to the biodegradable, sustained-release, preservative-free bimatoprost implant which is preloaded in an applicator for administration; together they comprise the Bimatoprost SR product. The Bimatoprost SR implant is injected into the anterior chamber (AC) via the corneal limbus using the prefilled applicator. The biodegradable polymer matrix gradually degrades to carbon dioxide and water so that there is no need to remove the Bimatoprost SR implant once the drug has been released. The Bimatoprost SR implant used in Amendment 2 of this study contains a total preservative-free bimatoprost load of 10 µg. Intracameral administration of the Bimatoprost SR implant is expected to reduce the total daily drug exposure to the eye by approximately 42-fold compared with topical LUMIGAN® 0.03% application over 4 to 6 months, as well as possibly reduce the adverse effects observed with topical glaucoma medications. Based on in vitro data, the implant was expected to have a drug release duration of approximately 3 to 4 months. In a completed Phase 1/2 study (192024-041D), based on investigator reported assessments, 50% of the visible Generation 2 implants (currently used in ongoing Phase 3 studies) had decreased to 0 to 25% of the original size by Month 12. Although the biodegradation process of the Bimatoprost SR implant exceeds the drug release duration, experience from preclinical studies, the 192024-041D study, and approved intravitreal implants composed of similar biodegradable polymers provide support for the use of the implant in this Phase 3b clinical trial with potential repeated administration.

2.1. Study Rationale

Results of the 192024-041D Phase 1/2 completed study indicated that Bimatoprost SR provides prostaglandin analog-like IOP-lowering efficacy. Additionally, the safety profile of Bimatoprost SR at dose strengths of 20 µg (2 × 10 µg) or less in the Phase 1/2 study was acceptable and supports additional clinical studies in humans. Global Phase 3 studies with repeat administrations of Bimatoprost SR 10 and 15 µg dose strengths at 16-week intervals are completed or ongoing. Following implementation of Amendment 1, Study 1698-301-007 is a multicenter, open label Phase 3b study to evaluate the duration of IOP-lowering effect and safety of up to two PRN administrations (Amendment 4) of 10 µg 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). With implementation of Amendment 1, participants enrolled to receive 15 µg Bimatoprost SR under the original protocol will no longer receive any additional Bimatoprost SR administrations and will be followed for at least 12 months after the last administration of Bimatoprost SR in either eye. With implementation of Amendment 4, PRN Cycle 3 is no longer applicable for any eligible eye.

The purpose of this study is to obtain data on as needed administration of Bimatoprost SR.

2.2. Background

2.2.1. Glaucoma and Treatment

Glaucoma is a family of diseases commonly characterized by progressive optic neuropathy with associated visual field defects and is the leading cause of irreversible blindness in the world. Glaucoma is classified by Becker-Shaffer into 3 broad types: developmental, angle-closure, and open-angle glaucoma (Stamper 2009). Open-angle glaucoma is further categorized into primary OAG (POAG, sometimes also referred to as chronic OAG) and secondary OAG (which includes pigmentary and pseudoexfoliation glaucoma), the former being the predominant form of OAG. POAG is characterized as a multifactorial optic neuropathy with a characteristic acquired atrophy of the optic nerve and loss of ganglion cells and their axons, developing in the presence of open AC angles, and manifesting characteristic visual field abnormalities (American Academy of Ophthalmology 2010a). Globally, over 60 million people are estimated to be affected by glaucoma (the majority of whom have OAG) and these numbers are expected to increase over time (Quigley 2006, Varma 2011, Cook 2012). Approximately 10% of eyes with elevated IOP will progress to OAG over the course of a decade (Quigley 1994).

Although many risk factors have been associated with OAG, elevated IOP remains the most prominent factor and the only factor existing that ophthalmic intervention can reliably affect (Stamper 2009). A number of controlled trials have demonstrated that lowering IOP will slow or delay the appearance or progression of glaucomatous damage. Large, randomized clinical trials such as the Ocular Hypertension Treatment Study (Kass 2002) and the Early Manifest Glaucoma Trial (Heijl 2002) addressed the value of early detection and lowering of elevated IOP in ocular hypertension or POAG. The effects and parameters of various interventions in eyes with established glaucomatous damage were addressed by the Collaborative Initial Glaucoma Treatment Study (Lichter 2001) and the Advanced Glaucoma Intervention Study (AGIS 2000).

2.2.2. Bimatoprost (LUMIGAN)

Bimatoprost is a member of a series of unique prostanoid compounds that are potent and efficacious ocular antihypertensive agents (Woodward 1994, 2001, and 2004). Bimatoprost appears to mimic the activity of biologically active prostamides (Study BIO 99 308, Matias 2004). Chemically, prostamides differ from prostaglandin analogs by being neutral because they lack carboxylic acids (Krauss 2004). Prostamides can be biosynthetically derived from anandamide, an endogenous membrane lipid (Kozak 2002, Weber 2004, Woodward 2001, Yu 1997). The prostamide pathway leads to the biosynthesis of novel lipid amides that lower IOP.

The IOP-lowering efficacy of LUMIGAN (bimatoprost ophthalmic solution) 0.03% is well established. In Phase 3 studies in patients with POAG or OHT, LUMIGAN administered once daily as monotherapy was superior to timolol at all timepoints (Higginbotham 2002). This was further substantiated in the extension studies which followed patients in a masked manner for up to 4 years (Cohen 2004, Williams 2008, Study 192024-014). In clinical studies of patients with OAG or OHT with a mean baseline IOP of 26 mm Hg, the IOP-lowering effect of LUMIGAN

administered once daily in the evening was 7 to 8 mm Hg (Cohen 2004, LUMIGAN Package Insert 2012, Williams 2008). LUMIGAN was approved by the US FDA in 2001. Worldwide, LUMIGAN 0.03% is currently licensed and marketed in more than 80 countries and LUMIGAN 0.01% is licensed and marketed in more than 40 countries. Preservative-free bimatoprost ophthalmic solution 0.03% has been approved since November 2012 for lowering IOP and is currently marketed in 10 countries.

2.2.3. Other Biodegradable Ocular Implants

A number of SR drug delivery implants using the AbbVie polylactic acid (PLA) and/or polylactic co-glycolic acid (PLGA) biodegradable platform preceded the development of the Bimatoprost SR implant. The extensive clinical experience with previous intraocular implants demonstrates the safety and tolerability of an intraocular biodegradable implant administered into the eye via an applicator system. For example, late phase clinical trials of SR implants have been completed for the OZURDEX® dexamethasone intravitreal implant using the NOVADUR® drug delivery system for intraocular injections. Because Bimatoprost SR is similar to OZURDEX in a number of aspects and uses the NOVADUR drug delivery system for intraocular injections, these data may be supportive of the safety and tolerability of Bimatoprost SR in humans.

2.2.4. Clinical Studies with Bimatoprost SR

Study 192024-041D was a Phase 1/2 paired-eye comparison study evaluating the safety and efficacy of 4 dose strengths of Bimatoprost SR (6, 10, 15, or 20 µg [2 ×10 µg implants]), as single or repeat administrations in 1 eye (study eye), versus the use of topical LUMIGAN 0.03% once daily in the contralateral eye (nonstudy eye). The objective of this study was to evaluate the safety and IOP-lowering efficacy of Bimatoprost SR in participants with OAG.

A total of 109 participants received at least a single administration of Bimatoprost SR, and 24 participants received a repeat administration of Bimatoprost SR. A trend in dose response was observed across the 4 dose strengths that were tested. Data in this study suggest that the implant may provide topical prostaglandin analog-like efficacy up to 3 to 4 months post implantation in the majority of participants. Data following the second administration in the retreated participants showed similar IOP-lowering efficacy to that observed following the first administration of Bimatoprost SR.

Among all Generation 2 dose strengths, most participants (> 66%) were still maintained on monotherapy with the initial Bimatoprost SR implant by Month 6. Additionally, at least 33% of participants had not received rescue topical IOP-lowering medication or a second Bimatoprost SR administration by Month 12. At Month 24, at least 23% of participants had not received rescue topical IOP-lowering medication or a second administration of Bimatoprost SR.

Bimatoprost SR showed an acceptable safety profile with single and repeat administrations in Study 192024-041D. Most adverse events were ocular, mild or moderate in severity, occurred within the first 2 days after Bimatoprost SR administration, and were considered related to the study drug administration procedure. There were no reports of serious study drug-related adverse

events, and no new safety concerns were observed after the second treatment. Please refer to the investigator's brochure for details on reported safety findings.

The implant has been investigated in Phase 3 studies to evaluate efficacy and safety following a fixed administration schedule of every 16 weeks for up to 3 administrations. Two identical global Phase 3 studies [completed Study 192024-091(NCT02247804) and Study192024-092 (NCT02250651)] were initiated in late 2014 to evaluate efficacy and safety following a fixed administration schedule of every 16 weeks for up to 3 administrations. These completed studies assessed the safety and efficacy of Bimatoprost SR in multicenter, randomized, masked, parallel-group comparison studies of 2 dose strengths of Bimatoprost SR (10 and 15 µg) to an active control (timolol maleate 0.5%). Two additional global Phase 3 studies (completed Studies 192024-093 [NCT02507687] and 192024-095 [NCT02636946]) were initiated in late 2015. These studies assessed the safety and efficacy of Bimatoprost SR in multicenter, randomized, masked, paired-eye comparison studies of up to 2 dose strengths of Bimatoprost SR (10 µg or 15 µg) to an active control (360° selective laser trabeculoplasty). A long-term safety and extension study (Study 1698-302-007 [NCT03891446], initiated in early 2019) is already in progress. This study will enroll participants from all 4 Phase 3 studies who were treated with Bimatoprost SR. Eligible patients from Study 192024-093 or may receive "as needed" administration of Bimatoprost SR if they qualify. A Phase 3b study (Study 1698-304-007 [NCT04285580], initiated in 2020) is completed. This multicenter, open-label study evaluated the 24-hour IOP lowering effect of Bimatoprost SR 10 µg.

2.3. Benefit/Risk Assessment

Currently available approaches to lowering IOP include topical pharmacological therapy, laser trabeculoplasty (LT), incisional surgery, and cyclodestructive procedures. Each type of approach has its own risk-benefit ratio. Because the risk with topical drugs appears to be lower than that of surgical procedures, both historical and contemporary practice has been to attempt pharmacological treatment before resorting to other more invasive alternatives.

Although a variety of effective topical ocular antihypertensive medications (including bimatoprost) are available, patient nonadherence to topical therapy is one of the major challenges to preventing vision loss due to glaucoma, as consistent IOP reduction is associated with reduced risks of the development and progression of optic nerve damage (Friedman 2009, Tsai 2009). One literature review found that up to 80% of patients deviated from their prescribed medication regimen (Olthoff 2005). In addition, most patients with OAG or OHT are elderly, and many have inherent difficulties applying daily antihypertensive eye drops due to physical and/or cognitive disabilities such as arthritis and poor memory (European Glaucoma Society Guidelines 2014, Tsai 2009). Guidelines have been developed and provided to clinicians for assisting patients with being adherent (Budenz 2009). In addition, surgical interventions, both laser based (eg, LT) and incisional, are recommended as treatment options for patients with OAG and OHT who have challenges with topical medication adherence or tolerance (European Glaucoma Society Guidelines 2014). LT is a safe and noninvasive procedure; however, repeatability of LT is controversial (Realini 2008). Patients will often require adjunctive therapy after LT and may

eventually require incisional surgery to control their IOP (Francis 2005, Koucheki 2012). Incisional surgery presents the risk of significant sight-threatening complications, such as the globe perforation, suprachoroidal hemorrhage, hypotony maculopathy, corneal decompensation, and cataract formation or progression that may occur with filtering surgery (Mosaed 2009). AbbVie has developed a sustained-release bimatoprost implant as an additional therapeutic option for lowering intraocular pressure in patients with OAG and OHT who are not adequately managed by topical medication for reasons other than the efficacy of the medication.

