

STATISTICAL ANALYSIS PLAN

A Prospective, Multicenter, Randomized, Parallel-Arm, Double Masked, Vehicle Controlled Phase 3a Study Evaluating the Safety and Efficacy of OTX-TP in the Treatment of Subjects with Open-Angle Glaucoma or Ocular Hypertension

Sponsor: Ocular Therapeutix, Inc
34 Crosby Drive, Suite 105
Bedford, MA 01730 USA

Protocol Number: OTX-16-002

Author: Elizabeth Kumm
Principal Biostatistician
Statistics & Data Corporation

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Statistical Analysis Plan Approval

Prepared by: Elizabeth Kumm 02Jan2018
Elizabeth Kumm
Principal Biostatistician
Statistics & Data Corporation

Reviewed by: Kirk Bateman 02Jan2018
Kirk Bateman
Director, Biostatistics
Statistics & Data Corporation
Date

Approved by: Swati Sane 02Jan2018
Swati Sane
Director, Data Management and Biostatistics
Ocular Therapeutix, Inc.
Date

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best Corrected Visual Acuity
BOCF	Baseline Time-consistent Observation Carried Forward
CI	Confidence intervals
C/D	Cup to Disc
CS	Clinically Significant
CSR	Clinical Study Report
DM	Data Management
eCRF	Electronic Case Report Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCS	Not Clinically Significant
OTX	Ocular Therapeutix, Inc
OTX-TP	Sustained Release Travoprost Intracanalicular Depot
PDF	Portable Document Format
PLA	poly (-lactic-acid)
PP	Per Protocol
PT	Preferred Term
PV	Placebo Vehicle Intracanalicular Depot
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO DDE	World Health Organization Drug Dictionary Enhanced

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol OTX-16-002, Revision E dated 02May2017

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the CSR.

2. Study Objectives

The objective of this study is to evaluate the safety and intraocular pressure (IOP)-lowering efficacy of OTX-TP, a sustained release travoprost drug product, placed in the canaliculus of the eye in the treatment of subjects with open-angle glaucoma or ocular hypertension.

3. Study Variables

Primary Variable

The primary efficacy variable is mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.

Secondary Variables

The secondary efficacy variables include the following:

- Mean change from baseline IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.
- Mean percent change from baseline IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.

Other Variables

Additional variables on which data will be collected include the following:

- Ocular complaints
- Visualization of intracanalicular depot by the Investigator at each time point
- Ease of insertion of intracanalicular depot
- Number of intracanalicular depots required in each eye for the 12 week period per subject.

Safety Variables

The safety variables include the following:

- BCVA
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Subject ocular comfort assessment
- Dilated fundus exam
- Adverse events

Statistical Hypotheses

The null and alternative hypotheses, based on the primary variables, are as follows:

- H_0 : The difference between study eyes that received sustained release travoprost (OTX-TP) and study eyes that received Placebo Vehicle (PV) (calculated as OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is ≥ 0 mmHg for at least one time point over all visits.
- H_1 : The difference between study eyes that received OTX-TP and study eyes that received PV (calculated as OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is < 0 mmHg for all time points over all visits.

4. Study Design and Procedures

General Study Design

This is a prospective, multicenter, randomized, parallel-arm, double masked, placebo vehicle controlled Phase 3a trial to evaluate the safety and IOP-lowering efficacy of OTX-TP, a sustained release drug product placed in the canaliculus of the eyelid in subjects with open-angle glaucoma or ocular hypertension. A total of up to 550 subjects (1100 eyes) with a clinical diagnosis of open-angle glaucoma or ocular hypertension in both eyes will receive either OTX-TP or PV to evaluate the safety and efficacy of OTX-TP.

The subjects enrolled in this parallel-arm study will be randomized to receive either OTX-TP intracanalicular depot (OTX-TP) or PV intracanalicular depot (PV), respectively. Subjects randomized to the treatment group will receive OTX-TP in either the superior or inferior canaliculus of each affected eye on Day 1. Subjects randomized to the control