For patients with OAG and/or OHT who are not adequately controlled by topical medications due to reasons other than medication efficacy, Bimatoprost SR offers ocular antihypertensive therapy that is not dependent on patient self-administration, potentially positively impacting both treatment adherence and patient quality of life. Based on data from a completed Phase 1/2 study and a completed masked Phase 3 study, and the safety monitoring of ongoing masked Phase 3 studies, continued development and understanding of the duration of action of Bimatoprost SR is warranted.

Overall, the benefit: risk profile of Bimatoprost SR in patients that received up to 2 administrations remains favorable in this ongoing study. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Bimatoprost SR may be found in the investigator's brochure.

3. Objectives and Endpoints

Objectives	Endpoints
• 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

4. Study Design

4.1. Overall Design

This is a multicenter, open-label Phase 3b study 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). A study flow chart is presented in Section 1.2 (Schema). Enrollment of up to approximately 490 participants in total is planned, with 62 already enrolled in the 15 µg group under the original protocol and up to approximately 425 in total to be enrolled in the 10 µg group. Participants who prematurely discontinue from the study will not be replaced.

Starting with Protocol Amendment 4, in the study eye, participants will receive a 10 µg Bimatoprost SR implant on Day 1 Cycle 1 Administration. If retreatment criteria are met, up to one additional Bimatoprost SR administrations (Cycle 2 Administration) may be performed between 16 weeks after the Cycle 1 Bimatoprost SR administration through completion of the PRN treatment period (up to and including the Month 36 visit from Day 1 Cycle 1 administration) (Table 4-1). In the fellow eye, participants will receive standard of care treatment for the duration of the study unless the fellow eye meets the treatment criteria for Fellow Eye Administration (Sections 5.1.2 and 5.2.2). From Week 16 through completion of the PRN treatment period, participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one week and three weeks after Cycle 2 Administration (Table 4-1). However, through the PRN treatment period, if the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, the fellow eye may receive a single administration of Bimatoprost SR, return for a Day 2 Safety Visit, a Week 4 follow up visit, and then return to the study eye schedule of visits as appropriate. Bimatoprost SR administration in the fellow eye must be separated by at least one week from administration in the study eye. Upon the decision to administer Bimatoprost SR in the fellow eye, standard of care treatment will be stopped at least one day prior to Fellow Eye Administration.

Prior to Protocol Amendment 4, if the study eye meets retreatment criteria, study eye may receive up to two additional administrations (Cycle 2 Administration and Cycle 3 Administration) of 10 µg Bimatoprost SR beginning not less than 16 weeks after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period (Table 4-1). In the fellow eye, participants may receive standard of care treatment for the duration of the study unless the fellow eye meets the treatment criteria for Fellow Eye Administration (Sections 5.1.2 and 5.2.2). From Week 16 through completion of the PRN treatment period, participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one week and three weeks after Cycle 2 Administration or Cycle 3 Administration.

With implementation of Amendment 1, participants enrolled to receive 15 µg Bimatoprost SR under the original protocol will no longer receive any additional administrations of Bimatoprost SR and will be followed for safety purposes for at least 12 months after the last administration of

Bimatoprost SR in either eye. Although these participants will no longer receive additional retreatment, rescue IOP-lowering medication should only be initiated in the event that the study eye IOP does not meet or does not maintain IOP-lowering expectations (see Section 6.4.2 for details).

Table 4-1 Treatment Schedule by Eye

Treatment Visits	Study Eye	Fellow Eye
Bimatoprost SR Day 1 Cycle 1 Administration	Bimatoprost SR 10 µg	Standard of Care or Bimatoprost SR 10 µg[a]
Bimatoprost SR Cycle 2 Administration: Week 16 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.

Note: Prior to Protocol Amendment 4, if the study eye meets retreatment criteria, study eye may receive up to two additional administrations of Bimatoprost SR beginning not less than 16 weeks after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period. Participants who meet retreatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye recommended between one and three weeks after Cycle 2 or Cycle Administration. Starting with Protocol Amendment 4, if study eye meets retreatment criteria, study eye may receive up to one additional administration of Bimatoprost SR beginning not less than 16 weeks after the Cycle 1 Bimatoprost SR administration and continuing through completion of the PRN treatment period. Participants who meet treatment criteria for the fellow eye may receive a single administration of Bimatoprost SR in the fellow eye, recommended between one and three weeks after Cycle 2 Administration.

In order to provide adequate time to achieve a sufficient number of participants with multiple administrations of Bimatoprost SR, a minimum 18-month and up to 36-months of PRN treatment period will be implemented in Amendment 2. For participants enrolled earlier in the study, the PRN treatment period may be up to 36 months depending on when the last patient reaches the end of their PRN treatment period.

The duration of the study for each participant is at least 32 months, consisting of a screening period of up to 10 days before washout; a 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 patient 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 administration.

4.1.1. Clinical Hypotheses

- Bimatoprost SR will be effective in lowering IOP for greater than 16 weeks after single and repeated PRN administration 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).
- Bimatoprost SR will have an acceptable safety profile after single and repeated PRN administration 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).

4.2. Scientific Rationale for Study Design

This Phase 3b study is designed to mimic clinical practice and collect information on the duration of effect of PRN administration of Bimatoprost SR. As the retreatment rate will vary in a real-world setting, a flexible duration for the PRN treatment period and increased sample size will be implemented in Amendment 2. These changes will provide the adequate time and sample size needed to achieve a sufficient number of participants with multiple administrations of Bimatoprost SR. Because OAG is a bilateral disease, this study is also investigating the safety of the Bimatoprost SR implant when additionally administered to the fellow eye.

All enrolled participants will have a minimum of 18-month PRN treatment period and all patients will have at least 12 months follow up after the last administration. Therefore, the duration of the study for each participant is at least 32 months, consisting of a screening period of up to 10 days before washout; a washout period of up to 56 days before the initial Bimatoprost SR administration, and a minimum 18-month PRN treatment period. Data available from the Phase 1/2 Study 192024-041D suggest that the IOP-lowering effect provided by the Generation 2 Bimatoprost SR implant (currently used in ongoing Phase 3 studies) is closely aligned with that of topical LUMIGAN administration up to Week 12/Week 16. Prior to Protocol Amendment 4,

the study duration allowed for up to 3 Bimatoprost SR PRN administrations in the study eye, at intervals of a minimum of 16 weeks after the previous Bimatoprost SR administration and no more than 2 in a 12-month period. Starting with Protocol Amendment 4, the study duration allows for up to 2 Bimatoprost SR PRN administrations in the study eye, at an interval of a minimum of 16 weeks after the first Bimatoprost SR administration.

4.3. Justification for Dose Strengths

Data available from the Phase 1/2 Study 192024-041D demonstrated that 10 µg and 15 µg dose strengths have an acceptable safety profile.

Under the original protocol, the 10 µg and 15 µg dose strengths of Bimatoprost SR were being evaluated in the Phase 3 studies. Therefore, the same dose strengths were selected for this Phase 3b study to provide additional information on the duration of effect.

After a thorough review of the long-term Bimatoprost SR safety data from the recently completed and ongoing studies, AbbVie has discontinued the administration of the Bimatoprost SR 15 µg dose strength to patients. The discontinuation was based on the conclusion that corneal adverse events associated with repeated administrations of the 15 µg dose strength are no longer supported by a favorable benefit: risk consideration. The Bimatoprost SR 10 µg dose strength continues to be supported by a favorable benefit: risk for further development.

4.4. Start of Study Definition

The start-of-study is defined as the date of the first site activated.

4.5. End of Study Definition

The end-of-study is defined as the date of end-of-study participation by the last subject in the last country where the study was conducted. 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. With implementation of Amendment 1, participants enrolled to 15 µg Bimatoprost SR under the original protocol will be followed for safety purposes for at least 12 months after the last administration of Bimatoprost in either eye. When participants early exit or discontinue prior to the Month 48/Study Exit visit, the site should complete all procedures for the Month 48/Study Exit visit at the participant's last visit. At the Month 48/Study Exit visit, if the investigator determines any safety concerns warrant participant follow up, the participant may be followed post exit until safety concerns are resolved based on the investigator's discretion.

5. Study Population

The study population consists of participants with OAG or OHT and an open iridocorneal angle inferiorly by clinical gonioscopy in the study eye, where the study eye requires IOP-lowering treatment but is not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence).

The eye that meets the entry criteria at study entry (Sections 5.1.1 and 5.2.1) will be selected as the study eye. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 (9:00 AM ± 1 hour) will be selected as the study eye. If both eyes have the same IOP, then the right eye will be designated as the study eye. The eye that is not selected as the study eye will be designated as the fellow eye.

Note: participants do not need to meet Fellow Eye Administration criteria to qualify for study entry. Fellow Eye Administration criteria are only for fellow eyes that are being considered for Bimatoprost SR administration.

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria at Study Entry

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be at least 18 years of age at the time of signing the informed consent
2.	**Sex**
2.01	Male or female
3.	**Informed Consent**
3.01	Written informed consent and authorization for use and release of personal health information are obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent [EU sites]). Participants must not be incarcerated and must be freely willing and able to provide informed consent (eg, adults under legal protection measure [eg, under guardianship/curatorship] or unable to express their consent and select adults under psychiatric care are not eligible). Investigator's discretion should be applied.
4.	**Contraceptives**

4.01	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow up period
4.02	A female participant is eligible to participate if she is not pregnant (ie, has a negative urine pregnancy result at Baseline; see Appendix 7), not breastfeeding, and at least one of the following conditions applies: a. Not a WOCBP as defined in Appendix 7 OR b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 7 during the study period
5.	**Other General Criteria**
5.01	Participant is willing to withhold his/her IOP treatments according to the study requirements, and in the opinion of the investigator, can do so without significant risk Note: If participants cannot discontinue their currently prescribed therapy for up to 8 weeks to meet the Washout period for study entry, the investigator may switch the participant's medication to one that requires a shorter washout interval during the washout of the original medication
5.02	Participant has the ability to understand and willingness to follow study instructions and is likely to complete all required visits and procedures
5.03	In the investigator's opinion, participant's IOP is not adequately managed with topical medication for reasons other than medication efficacy (eg, due to intolerance or nonadherence)
6.	**Ocular Inclusion Criteria**
6.01	Diagnosis of either OAG (ie, primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in the **study eye**, requiring IOP-lowering treatment
6.02	In the investigator's opinion, the **study eye** can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy if medication was taken as directed

6.03	The iridocorneal angle in the **study eye** must be, in the opinion of the investigator, able to safely receive at least 1 Bimatoprost SR implant using the following criteria: a. Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle b. Peripheral anterior chamber depth by Van Herick examination ≥ ½ corneal thickness
6.04	At the Baseline visit, participant has been appropriately washed out of all IOP-lowering medications
6.05	At the Baseline visit (9:00 AM ± 1 hour), IOP of ≥ 22 and ≤ 34 mm Hg in the **study eye**
6.06	Central corneal endothelial cell density by specular microscopy deemed acceptable, in the opinion of the investigator (at Screening, a minimum endothelial cell density of 2000 cells/mm^2 in the **study eye** by automated analysis)
6.07	At the Baseline visit: BCVA (Snellen equivalent, by manifest refraction) of 20/50 or better in the study eye and 20/100 or better in the fellow eye

5.1.2. Inclusion Criteria for Fellow Eye Administration

Note: participants do not need to meet Fellow Eye Administration criteria to qualify for study entry. Fellow Eye Administration criteria are only for fellow eyes that are being considered for Bimatoprost SR administration.

Bimatoprost SR administration in the fellow eye must occur within one month of Fellow Eye Administration Inclusion/Exclusion Criteria assessment. Participants are eligible to receive study treatment in the fellow eye if all of the following inclusion criteria apply:

1.	**Ocular Inclusion Criteria**
1.01	Diagnosis of either OAG (ie, primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in the **fellow eye**, requiring IOP-lowering treatment
1.02	In the investigator's opinion, the **fellow eye** can be treated adequately with topical prostamide, prostaglandin, or prostaglandin analog (eg, LUMIGAN, Xalatan, Travatan) eye drops as the sole therapy if medication was taken as directed

1.03	The iridocorneal angle in the **fellow eye** must be, in the opinion of the investigator, able to safely receive at least 1 Bimatoprost SR implant using the following criteria: a. Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle b. Peripheral anterior chamber depth by Van Herick examination ≥ ½ corneal thickness
1.04	Central corneal endothelial cell density by specular microscopy deemed acceptable, in the opinion of the investigator (performed and reviewed for clearance by the investigator within the month prior to Bimatoprost SR administration, a minimum endothelial cell density of 2000 cells/mm^2 in the **fellow eye** by automated analysis)
1.05	BCVA (Snellen equivalent, by manifest refraction) of 20/50 or better in the fellow eye performed at the previous study visit within one month prior to Bimatoprost SR administration

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria at Study Entry

Participants are excluded from the study if any of the following criteria apply:

1.	**General Exclusion Criteria**
1.01	Uncontrolled systemic disease
1.02	Females who are pregnant, nursing, or planning a pregnancy during the study OR who are WOCBP and will not follow contraceptive guidance (see Appendix 7)
1.03	Known allergy or sensitivity to any study medication or its components, any component of the delivery vehicle, procedure-related materials, or diagnostic agents used during the study (eg, topical anesthetic, dilating drops, fluorescein, povidone-iodine)

1.04	Participants who have a condition or are in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study Note: the investigator should consider a participant's overall health condition, including COVID-19 infection. This should include assessing if the patient is suspected of; quarantined for; or diagnosed with active COVID-19 infection, and whether or not the participant has any symptoms
1.05	Concurrent or anticipated enrollment in an investigational drug or device study or participation in such a study within 2 months prior to the Baseline visit through the final study visit
1.06	Previous use of commercially available Bimatoprost SR in the study eye; concurrent enrollment in another AbbVie Bimatoprost SR study; or previous enrollment in which a Bimatoprost SR implant was received in the study eye Note: Participants with an eye that has not been previously treated with Bimatoprost SR or participants previously enrolled in Bimatoprost SR studies 192024-091/-092, and -041D who have an eye that was not treated with Bimatoprost SR in that study may be enrolled, provided that the eye that did not receive Bimatoprost SR meets entry criteria for this study.
1.07	Known history of bleeding disorder or prolonged bleeding after surgery (in the opinion of the investigator) Note: Participants receiving pharmacologic blood thinners (eg, aspirin, Coumadin) may be enrolled at the investigator's discretion
2.	**Ocular Exclusion Criteria**
2.01	History of previous laser trabeculoplasty in the **study eye**
2.02	History or evidence of clinically relevant, substantial ocular trauma (eg, a traumatic cataract, traumatic angle recession, etc.) in the **study eye**

2.03	The following surgical history in the **study eye**: a. History or evidence of complicated cataract/lens surgery: eg, surgery resulting in complicated lens placement (such as anterior chamber intraocular lens implant [IOL], sulcus IOL, aphakia, etc.) or intraoperative complications (such as a posterior capsular tear [with or without vitreous loss], substantial iris trauma, etc.) Note: history of uncomplicated cataract surgery is not an exclusion b. History of phakic IOL insertion for refractive error correction
2.04	Intraocular surgery (including cataract surgery) in the **study eye** within the 6 months prior to treatment administration (Day 1 Cycle 1 Administration)
2.05	Any history of corneal graft, including partial grafts (eg, Descemet's Stripping Endothelial Keratoplasty [DSEK], Descemet's Membrane Endothelial Keratoplasty [DMEK]); or incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions in the **study eye**
2.06	Corneal or other ocular abnormalities that would preclude accurate readings with an applanation tonometer, specular microscope, and/or a contact pachymeter, or could confound study results in **either eye**, eg, moderate to severe corneal dystrophy, including Anterior Basement Membrane Disease (ABMD; ie, Map-Dot-Fingerprint) and guttata. Mild ABMD or mild guttata are not exclusionary by clinical examination if, in the opinion of the investigator, the condition is stable and not likely to cause corneal changes during the course of the study
2.07	Active or recurrent ocular disease in the **study eye** (eg, uveitis, ocular infection, chronic moderate to severe blepharitis or severe dry eye, ocular seasonal allergies) or sight threatening diseases (eg, neovascular age-related macular degeneration [AMD], diabetic macular edema) that, in the opinion of the investigator, would put the participant at a significant risk or would interfere with the interpretation of the study data Note: Participants with slowly progressive eye diseases (ie, mild cataracts, non-neovascular AMD) can be enrolled at the discretion of the investigator. If a participant has a potentially exclusionary condition or disease in one eye that tends to be bilateral or is likely to affect both eyes, the investigator should consider excluding that participant

2.08	Any history of external ocular or intraocular malignancy, and/or any history of benign ocular neoplasia in the **study eye** that in the investigator's opinion resulted in clinically significant ocular morbidity
2.09	History of herpetic ocular diseases in the **study eye** (including herpes simplex virus and varicella zoster virus)
2.10	Active ocular surface findings other than bulbar conjunctival hyperemia, on either macroscopic or slit-lamp examination, > +1 (mild) at Baseline in the **study eye**
2.11	The anticipated wearing of contact lenses in the **study eye** during the study that deviates from the following (contact lens wear is allowed during the study, but is to be temporarily discontinued before study visits, and before and after an Administration Day according to the following): a. Use of soft lenses should be discontinued at least 3 days prior to Baseline, and use of rigid gas permeable or hard contact lenses should be discontinued at least 1 week prior to Baseline b. Use of soft lenses should be discontinued at least 3 days and use of rigid gas permeable or hard contact lenses should be discontinued at least 1 week prior to a scheduled study visit or Administration Day visit c. Use of contact lenses of any kind should be discontinued for 1 week following any Bimatoprost SR administration
2.12	Central corneal thickness of < 480 or > 620 micrometers in the **study eye**
2.13	Anticipated need for any incisional or laser ocular surgery in the **study eye** during the study
2.14	History of anatomically narrow angle resulting in evidence of angle changes or any history of closed angle glaucoma, in the **study eye** Note: historically narrow angled participants whose angle has been opened by cataract surgery or peripheral iridotomy may be eligible for enrollment if they have no evidence of angle abnormalities
2.15	History or evidence of a peripheral iridotomy/iridectomy in the inferior iris in the **study eye**
2.16	Any history of trabeculectomy or other types of glaucoma surgery, including a glaucoma seton or aqueous bypass stents in the **study eye**

2.17	Peripheral anterior synechiae (PAS) in the inferior iridocorneal angle on gonioscopic examination at Screening in the **study eye**
2.18	Visual field loss in **either eye** that, in the opinion of the investigator, is functionally significant (eg, split fixation, field defect within the central 10 degrees that is visually significant or likely to cause central visual impairment upon progression) or shows evidence of progressive visual field loss within the year prior to Baseline Note: The same test methodology should be used for all study-related examination for a given participant
2.19	Evidence of macular edema in **either eye** during screening or in participant's medical history
2.20	Anticipated use of corticosteroids in **either eye** (except as described in Section 6.4.1, Permitted Interventions) or systemically during the study, or historical use prior to Baseline within: a. 3 years: intraocular fluocinolone acetonide b. 6 months: intraocular corticosteroid(s) other than fluocinolone; any injectable periocular or sub-Tenon's/subconjunctival corticosteroid c. 2 months: systemic (eg, oral, intramuscular, intravenous) or topical ocular corticosteroids d. 2 weeks: dermal corticosteroids applied to skin of the eyelid(s), around the eye, or adnexa
2.21	Anticipated use of other topical ocular medications in **either eye** except as described in Section 6.4.1 (Permitted Interventions)

5.2.2. Exclusion Criteria for Fellow Eye Administration

Note: participants do not need to meet Fellow Eye Administration criteria to qualify for study entry. Fellow Eye Administration criteria are only for fellow eyes that are being considered for Bimatoprost SR administration which is in addition to all study entry criteria required for that eye.

Bimatoprost SR administration in the fellow eye must occur within one month of Fellow Eye Administration Inclusion/Exclusion Criteria assessment. Participants are eligible to receive study treatment in the fellow eye if none of the following exclusion criteria apply:

1.	**Ocular Exclusion Criteria**
1.01	History of laser trabeculoplasty within 3 months prior to treatment administration in the **fellow eye** (Fellow Eye Administration)
1.02	History or evidence of clinically relevant, substantial ocular trauma (eg, a traumatic cataract, traumatic angle recession, etc) in the **fellow eye**
1.03	The following surgical history in the **fellow eye**: a. History or evidence of complicated cataract/lens surgery: eg, surgery resulting in complicated lens placement (such as anterior chamber intraocular lens implant [IOL], sulcus IOL, aphakia, etc.) or intraoperative complications (such as a posterior capsular tear [with or without vitreous loss], substantial iris trauma, etc.) Note: history of uncomplicated cataract surgery is not an exclusion b. History of phakic IOL insertion for refractive error correction
1.04	Intraocular surgery (including cataract surgery) in the **fellow eye** within the 6 months prior to treatment administration (Fellow Eye Administration)
1.05	Any history of corneal graft, including partial grafts (eg, Descemet's Stripping Endothelial Keratoplasty [DSEK], Descemet's Membrane Endothelial Keratoplasty [DMEK]); or incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions in the **fellow eye**
1.06	Corneal or other ocular abnormalities that would preclude accurate readings with an applanation tonometer, specular microscope, and/or a contact pachymeter, or could confound study results in the **fellow eye**, eg, moderate to severe corneal dystrophy, including Anterior Basement Membrane Disease (ABMD; ie, Map-Dot-Fingerprint) and guttata. Mild ABMD or mild guttata are not exclusionary by clinical examination if, in the opinion of the investigator, the condition is stable and not likely to cause corneal changes during the course of the study

1.07	Active or recurrent ocular disease in the **fellow eye** (eg, uveitis, ocular infection, chronic moderate to severe blepharitis or severe dry eye, ocular seasonal allergies) or sight threatening diseases (eg, neovascular age-related macular degeneration [AMD], diabetic macular edema) that, in the opinion of the investigator, would put the participant at a significant risk or would interfere with the interpretation of the study data Note: Participants with slowly progressive eye diseases (ie, mild cataracts, non-neovascular AMD) can be enrolled at the discretion of the investigator. If a participant has a potentially exclusionary condition or disease in one eye that tends to be bilateral or is likely to affect both eyes, the investigator should consider excluding that participant
1.08	Any history of external ocular or intraocular malignancy, and/or any history of benign ocular neoplasia in the **fellow eye** that in the investigator's opinion resulted in clinically significant ocular morbidity
1.09	History of herpetic ocular diseases in the **fellow eye** (including herpes simplex virus and varicella zoster virus)
1.10	Active ocular surface findings other than bulbar conjunctival hyperemia, on either macroscopic or slit-lamp examination, > +1 (mild) performed at the previous study visit within one month prior to Bimatoprost SR administration in the **fellow eye**
1.11	The anticipated wearing of contact lenses in the **fellow eye** during the study that deviates from the following (contact lens wear is allowed during the study, but is to be temporarily discontinued before study visits, and before and after an Administration Day according to the following): a. Use of soft lenses should be discontinued at least 3 days prior to Baseline, and use of rigid gas permeable or hard contact lenses should be discontinued at least 1 week prior to Baseline b. Use of soft lenses should be discontinued at least 3 days and use of rigid gas permeable or hard contact lenses should be discontinued at least 1 week prior to a scheduled study visit or Administration Day visit c. Use of contact lenses of any kind should be discontinued for 1 week following any Bimatoprost SR administration
1.12	Central corneal thickness of < 480 or > 620 micrometers in the **fellow eye**
1.13	Anticipated need for any incisional or laser ocular surgery in the **fellow eye** during the study

1.14	History of anatomically narrow angle resulting in evidence of angle changes or any history of closed angle glaucoma, in the **fellow eye** Note: historically narrow angled participants whose angle has been opened by cataract surgery or peripheral iridotomy may be eligible for enrollment if they have no evidence of angle abnormalities
1.15	History or evidence of a peripheral iridotomy/iridectomy in the inferior iris in the **fellow eye**
1.16	Any history of trabeculectomy or other types of glaucoma surgery, including a glaucoma seton or aqueous bypass stents in the **fellow eye**
1.17	Peripheral anterior synechiae (PAS) in the inferior iridocorneal angle on gonioscopic examination at Screening in the **fellow eye**
1.18	Evidence of macular edema in the **fellow eye** during screening or in participant's medical history
1.19	Clinically significant, persistent corneal edema or other significant corneal findings potentially resulting from the implant or persistent and progressive corneal endothelial cell density decrease ≥ 15% from baseline confirmed at 2 consecutive visits on separate days in the **study eye**
1.20	Previous administration of Bimatoprost SR (including commercially available Bimatoprost SR) in the **fellow eye**

5.3. Lifestyle Considerations

Not applicable; no restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study (eg, randomized/stratified/enrolled). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened unless the participant's condition has changed, in the investigator's opinion.

6. Study Intervention

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention Administered

Details regarding the study treatment administered is summarized in Table 6-1.

Table 6-1 Study Treatment Administered

Study Treatment Name	Bimatoprost SR
Dosage Formulation	Bimatoprost SR is an intraocular implant that contains preservative-free bimatoprost dispersed in a biodegradable polymer matrix (including PLA and/or PLGA). Implants are preloaded into an applicator to facilitate insertion of the implant into the AC of the eye.
Unit Dose Strength(s)/ Dosage Level(s)	A dose strength of 10 µg (formula number 11047X) bimatoprost will be administered.
Route of Administration	Intracameral
Administration Instructions	Bimatoprost SR is inserted directly into the AC of the eye using the prefilled applicator.
Packaging and Labeling	Study treatment will be provided in a sterile, laminated foil pouch in an individual carton. Each package will be labeled as required per country requirement.
Manufacturer	AbbVie (formerly Allergan)
Number and Timing of Treatments (Study Eye)	**After Amendment 4:** Participants may receive up to 2 administrations of Bimatoprost SR If the study eyes meets retreatment criteria (Section 6.5) study eye may receive a single readministration of Bimatoprost SR in the study eye, following a minimum of 16 weeks after the Cycle 1 Bimatoprost SR administration through completion of the PRN treatment period. *Day 1 Cycle 1 Study Eye Administration:* On the first Bimatoprost SR administration visit (Day 1 Cycle 1 Administration), participants will receive an intracameral administration of Bimatoprost SR 10 µg in the study eye and standard of care treatment in the fellow eye (provided, in the investigator's opinion, there is no known crossover effect of the fellow eye's standard of care treatment to the study eye). *Cycle 2 Study Eye Administration (from 16 weeks after Day 1 Cycle 1 Administration up to and including completion of the Month 36 visit from Day 1 Cycle 1 Administration):* **Prior to Amendment 4:** If the study eye meets retreatment criterion, study eye may receive up to two additional administrations of Bimatoprost SR beginning not less than 16 weeks

Study Treatment Name	Bimatoprost SR
	after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period. *Day 1 Cycle 1 Study Eye Administration:* On the first Bimatoprost SR administration visit (Day 1 Cycle 1 Administration), participants will receive an intracameral administration of Bimatoprost SR 10 µg in the study eye and standard of care treatment in the fellow eye (provided, in the investigator's opinion, there is no known crossover effect of the fellow eye's standard of care treatment to the study eye). *Cycle 2 Study Eye Administration (from 16 weeks after Day 1 Cycle 1 Administration up to and including completion of the Month 36 visit from Day 1 Cycle 1 Administration).* *Cycle 3 Study Eye Administration (minimum of 16 weeks after Cycle 2 Administration and up to and including completion of the Month 36 visit from Day 1 Cycle 1 Administration).*
Number and Timing of Treatments (Fellow Eye)	From Week 16 through completion of the PRN treatment period, if participants meet treatment criteria for the fellow eye (Sections 5.1.2 and 5.2.2) and, in the investigator's opinion, it is safe for the fellow eye to receive an administration of Bimatoprost SR, the fellow eye may receive a single administration of Bimatoprost SR, recommended between one week and three weeks after Cycle 2 Administration. However, through the PRN treatment period, if the fellow eye meets treatment criteria outside of the suggested Cycle 2 Administration schedule of visits in the study eye, the fellow eye may receive a single administration of Bimatoprost SR, return for a Day 2 Safety Visit, a Week 4 follow up visit, and then return to the schedule of visits as appropriate. Bimatoprost SR administration in the fellow eye must be separated by at least one week from any Bimatoprost SR administration in the study eye. Upon the decision to administer Bimatoprost SR in the fellow eye, standard of care treatment will be stopped at least one day prior to Fellow Eye Administration. Fellow eye administration is limited to a single administration.

6.1.1. Washout Before the Study

All participants must provide informed consent prior to beginning any drug washout for the purposes of inclusion in this study. Participants currently being treated with IOP-lowering medication(s) in either eye will begin washout of these medication(s) following completion of the screening procedures. The screening and washout periods may not be concurrent. The washout period will be up to 56 days depending on the minimum washout period schedule below.

If participants cannot discontinue their prescribed therapy for up to 8 weeks to meet the washout period for study entry, the investigator may switch the participant's medication to one that requires a shorter washout interval during the washout of the original medication (Table 6-2). Nonetheless, the investigator should adhere to the minimum washout period for all IOP-lowering medications as indicated in Table 6-2.

If, after initial washout, the IOP does not meet entry criteria and the investigator believes this is due to inadequate washout, if time remains in the washout period he/she may perform additional washout, as long as the total washout period does not exceed 56 days.

Table 6-2 Minimum Washout Period by Ophthalmic Medication Class

Ophthalmic Medications	Minimum Washout Period
Parasympathomimetics (eg, PILAGAN®, Carbachol, Pilocar®)	4 days
Carbonic Anhydrase Inhibitors (topical or systemic) (eg, Diamox®, Trusopt®, Azopt®)	4 days
Sympathomimetics (eg, PROPINE®, Epifrin®)	14 days
Alpha-agonists (eg, ALPHAGAN P, Iopidine®)	14 days
Beta-adrenergic blocking agents (eg, Timoptic®, BETAGAN®, Betoptic®, Betoptic-S®, Opti-Pranolol®, Ocupress®, Timoptic XE®)	28 days
Rho-kinase inhibitors (eg, Rhopressa®, Glanatec®)	28 days
Prostamides, prostaglandins and prostaglandin analogs, as well as combination products that include these medications (eg, LUMIGAN, Xalatan, Travatan, Rescula®, GANFORT®)	28 days
Combination therapy (for example, COMBIGAN® [28 days], Cosopt® [28 days], GANFORT® [28 days], Simbrinza® [14 days], Azarga® [28 days], etc)	longest minimum duration of any component based on medication class

For participants undergoing a washout, interim safety evaluation(s) of IOP at any time during the washout period may be performed at the discretion of the investigator.

Note: Medications should only be discontinued (washed out) if the investigator feels that it is safe and appropriate, and if the participant is willing to discontinue the medication for the duration of the study. If the medication cannot be discontinued, then the participant will not be eligible for study entry.

6.1.2. Instructions for Use and Administration

Study treatments must only be administered to participants who meet the eligibility criteria in accordance with conditions specified in this protocol.

6.1.2.1. Participant Preparation

Administration day assessments (including vital signs and query for concomitant medications and adverse events) should be completed. At least 3 administrations of a broad-spectrum topical ophthalmic antibiotic drop and topical anesthetic drop will be administered to the study eye approximately every 5 minutes beginning approximately 15 minutes prior to the procedure. With the participant in a supine position, the eye and conjunctival fornices should be irrigated with 5% ophthalmic povidone-iodine solution and the lids and surrounding orbital area should be prepped and draped according to the standard protocol detailed in the Procedure Manual.

6.1.2.2. Study Treatment Location

At the discretion of the investigator, Bimatoprost SR administration may be performed at an Ambulatory Surgical Center (ASC; free standing or hospital based) or in the office setting (eg, in a procedure room with an operating microscope). As a standard ASC technique, an intravenous catheter may be placed and intravenous sedatives may be used at the discretion of the investigator and/or anesthesiologist. The ASC may have SOPs that require an electrocardiogram and/or a chest radiograph performed prior to the procedure. A separate standard consent to have the procedure at an ASC may be required per the SOPs at the facility.

Sterile technique should be practiced at all times.

6.1.2.3. Administration Technique

Intracameral administration of Bimatoprost SR must be performed by an ophthalmologist who has had adequate training and has been approved by AbbVie to perform the procedure. The principal investigator at a site may designate an ophthalmologist subinvestigator to perform the procedure, subject to AbbVie approval and training. The study medication kit should be readily available during the procedure.

The procedure is described in detail in the Procedure Manual. In brief, following the sterile preparation and sterile field setup, an appropriately sized sterile lid speculum should be placed between the eyelids of the participant. The entrance site for the applicator needle is just anterior to the insertion of the conjunctiva through the clear cornea in the superior or temporal quadrant. The trajectory of the needle should be parallel to the iris plane. The eye is stabilized by either counter traction with a sterile toothed forceps or counter pressure with a cotton tipped applicator as the needle is advanced through the cornea. The actuator button is depressed until an audible and/or palpable click is heard. The Bimatoprost SR implant should be visible exiting the needle bevel into the aqueous humor. The needle is then immediately removed from the AC, and the wound is checked for aqueous leakage. Following removal of the lid speculum and sterile drape, additional drops of broad-spectrum antibiotics should be applied.

A user experience questionnaire will be completed after each Bimatoprost SR administration.

The procedure for retreatment of Bimatoprost SR is the same.

6.1.2.4. Immediate Posttreatment Observation

Following Bimatoprost SR administration, the participant is allowed to sit upright and is kept for a minimum of 1 hour of observation. The surgeon will examine the Bimatoprost SR treated eye to ensure that the AC is formed prior to the participant being released.

The participant will be supplied a bottle of topical ophthalmic antibiotic drops and instructions to use them for the next 3 days (including the day of the administration) in the Bimatoprost SR treated eye and to follow up as per protocol.

Prior to leaving the site, participants should be instructed to contact the study site immediately if they experience any adverse events after treatment. If the participant reports having experienced adverse events, these must be recorded on the appropriate eCRF.

The same posttreatment observation and antibiotic requirements apply any treatment of Bimatoprost SR in either eye.

6.2. Preparation/Handling/Storage/Accountability

Bimatoprost SR is loaded into the single use applicator during manufacturing and is provided within the applicator as a sterile, finished product. Study site personnel should notify AbbVie immediately to advise or any situation in which the Bimatoprost SR applicator is defective.

The study medications must be stored in a secure area and administered only to participants entered into the clinical study, at no cost to the participant, in accordance with the conditions specified in this protocol. Only assigned study personnel authorized by the investigator may have access to medications. Bimatoprost SR must be stored in the original sealed foil pouch.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medications received and any discrepancies are reported and resolved before use of the study medications.

Only participants enrolled in the study may receive study medications, and only authorized site staff may supply or administer study medications. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. More details regarding storage conditions of study medications are available in the Procedure Manual.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee). All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug/device accountability procedures.

All unused study medications and empty packages, including any malfunctioning applicators, must be returned to the sponsor at the termination of the study. Unit counts will be performed when the study medication is returned, and all study medications must be accounted for. Unused drug supplies will be returned to the sponsor.

6.3. Measures to Minimize Bias

Prior to initiation of study treatment, each participant who provides informed consent will be assigned a participant number that will serve as the participant identification number on all study documents.

For participants enrolled prior to Amendment 1, this was a dual arm study in which participants were randomized using a 1:1 ratio to either receive 10 µg or 15 µg Bimatoprost SR in the study eye; central block randomization was done by site and stratified by Baseline Hour 0 IOP (baseline study eye IOP ≤ 25 mm Hg or > 25 mm Hg). The participant, investigator, and the site staff were masked to the study treatment dose strength assignment. For participants enrolled after Amendment 1, all participants will receive 10 µg Bimatoprost SR open label and no randomization, masking, or stratification will be performed.

IOP measurement will be performed by using a 2-person reading method to minimize bias.

The study site will keep an accurate drug disposition record that specifies the kit number administered to each participant and the date of administration.

6.4. Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken.

6.4.1. Permitted Interventions

Ophthalmic Treatments

The fellow eye will receive standard of care for IOP lowering, provided, in the investigator's opinion, there is no crossover effect to the study eye. If the fellow eye requires laser or surgical treatment, it must be performed not less than 3 days after any Bimatoprost SR administration in the study eye.

From Week 16 through completion of the PRN treatment period, participants who meet treatment criteria for the fellow eye (Sections 5.1.2 and 5.2.2) may receive a single administration of Bimatoprost SR in the fellow eye. Upon the decision to administer Bimatoprost SR in the fellow eye, standard of care medication will be stopped at least one day prior to Fellow Eye Administration. A second Bimatoprost SR administration in the fellow eye will not be permitted.

Intermittent use of artificial tear products is allowed if they are not taken ≤ 15 minutes before any study procedure or examination in either eye. Intermittent use of ocular decongestants or antihistamines is allowed if not taken within 2 days prior to a scheduled visit. Use of artificial tear products and ocular decongestants or antihistamines may be restarted in the treated eye 3 days after any Bimatoprost SR administration procedure.

Use of postinjection topical ocular antibiotics is expected following the Bimatoprost SR administration procedure (see Procedure Manual). Use of topical ophthalmic corticosteroids and NSAIDs from the Administration Day (Day 1 Cycle 1 Administration and, if necessary, Cycle 2, and Fellow Eye Administration) through Day 7 following administration is allowed at the investigator's discretion.

Implant Removal

In the event that the Bimatoprost SR implant requires removal for significant safety reasons, this may be performed at the discretion of the investigator. The investigator may contact the medical safety physician at AbbVie for further discussion as needed (see Procedure Manual for details).

Note that in the event that the investigator performs an incisional surgical procedure on the Bimatoprost SR implanted eye during which ocular fluid is to be removed, ocular fluid/implant samples may be collected for analysis at the investigator's discretion (see Procedure Manual for details).

Systemic Medications

Systemic beta-blocker containing medications are permitted, provided that the treatment regimen has remained stable for at least 2 months prior to Screening and is not anticipated to change during the duration of the study.

The use of systemic NSAIDs is also permitted.

In addition, therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, these medications should be administered in dosages that remain constant throughout the entire duration of the study. If the permissibility of a specific medication/treatment is in question, please contact AbbVie.

6.4.2. Rescue Treatment

In the event that the study eye IOP does not meet or does not maintain IOP-lowering expectations, and/or the participant does not meet Bimatoprost SR administration criteria as determined by the investigator, rescue IOP-lowering treatment [medication(s) or procedure(s) or both] can be initiated at the investigator's discretion. Inadequate control of IOP should be confirmed at a subsequent visit (scheduled or unscheduled visit) not on the same day. Rescue treatment can be initiated at the investigator's discretion at any time during the study if it is in the best interest of the participant. From Week 16 through completion of the PRN treatment period, the participant should be considered for retreatment if he or she qualifies; please see Retreatment Criteria in Section 6.5 for details.

For participants who need additional IOP-lowering treatment but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12-month period, topical IOP-lowering medication (intermittent rescue) may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator).

6.4.3. Prohibited Interventions During the Study

The decision to administer a prohibited medication and/or treatment is done with the safety of the study participant as the primary consideration. When possible, AbbVie should be notified before the prohibited medication/treatment is administered.

During the study, participants should not participate in other investigational drug or device studies.

Nonstudy IOP-lowering Treatments

Fellow eye:

The fellow eyes of participants will receive standard of care for IOP lowering, provided, in the investigator's opinion there is no crossover effect to the study eye. Use of any concurrent nonstudy IOP-lowering treatment in the fellow eye with any known effect on study outcomes in the study eye (eg, crossover effect) is prohibited during the study. If applicable, upon the decision to administer Bimatoprost SR in the fellow eye, standard of care treatment will be stopped at least one day prior to Fellow Eye Administration and use of any topical ophthalmic medication containing an ocular antihypertensive is prohibited as concurrent therapy in the fellow eye, unless necessary for the safety of the participant due to inadequate control of IOP as determined by the investigator.

Study eye:

Prior to completion of the PRN treatment period, the investigator will be expected to attest to the need for additional nonstudy IOP-lowering (rescue) treatment in the study eye for safety reasons.

Note: for participants who need additional IOP lowering treatment but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12-month period, topical IOP-lowering medication (intermittent rescue) may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator). After all retreatment requirements have been met, if the decision to administer Bimatoprost SR in the study eye is made, topical IOP-lowering medications shall be stopped at least one day prior to Bimatoprost SR administration.

Contact Lenses

Use of soft contact lenses within 3 days and/or use of rigid gas permeable or hard contact lenses within 1 week prior to a scheduled study visit or any Administration Day, and/or use of contact lenses of any kind within 1 week following any Bimatoprost SR administration in the eye receiving administration is prohibited.

Other Treatments

The following medications (or classes of medications) and treatment procedures are not permitted as concurrent therapy during the study through completion of the PRN treatment period or 12 months after the last Bimatoprost SR administration, whichever is longer, unless the participant has already been treated with rescue IOP-lowering medication in the Bimatoprost SR treated eye(s):

- Subconjunctival, sub-Tenon's, intravitreal, or other ophthalmic injections of any medications in bimatoprost SR treated eye(s).
- Use of any topical ophthalmic medications (except as described in Section 6.4.1) in study eye and if applicable, the fellow eye after Fellow Eye Administration.
- Surgical (incisional and laser) procedures that are not related to study-specific Bimatoprost SR procedures in any Bimatoprost SR treated eye. Non Bimatoprost SR treated fellow eyes can follow standard of care for IOP lowering as needed. Participants may exit the study early if an ophthalmic incisional or laser procedure is required in a Bimatoprost SR treated eye (See Section 7.2 for early exit procedures).
- Use of bimatoprost for hypotrichosis during the study period in either eye
- Use of cyclosporine ophthalmic solution during the study period in either eye
- Systemic use of carbonic anhydrase inhibitors
- Any initiation of or alterations in systemic regimen of beta-blocker containing medications from 2 months prior to Screening through the final study visit
- Use of corticosteroids in either eye (except as described in Section 6.4.1 for postinjection use) or systemically during the study or historical use prior to Baseline within:
    - 3 years: intraocular fluocinolone acetonide
    - 6 months: intraocular corticosteroid(s) other than fluocinolone; any injectable periocular or sub-Tenon's/subconjunctival corticosteroid
    - 2 months: systemic (eg, oral, intramuscular, intravenous) or topical ocular corticosteroids
    - 2 weeks: dermal corticosteroid applied to skin of the eyelid(s), around the eye, or adnexa

6.5. Dose Modification

Dose modification is not applicable.

Retreatment Criteria

Prior to Protocol Amendment 4, if the study eye meets retreatment criterion, study eye may receive up to two additional administrations of Bimatoprost SR beginning not less than 16 weeks after the previous Bimatoprost SR administration and continuing through completion of PRN treatment period.

Starting with Protocol Amendment 4, participants may receive up to one additional administration of Bimatoprost SR in the study eye, following a minimum of 16 weeks after Cycle 1 Bimatoprost SR administration through completion of the PRN treatment period, if they meet the following criteria:

- There is a clinically meaningful increase in IOP (eg, < 20% change from baseline IOP) in the study eye confirmed at a subsequent visit (scheduled or unscheduled) not on the same visit day; and/or, in the investigator's opinion, there are clinical signs or symptoms of disease worsening (eg, disc hemorrhage, worsened visual field).
- Each previously administered implant is < 25% of the original size
- Retreatments may not occur less than 16 weeks after a previous Bimatoprost SR administration
- The participant has not received any rescue treatment in the study eye
    - Note: For participants who need additional IOP lowering medication but do not meet retreatment criteria due to implant size requirements, or due to the limitation of 2 implant administrations in a 12-month period, topical IOP-lowering medication (intermittent rescue) may be used until all retreatment requirements have been met (intermittent rescue should only be used in participants who are suitable for temporary use of topical IOP-lowering medications, as determined by the investigator). After all retreatment requirements have been met, if the decision to readminister Bimatoprost SR in the study eye is made, topical IOP-lowering medications shall be stopped at least one day prior to Bimatoprost SR administration
- There is no evidence of any of the following:
    - Significant corneal findings related to presence of the implant (including corneal edema, peripherally adjacent to the implant location and/or central) at any visit

- Endothelial cell density less than 2000 cells/mm^2 by specular microscopy by automated analysis, confirmed at 2 consecutive visits on separate days
- Persistent and progressive corneal endothelial cell density decrease ≥ 15% from baseline confirmed at 2 consecutive visits on separate days (scheduled or unscheduled)
- Remaining implant size or position from prior administration(s) that, based on the investigator's evaluation, precludes placement of another implant (eg, may cause chronic contact of the implants with the corneal endothelium)
- Clinically significant intraocular inflammatory findings (eg, PAS, uveitis, iridocyclitis, macular edema, etc) at any visit. Note: mild intraocular inflammation related to the administration procedure itself that resolves rapidly (with or without NSAIDs or steroids) is not prohibitive

- In the investigator's opinion, it is safe for the study eye to receive an additional administration of Bimatoprost SR

Signs or symptoms will be documented in the eCRF.

6.6. Intervention after the End of the Study

No interventions after the end of the study are planned; participants will be treated per SOC by their health care provider.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is treated ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Reasons for discontinuation from the study may include the following commonly used or other acceptable terms, which are defined in Appendix 5:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Completed	Disease relapse
Lack of efficacy	Failure to meet randomization criteria
Lost to follow-up	Progressive disease
Other	Technical problems
Physician decision	
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to AbbVie and will be clearly documented on the appropriate case report form.

7.1. Discontinuation of Study Intervention

The Bimatoprost SR implant is designed to bioerode in the anterior chamber of the eye and is not meant to be removed. In the event that the Bimatoprost SR implant requires removal for significant safety reasons, please see Section 6.4.1 for guidance on implant removal and Section 7.2 for follow up requirements for participant discontinuation in the event the implant is removed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

- If a participant develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, would put the participant at an unacceptable medical risk by continuing study participation, the participant will be withdrawn from the study.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Participants may exit the study early not less than 12 months after the last Bimatoprost SR administration, if they have received rescue treatment in the Bimatoprost SR treated eye, and there are no safety concerns in the opinion of the investigator. If the implant has been removed and there are no implants in either eye, the participant may discontinue the study if, based on investigator assessment, the eye is in stable condition, at which time they should complete the Month 48/Exit visit procedures. In the event that both eyes are treated with Bimatoprost SR and an implant is removed in only one eye, the participant should continue to be followed according to the study visit schedule after the eye is in stable condition after implant removal.
- In the event a participant withdraws consent from the clinical study, use of the participant's collected genetic samples will continue unless the participant explicitly requests collected samples not be used for analysis. When AbbVie is informed that the participant has withdrawn from the study and no longer wishes the samples collected to date be used, the samples will not be analyzed, no additional genetic samples will be collected from the withdrawn participant or added to the existing data or database(s), and the samples will be destroyed. A participant may withdraw consent from optional genetic research at any time and remain in the clinical study. Analysis results obtained from optional genetic samples processed before the participant withdrew consent will remain part of the study results.

The investigator should consider withdrawing a participant from the study early if any of the following criteria are met:

- Participant develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, compromises the participant's ability to participate in the study
- Participant is unwilling or unable to continue to comply with study procedures
- Participant is unwilling or unable to continue in the study

Whenever possible, the decision to withdraw a participant from the study or study treatment should be discussed with AbbVie.

7.3. Lost to Follow Up

A participant will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- A detailed listing of study assessments by day is presented in Appendix 8.
- Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Protocol waivers or exemptions are not allowed.
- Significant safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants who receive at least one administration and complete all visits through Month 48/Study Exit will have a minimum of 31 visits. The schedule includes the following:

- Screening (up to 10 days); Washout period of up to 56 days; and Baseline (up to 3 days)
- Bimatoprost SR Day 1 Cycle 1 Administration; Cycle 1 Day 2 Safety Visit; Cycle 1 Week 4 Visit; Cycle 1 Week 8 Visit; Cycle 1 Week 12 Visit; Cycle 1 Week 16 Visit; and follow up study visits at Week 24 and Months 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 38, 40, 42, 44, 46 and 48/Study Exit.
    - If the participant meets retreatment criteria for Cycle 2 (or 3) administration (Section 6.5), Bimatoprost SR Cycle 2 (or 3) Administration Day; Cycle 2 (or 3) Day 2 Safety Visit; Cycle 2 (or 3) Week 4 Visit; Cycle 2 (or 3) Week 8 Visit; Cycle 2 (or 3) Week 12 Visit; and Cycle 2(or 3) Week 16 Visit.
    - Note: Following the Cycle 2 (or 3) Week 16 Visit, participants should resume the schedule of visits and evaluations as appropriate (Table 1-2 and Table 1-4).
    - Note: with implementation of Amendment 4, PRN Cycle 3 Administration is no longer applicable for any eligible eye.

- If the fellow eye meets Fellow Eye Administration Criteria during the recommended study eye Cycle 2 Administration schedule of visits (only one fellow eye injection is permitted) (Section 5), fellow eye administration must be separated by at least 7 days from study eye administration and the participant must return for a next day safety visit, as outlined in Table 1-5 Cycle 2 Day 7 Fellow Eye Administration; Cycle 2 Day 8 Fellow Eye Safety Visit.
- However, from Week 16 through completion of the PRN treatment period (up to and including the Month 36 visit), if the fellow eye meets treatment criteria outside of the recommended Study Eye Cycle 2 Administration schedule of visits, the participant will attend Fellow Eye Administration; Fellow Eye Day 2 Safety Visit; Fellow Eye Week 4 Visit follow up visit, and then return to the schedule of visits as appropriate (Table 1-6, Table 1-2 and Table 1-4.

IOP evaluations will occur at Hour 0 (09:00 AM ± 1 hour) at each visit.

8.1. Efficacy Assessments

Efficacy assessments are to be completed as outlined in the Schedule of Activities (Section 1.3).

To evaluate the duration of effect of Bimatoprost SR, study participants will be monitored for clinically meaningful IOP control and be evaluated for the need for retreatment or rescue at the investigator's discretion. A 2-person reading method will be used for all efficacy IOP measurements, wherein 1 person adjusts the dial in a masked fashion and a second person reads and records the value. The right eye is to be measured first and the left eye measured second. Two consecutive IOP 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 the study.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1. Physical Examinations

The participant will be examined by qualified medical personnel for any physical abnormality of the following systems: general appearance; head, eyes, ears, nose, and throat; heart/cardiovascular; lungs; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; and skin. Height and weight will also be measured and recorded.

8.2.2. Vital Signs

Vital signs will be assessed as follows:

- Temperature, pulse rate, and BP will be assessed.
- BP and pulse rate measurements will be assessed with participants in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a seated position.

8.2.3. Pregnancy Testing

Pregnancy testing will be conducted at Baseline and at the study exit visit. Urine pregnancy tests will be used unless the study site requires the use of serum testing, in which case serum testing will be used. WOCBP must have a negative test result before receiving study treatment. This test may also be performed at any other visit, at the investigator's discretion. At each visit, the investigator should discuss contraceptive use compliance with WOCBP females of childbearing potential (see Appendix 7 for more details).

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the Schedule of Activities (Section 1.3) for the timing and frequency.

At Screening, the investigator or qualified subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.

8.2.5. Ocular Safety Assessments

8.2.5.1. Macroscopic Conjunctival Hyperemia Assessment

Macroscopic conjunctival hyperemia will be assessed using the appropriate assessment guide (see the Procedure Manual for further details).

8.2.5.2. Best-corrected Visual Acuity

Visual acuity tests will be performed at all visits except on any of the Bimatoprost SR administration days. Manifest refraction using Snellen equivalent with a logMar chart (see Procedure Manual) will be performed at Screening, Baseline, and Months 12, 24, 36 and 48/Study Exit. At all other visits, the visual acuity technician will use the last manifest refraction performed and determine the Snellen equivalent visual acuity using the logMar chart. If there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a

repeat manifest refraction in both eyes and BCVA will be performed. See the Procedure Manual for further details.

8.2.5.3. 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. See the Procedure Manual for further details. Visual field data may also be submitted to an AbbVie designated vendor for additional evaluation.

8.2.5.4. Specular Microscopy

Endothelial cell density will be assessed using specular microscopy performed on the central cornea at all sites. The determination of central endothelial cell density for study entry as well as study visit measures will be by the study investigator using automated analysis. See the Procedure Manual for further details. The same instrument should be used throughout the study for a given participant. Specular microscopy images will also be submitted to a reading center for a centralized evaluation across sites.

8.2.5.5. Biomicroscopy

Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, cornea, AC (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. Please see the Procedure Manual for details).

8.2.5.6. Gonioscopy/Angle Assessment

Gonioscopic examinations will be performed by the study investigator as described in the Procedure Manual. At Screening, the investigator's eligibility assessments must confirm participant eligibility for participation in the study. In subsequent gonioscopic examinations during the study, the investigator will evaluate the inferior iridocorneal angle and the Bimatoprost SR implant.

8.2.5.7. Pachymetry

Corneal thickness using ultrasound (contact) pachymetry will be performed on the central cornea. The same instrument should be used throughout the study for a given participant. Pachymetry may be performed any time after gonioscopy. See the Procedure Manual for further details.

8.2.5.8. Dilated Ophthalmoscopy

The stereoscopic fundus assessments should be conducted through a dilated pupil. The examinations will include evaluation of the macula, vitreous, and retina.

8.2.5.9. Optic Disc Examination

The cup/disc ratio and presence of optic disc pathology will be determined using stereoscopic evaluation.

8.3. Adverse Events and Serious Adverse Events

The definitions of an adverse event (AE) or serious adverse event (SAE) can be found in Appendix 3.

AEs may be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

Additionally, the investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs from the signing of the informed consent form (ICF) until the study exit visit will be collected at the timepoints specified in the Schedule of Activities (Section 1.3), and as observed or reported spontaneously by study participants.

All SAEs from the signing of the ICF until the study exit visit will be collected at the timepoints specified in the Schedule of Activities (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences or worsening of medical conditions that begin before the start of study treatment but after obtaining informed consent will be recorded in the AE section of the eCRF.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by AbbVie to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow up period, the investigator will provide AbbVie with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to AbbVie within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for SAEs

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements, including reporting to the Eudravigilance database per EU Clinical Trial Regulation 536/2014.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- Investigator safety reports must be prepared for serious unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.
- An investigator who receives an investigator safety report describing a serious adverse event (SAE) or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- If a pregnancy is confirmed after the participant has received the study treatment, the participant may choose to exit the study after appropriate safety follow up or to remain in the study for all safety and efficacy follow up assessments through the study exit visit.
- Details of all pregnancies in female participants will be collected from the signing of the ICF and through the duration of the pregnancy.
- If a pregnancy is reported, the investigator should inform AbbVie within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous or elective abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Medication Errors

Medication error refers to any unintended error in the dose strength and/or administration of the study treatments as per instructions in the protocol and/or the Procedure Manual. Medication errors generally fall into 4 categories as follows:

- Wrong study drug/device
- Wrong dose (including treatment regimen, strength, form, concentration, amount)

- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant) or wrong eye

8.4. Treatment of Overdose

Not applicable.

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

PD parameters are not evaluated in this study.

8.7. Optional Biomarker Research Endpoints

US sites only: Optional whole blood DNA samples will be collected at a single time point anytime during the study (Section 1.3) to evaluate known and/or novel disease or drug-related genetic biomarkers in circulation. The analyses may include but are not limited to evaluation of variants in the prostaglandin receptor and metalloproteinase genes that may affect the degree of IOP lowering and duration of response the participant may have to Bimatoprost SR; and genetic factors contributing to the disease or Bimatoprost SR (or other study treatment) in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to the disease, related conditions, or drug response. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to Bimatoprost SR or drugs of this class. The samples may also be used for the development of diagnostic tests related to OAG, OHT, and Bimatoprost SR (or drugs of this class).

All samples should be labeled and shipped as outlined in the study-specific laboratory procedure manual.

AbbVie (or people/ or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on Bimatoprost (or drugs of this class), OAG or OHT, and related conditions continues, but for no longer than 20 years after study completion, or per local requirements.

The results from these analyses are exploratory in nature, will not be suitable for clinical decision-making or patient management, may not be included in the study report, and may be performed by a non-GLP laboratory.

8.8. Other Assessments

8.8.1. Gonioscopic Photography

At selected sites only (those with qualified equipment), at selected visits, goniophotographic images of the inferior iridocorneal angle will be taken in conjunction with the gonioscopic examination in both eyes of consenting participants. See the Procedure Manual for details. The participant's decision about whether to allow gonioscopic photography will not affect their eligibility for participation in the study.

8.8.2. Anterior Segment Imaging

At selected sites only, anterior segment imaging may be performed using AbbVie-approved instruments. Please see the Procedure Manual for further details. The participant's decision about whether to allow anterior segment imaging will not affect their eligibility for participation in the study.

8.8.3. Implant Administration (and/or Removal) Video Recording

The procedure of administering (and if necessary, the removal of) Bimatoprost SR may be video recorded in consenting participants. The video recording will be made of the eye as viewed through an operating microscope. The video recordings may be used to review the study procedure and/or for general research, education, or informational purposes. Please see the Procedure Manual for further details. The participant's decision about whether to allow video recording will not affect their eligibility for participation in the study.

8.8.4. Posterior Segment Imaging

At selected sites only (those with qualified equipment), posterior segment imaging (eg, posterior segment optical coherence tomography [OCT]) may be performed using AbbVie -approved instruments. See the Procedure Manual for details. The same instrument should be used throughout the study for a given participant. The participant's decision about whether to allow posterior segment imaging will not affect their eligibility for participation in the study.

8.9. Health Economics

The participant will complete patient reported outcome (PRO) measures via paper administration that will be provided at the study site. Copies of all PRO measures are provided in the Procedure Manual.

8.9.1. Allergan Satisfaction with Treatment Experience Questionnaire (ASTEQ)

Participant satisfaction to implant treatment will be evaluated with the ASTEQ. The ASTEQ questionnaire is comprised of two modules: a Baseline Module and Implant Experience Module.

The Baseline Module of the ASTEQ is a two-item PRO designed to assess expectations of treatment for glaucoma or OHT. These items assess expectations of implant experience and

overall satisfaction with previous glaucoma treatments. The ASTEQ Implant Experience Module is a nine-item PRO designed to participants' satisfaction with the implant experience.

The ASTEQ Baseline Module will be administered at Baseline. The ASTEQ Implant Experience Module will be administered every Day 2 Safety Visit, Week 12, and at Months 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48/Study Exit.

8.9.2. Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM will be included as part of validation of the ASTEQ. The TSQM is a 14-item PRO design to assess level of satisfaction or dissatisfaction with a clinical trial medication.

The TSQM will be administered at every Day 2 Safety Visit, Week 12, and at Months 8 and 48/Study Exit.

8.9.3. Patient Mobility/Postural Behavior Questionnaire

US sites only: This is an exploratory questionnaire to assess participants' routine physical activities and behavioral manifestations. This questionnaire will be completed at any given time point during the study.

The results from these analyses are exploratory in nature, will not be suitable for clinical decision-making or patient management, and may not be included in the study report.

9. Statistical Considerations

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Sample Size Determination

Based on the Phase 1/2 study (192024-041D), approximately 70% of participants receiving the 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 participants 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 participants with multiple administrations of Bimatoprost SR.

9.3. Populations for Analyses

The analysis sets will consist of experimental units as defined below:

Note: The experimental unit will be participant eyes for efficacy analyses and ocular safety analyses and participant for systemic safety variables.

- Full Analysis Set (FAS): All participants study eyes that have received study treatment with at least one postbaseline IOP assessments will contribute to the FAS which will be used for efficacy analyses.
- Safety Analysis Set (SAS): All participants who have received at least 1 dose of study treatment in either eye will contribute to the SAS. All safety data collected from these participants will be included in the SAS.

9.4. Statistical Analyses

In general, continuous variables will be summarized by number of participants, mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing or unused data. This section provides the main features of the planned statistical analyses of the efficacy and safety endpoints.

9.4.1. Efficacy Analyses

9.4.1.1. Analysis Endpoints

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

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

9.4.1.2. Efficacy Analyses

For the time to event efficacy variable, the cumulative distribution function will be calculated by Kaplan-Meier method for each treatment group with the 95% CIs for the survival probability will be presented.

9.4.1.3. Other Analyses

Other efficacy variables include:

- Time to second administration of Bimatoprost SR in the study eye regardless of intermittent rescue.
- Time to third administration of Bimatoprost SR or first rescue treatment after second administration in the study eye.
- IOP raw values and change from baseline for study eye and for fellow eye treated with Bimatoprost SR.

IOP raw values and change from baseline will be summarized descriptively by treatment groups and visit.

To avoid confounding of efficacy data, IOP measurements obtained after initiating the use of nonstudy IOP-lowering treatment/rescue (medication[s] or procedure[s] or both) in the study eye will be excluded from efficacy analyses, unless otherwise specified.

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). General safety parameters will include AEs (including pregnancy) 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.

Ocular adverse events and safety variables will be tabulated by study eye and fellow eye, and nonocular safety variables will be summarized at participant level. A separate safety summary will be provided for participants who received Bimatoprost SR treatment in both eyes.

9.4.2.1. Adverse Events

MedDRA nomenclature will be used to code AEs. The number and percentage of participants reporting AEs will be tabulated based on primary system organ class and preferred terms. Summary tables will be generated for all AEs regardless of causality as well as treatment-related AEs for the entire study and by treatment cycle.

9.4.2.2. Vital Signs

Descriptive statistics for vital signs will be presented by study treatment group.

9.4.3. Ocular Safety Analyses

Ocular safety parameters (visual fields, BCVA, conjunctival hyperemia, biomicroscopy, dilated ophthalmoscopy [including optic disc assessment], pachymetry, gonioscopy, and specular microscopy) will be summarized by study treatment group. Reading center as well as automated specular microscopy data will be used for endothelial cell density related safety analyses. Reading center data will be the primary source of safety analysis of specular microscopy data.

9.5. Interim Analyses

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 which evaluated the use of an alternate applicator in approximately 30 participants.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
    - Applicable ICH/ISO GCP guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- **US sites only**: Optional genetic research samples will only be completed if the participant has voluntarily signed and dated a written consent form for the whole blood DNA testing that has been approved by an IRB/IEC, after the nature of the testing has been explained and the participant has had an opportunity to ask questions. The written consent may be part of the main consent form, or it may be a separate form. If the participant does not consent to this testing, it will not impact participation in the study.
- **US Sites only**: Exploratory questionnaire to assess participants routine physical activities and behavioral manifestations at any given time point during the study will only be completed if the participant has voluntarily signed and dated a written consent form.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor with sponsor permission.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and must follow ALCOA, ie, records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

10.1.9. Publication Policy

- AbbVie as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the sponsor.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Investigators are NOT employed by the organization sponsoring the study. There is an agreement between investigators and the sponsor (or its agents) that restricts the investigator's rights to discuss or publish study results after the study is completed.
- AbbVie requests that any investigator or institution that plans on presenting/publishing results, provide written notification of their request 60 days prior to their presentation/publication. AbbVie requests that no presentation/publication will be instituted until 12 months after a study is completed or after the first presentation/publication, whichever occurs first. A delay may be proposed for a presentation/publication if AbbVie needs to secure patent or proprietary protection.

10.1.10. Patients Confidentiality

To protect patients' confidentiality, all patients and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

For the personal data that AbbVie Deutschland GmbH & Co acting as sponsor of the submitted study ("AbbVie") controls and maintains, AbbVie has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

Before patient data are shared with AbbVie, the study doctor and staff will replace any information that could directly identify a patient (such as name, address, and contact information) with a generic code which AbbVie cannot link to that patient's identity to protect the confidentiality of the data.

AbbVie has a data protection impact assessment (DPIA) program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains and these processing activities respect privacy of clinical trial patients. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

10.1.11. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study treatment accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by a central laboratory or designated regional facility, including any repeat laboratory tests.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Refer to the Central Laboratory Manual for further details regarding central laboratory collection and shipment procedures.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.

Laboratory test results will be forwarded from the central laboratory or designated regional facility to the study site and to AbbVie or its designee. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. The investigator or qualified site personnel must review all laboratory results for any adverse events. Laboratory test results that represent adverse events should be reflected on an adverse event eCRF page.

Evaluation and management of abnormal laboratory results should be conducted according to local site practice.

Table 10-1 Protocol Required Safety Laboratory Assessments

Laboratory Assessments[a]	Parameters			
Hematology	Platelets RBC count Hemoglobin Glycated hemoglobin Hematocrit	RBC indices: MCV MCH MCHC Morphology	WBC count with differential (absolute): Neutrophils Bands Lymphocytes Monocytes Eosinophils Basophils	
Serum Chemistry	BUN, uric acid	Potassium	AST	Total, direct, and indirect bilirubin
	Creatinine	Sodium	ALT	Total protein
	Creatinine kinase	Magnesium, phosphorus	Bicarbonate	Total cholesterol
	Glucose	Calcium	Alkaline phosphatase	Chloride, albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Clarity, color, presence of blood • Microscopic examination (WBCs, RBCs, casts, bacteria, crystals, epithelial cells)			

[a] No laboratory assessments require fasting.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events Meeting the AE Definition
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to provide pertinent documentation related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to AbbVie in lieu of completion of the AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by AbbVie. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to AbbVie.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE or SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to AbbVie. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to AbbVie.**
- The investigator may change his/her opinion of causality in light of follow up information and send an SAE follow up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
• Any SAE must be immediately reported but no later than 24 hours after learning of the SAE. • Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@abbvie.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

Abbreviation/Term	Definition
ABMD	Anterior Basement Membrane Disease
AC	anterior chamber
AE	adverse event
AESI	adverse event of special interest
AGIS	Advanced Glaucoma Intervention Study
ALT	Alanine aminotransferase
AMD	age-related macular degeneration
AREDS	Age-related Eye Disease study
ASC	Ambulatory Surgical Center
AST	Aspartate aminotransferase
ASTEQ	Allergan Satisfaction with Treatment Experience Questionnaire
BCVA	best-corrected visual acuity
BP	blood pressure
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
DMEK	Descemet's Membrane Endothelial Keratoplasty
DSEK	Descemet's Stripping Endothelial Keratoplasty
eCRF	electronic case report form
EU	European Union
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FE	fellow eye
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IOL	intraocular lens implant
IOP	intraocular pressure

Abbreviation/Term	Definition
IRB	Institutional Review Board
ISO	International Organization for Standardization
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LT	laser trabeculoplasty
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drugs
OAG	open-angle glaucoma
OCT	optical coherence tomography
OHT	ocular hypertension
OU	both eyes
PAS	peripheral anterior synechiae
PD	pharmacodynamic
PK	pharmacokinetic
PLA	polylactic acid
PLGA	polylactic-co-glycolic acid
POAG	primary open angle glaucoma
PRN	*pro re nata* (as needed)
PRO	patient reported outcome
RBC	red blood cell
SAE	serious adverse event
SAS	Safety Analysis Set
SAP	statistical analysis plan
SD	standard deviation
SE	study eye
SITA	Swedish Interactive Thresholding Algorithm
SLT	selective laser trabeculoplasty
SoA	schedule of activities
SOC	standard-of-care
SOP	standard operating procedure

Abbreviation/Term	Definition
SR	sustained release
SUSAR	for suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
WBC	white blood cell
WOCBP	woman of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 3b Study to Evaluate the Duration of Effect of Bimatoprost SR in Participants with Open-Angle Glaucoma or Ocular Hypertension
	Clinical Study Sponsor	AbbVie, Inc.
	Trial Phase Classification	Phase 3b Trial
	Trial Indication	Open-angle glaucoma or ocular hypertension
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	30 to 48 Months
	Planned Country of Investigational Sites	Global
	Planned Number of Subjects	Up to approximately 490 in total
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	Open-angle glaucoma or ocular hypertension
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	Not specified
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not specified

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	Bimatoprost SR
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Prostaglandin analog
	Dose strength per Administration	10 µg
	Dose Units	1 implant
	Administration Frequency	Up to 3 PRN administrations in the study eye
	Route of Administration	Intracameral
	Current Therapy or Treatment	No
	Added on to Existing Treatments	No
	Control Type	None
	Comparative Treatment Name	N/A
Trial design	Study Type	Interventional
	Intervention Model	Open label
	Planned Number of Arms	1
	Trial is Randomized	No
	Randomization Quotient	N/A
	Trial Masking Schema	N/A
	Stratification Factor	N/A
	Adaptive Design	No
	Study Stop Rules	None

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

WOCBP

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female Participants

WOCBP are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective and Acceptable Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test at Baseline.
- Additional pregnancy testing should be performed at study exit, and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Urine pregnancy testing will be used unless the study site requires the use of serum testing, in which case serum testing will be used.

Collection of Pregnancy Information:

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to AbbVie within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on the participant and the neonate, and the information will be forwarded to AbbVie. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to AbbVie as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- If a pregnancy is confirmed after the participant has received study treatment, the participant may choose to exit the study after appropriate safety follow up or to remain in the study for all safety and efficacy follow up assessments through study exit visit.

10.8. Appendix 8: Study Schedule Supplement

10.8.1. Screening Visit

After informed consent and other documentation have been obtained, the procedures listed below are carried out. IOP measurements must be performed in 1 day; however, other procedures (eg, post dilation procedures) may be performed on a different day as long as the screening procedures are completed within a 10-day period, and procedures completed on the same day follow the schedule as set out in the protocol. Pupil dilation/diagnostic procedures are to be performed after the completion of the final IOP measurement of the day or on a different day.

- Collection of demographic data
- Collection of medical and ophthalmic history
- Collection of adverse events
- Collection of concomitant medications and procedures
- Physical examination
- Vital signs (at rest ≥ 5 minutes)
- Collection of blood and urine samples

The following procedures should be performed in both eyes in the order below (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examination** (perform before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - **Manifest refraction** (Manifest refraction will be used to provide a correction for best corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed.)
    - **BCVA**
- **IOP measurement at Hour 0**

- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Specular microscopy
    - Biomicroscopy
- **Gonioscopy/angle assessment** (Examination will also include, at selected sites only, gonioscopic photographs of both eyes in consenting participants.)
- Pachymetry (may be performed at any time after gonioscopy)
- **Pupil dilation** (post dilation examinations below may be performed in any order)
    - Dilated ophthalmoscopy
    - Optic disc examination

Eligibility is then determined and the IWRS is contacted.

10.8.2. Baseline Visit

The Baseline visit occurs after the washout period has been completed. Baseline visit procedures, excluding IOP measurements (which must be performed in 1 day), can be performed over a 3 day period; all must be completed by the day before the administration day. Pupil dilation/diagnostic procedures are to be performed after the completion of the final IOP measurement or on a different day.

- Collection of medical and ophthalmic history
- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Pregnancy test for WOCBP
- Completion of ASTEQ: Baseline Module

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examination** (perform before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment

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

- **IOP measurement at Hour 0**
- **Non-contact examinations**: The following may be performed at any time after IOP at Hour 0:
  - Visual field (If dilation is required to perform this test, then the visual field test should be performed with the scheduled dilated exams.)
  - Anterior segment imaging (non-contact; select sites/participants only; if using non-contact anterior segment instruments, perform with other non-contact assessments)
  - Biomicroscopy
  - Posterior segment imaging (select sites/participants only)
- Anterior segment imaging (contact; select sites/participants only; if using contact anterior segment imaging instruments, perform after all non-contact assessments).
- **Pupil dilation** (post dilation examinations below may be performed in any order)
  - Dilated ophthalmoscopy
  - Optic disc examination

Eligibility is then determined and Hour 0 IOP is entered into the IWRS.

10.8.3. Day 1 Cycle 1 Administration Visit

The following procedures are performed on the day of Bimatoprost SR administration:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Contact IWRS for kit allocation (this contact may take place one day prior to Day 1 Cycle 1 Administration, if needed)
- Administer assigned study treatment (Bimatoprost SR 10 µg)
- Contact the IWRS to confirm kit assignment if applicable
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

All participants must remain in the surgical facility for bilateral eye examination at least 1 hour after the Bimatoprost SR administration procedure.

Each participant will be supplied a bottle of topical ophthalmic antibiotic drops and instructions to use them for the next 3 days (including the day of the administration) in the Bimatoprost SR treated eye and to follow up with the study site as per protocol.

10.8.4. Cycle 1 Day 2 Safety Visit

The following procedures are performed on Cycle 1 Day 2:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Completion of ASTEQ: Implant Module and TSQM
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).

- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may perform in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**
- **Non-contact examination**: The following may be performed at any time after IOP at Hour 0:
    - Biomicroscopy

10.8.5. Weeks 4, 8, 12, and 16 Visits

The following procedures are performed at Weeks 4 (± 4 days), 8 (± 4 days), 12 (± 4 days), and 16 (± 4 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Completion of ASTEQ: Implant Module and TSQM (Week 12 only)
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may be performed in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA

- **IOP measurement at Hour 0**
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Specular microscopy (Week 16 only)
    - Biomicroscopy
- **Gonioscopy/angle assessment** (The examination will also include, at selected sites only, gonioscopic photographs in consenting participants.)
- Pachymetry (may be done any time after gonioscopy; Week 16 only)

10.8.6. Week 24 and Months 8, 10, 12, 14, 16, and 18 Visits

The following procedures are performed at Week 24 (± 4 days) and Months 8 (± 7 days), 10 (± 7 days), 12 (± 7 days), 14 (± 7 days), 16 (± 7 days), and 18 (± 7 days):

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Completion of ASTEQ: Implant Module (Months 8, 12, and 16 only) and TSQM (Month 8 only)
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examination** (perform before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**

- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Visual field (If dilation is required to perform this test, then the visual field test should be performed after gonioscopy/angle assessment with the schedule dilated exam; Week 24 and Months 12, and 18 only)
    - Manifest refraction (Manifest refraction will be used to provide a correction for best corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed; Month 12 only)
    - Specular microscopy (Months 8, 12, and 16 only)
    - Anterior segment imaging, (non-contact; select sites/participants only; if using non-contact anterior segment instruments, perform with other non-contact assessments before gonioscopy; Week 24 and Months 12 and 18 only)
    - Biomicroscopy
    - Posterior segment imaging (select sites/participants only; Week 24 and Months 12, and 18 only)
- **Gonioscopy/angle assessment** (The examination will also include, at selected sites only, gonioscopic photographs in consenting participants.)
- Pachymetry (may be performed at any time after gonioscopy; Months 8, 12, and 16 only)
- Anterior segment imaging (contact; selected sites/participants only; if using contact anterior segment imaging instruments, perform after gonioscopy; Week 24 and Months 12 and 18 only)
- **Pupil dilation** (post dilation examinations below may be performed in any order; Month 12)
    - Dilated ophthalmoscopy
    - Optic disc examination

10.8.7. Months 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48/Study Exit Visits

The following procedures are performed at Months 20 through 48/Study Exit (± 14 days)

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Pregnancy test for WOCBP (Month 48/Study Exit only)
- Completion of ASTEQ: Implant Module (Months 20, 24, 28, 32, 36, 40, 44 and Month 48/Study Exit only) and TSQM (Month 48/Study Exit only)
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examination** (perform before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Visual field (If dilation is required to perform this test, then the visual field test should be performed after gonioscopy/angle assessment with the scheduled dilated exams, Months 24, 30, 36, 42 and 48/Study Exit only)
    - Manifest refraction (Manifest refraction will be used to provide a correction for best corrected visual acuity testing. At all study visits, if there is a 2-line or more reduction in visual acuity from the last best-corrected visual acuity performed, a repeat manifest refraction in both eyes and best-corrected visual acuity will be performed; Months 24, 36 and 48/Study Exit only)

- Specular microscopy (Months 20, 24, 28, 32, 36, 40, 44 and 48/Study Exit only)
- Anterior segment imaging (non-contact; select sites/participants only; if using non-contact anterior segment instruments, perform with other non-contact assessments before gonioscopy; Months 24, 30, 36, 42 and 48/Study Exit only)
- Biomicroscopy
- Posterior segment imaging (select sites/participants only; Months 24, 30, 36, 42 and 48/Study Exit only)

- **Gonioscopy/angle assessment** (The examination will also include, at selected sites only, gonioscopic photographs in consenting participants.)
- Pachymetry (may be performed at any time after gonioscopy; Months 20, 24, 28, 32, 36, 40, 44 and 48/Study Exit only)
- Anterior segment imaging (contact; selected sites/participants only; if using contact anterior segment imaging instruments, perform after gonioscopy; Months 24, 30, 36, 42 and 48/Study Exit only)
- **Pupil dilation** (post dilation examinations below may be performed in any order; Months 24, 36 and 48/Study Exit only)
  - Dilated ophthalmoscopy
  - Optic disc examination

10.8.8. Cycle 2 Administration Visit, if performed

The following procedures are performed at the Cycle 2 Administration Visit:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Specular microscopy (Specular microscopy must be performed within the month prior to Bimatoprost SR administration and must be reviewed by the investigator for clearance prior to administration.)

- Contact IWRS for kit allocation (this contact may take place 1 day prior to the Cycle 2 Administration Day, if needed)
- Administer assigned study treatment
- Contact IWRS to confirm kit assignment if applicable
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

All participants must remain at the surgical facility for bilateral eye examination at least 1 hour after Bimatoprost SR administration procedure. Each participant will be supplied a bottle of topical ophthalmic antibiotic drops and instructions to use them for the next 3 days (including the day of the administration) in the Bimatoprost SR treated eye and to follow up with the study site as per protocol.

10.8.9. Cycle 2 Day 2 Safety Visit, if performed

The following procedures are performed on Cycle 2 Day 2:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Completion of ASTEQ: Implant Module and TSQM
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may perform in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA

- **IOP measurement at Hour 0**
- **Non-contact examination**: The following may be performed at any time after IOP at Hour 0:
    - Biomicroscopy

10.8.10. Cycle 2 Day 7 Fellow Eye Administration, if performed

The following procedures are performed at the Cycle 2 Day 7 (+ 14 days) Fellow Eye Administration Visit:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Contact IWRS for kit allocation (this contact may take place one day prior to the Cycle 2 Day 7 Fellow Eye Administration Day, if needed)
- Administer assigned study treatment
- Contact IWRS to confirm kit assignment if applicable
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

All participants must remain at the surgical facility for bilateral eye examination at least 1 hour after Bimatoprost SR administration procedure. Each participant will be supplied a bottle of topical ophthalmic antibiotic drops and instructions to use them for the next 3 days (including the day of the administration) in the Bimatoprost SR treated eye and to follow up with the study site as per protocol.

10.8.11. Cycle 2 Day 8 Fellow Eye Safety Visit, if performed

The following procedures are performed on the Cycle 2 Day 8 (+ 14 days) Fellow Eye Safety Visit:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)

- Completion of ASTEQ: Implant Module and TSQM
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may perform in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**
- **Non-contact examination**: The following may be performed at any time after IOP at Hour 0:
    - Biomicroscopy

10.8.12. Cycle 2 Weeks 4, 8, 12, and 16 Visits, if performed

The following procedures are performed at the Cycle 2 Weeks 4 (± 4 days), 8 (± 4 days), 12 (± 4 days), and 16 (± 4 days) visits:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may be performed in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Specular microscopy (Week 16 only)
    - Biomicroscopy
- **Gonioscopy/angle assessment** (The examination will also include, at selected sites only, gonioscopic photographs in consenting participants.
- Pachymetry (may be done any time after gonioscopy; Week 16 only)

10.8.13. Fellow Eye Administration, if performed

The following procedures are performed at the Fellow Eye Administration Visit that occurs outside of Cycle 2 Administration schedule of visits:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Specular microscopy (Specular microscopy must be performed within the month prior to Bimatoprost SR administration and must be reviewed by the investigator for clearance prior to administration.)
- Contact interactive response system for kit allocation (this contact may take place 1 day prior to the Fellow Eye Administration Day, if needed)
- Administer assigned study treatment
- Contact IWRS to confirm kit assignment if applicable
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).

- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

All participants must remain at the surgical facility for bilateral eye examination at least 1 hour after Bimatoprost SR administration procedure. Each participant will be supplied a bottle of topical ophthalmic antibiotic drops and instructions to use them for the next 3 days (including the day of the administration) in the Bimatoprost SR treated eye and to follow up with the study site as per protocol.

10.8.14. Fellow Eye Day 2 Safety Visit, if performed

The following procedures are performed on the Fellow Eye Day 2 Safety Visit that occurs outside of Cycle 2 Administration schedule of visits:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- Completion of ASTEQ: Implant Module and TSQM
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may perform in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**
- **Non-contact examination**: The following may be performed at any time after IOP at Hour 0:
    - Biomicroscopy

10.8.15. Fellow Eye Week 4, if performed

The following procedures are performed at the Fellow Eye Week 4 Visit (± 4 days) that occurs outside of Cycle 2 Administration schedule of visits:

- Collection of adverse events
- Collection of concomitant medications and procedures
- Vital signs (at rest ≥ 5 minutes)
- **US sites only**: Optional whole blood DNA Sample. This one-time sample may be collected at any post-Baseline study visit (if not collected at an earlier visit).
- **US sites only**: Patient Mobility and Postural Behavior Questionnaire will be completed (if not completed at an earlier visit). This one-time questionnaire can be completed at any post-Baseline study visit.

The following procedures should be performed in both eyes (procedures in bold should be done in the order shown):

- **Pre-Hour 0 examinations** (may be performed in any order before Hour 0 IOP):
    - Macroscopic conjunctival hyperemia assessment
    - BCVA
- **IOP measurement at Hour 0**
- **Non-contact examinations**: The following may be performed in any order, at any time before gonioscopy:
    - Biomicroscopy
- **Gonioscopy/angle assessment** (The examination will also include, at selected sites only, gonioscopic photographs in consenting participants.

10.9. Appendix 9: Responsibilities of The Investigator

Protocol 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

Protocol Date: 04 January 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP), as well as applicable laws, regulations, and guidelines. Certain laws, regulations, or guidelines may apply to conduct of the study at investigator's site even if such laws, regulations, or guidelines originate in a foreign jurisdiction. The investigator agrees and acknowledges that applicable laws or regulations may require AbbVie to submit inspection reports, instances of significant non-compliance with the study protocol, or other documents regarding conduct of the study at the investigator's site to regulatory authorities, and such documents may be publicly disclosed by such authorities. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (eg, IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting the following to AbbVie within 1 calendar day of becoming aware:
    - Any unanticipated problems involving risks to human subjects

- Any departure from relevant clinical trial regulation, GCP, or the trial protocol that has affected or is likely to affect to a **significant** degree the following:
  - Rights, safety, physical or mental integrity of the subjects in the clinical trial
  - Scientific value of the clinical trial, reliability or robustness of data generated

Where required by local regulation, inform relevant Ethics Committees / Institutional Review Boards and other appropriate individuals (eg, Co-ordinating Investigator, Institution Director).

10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

11. References

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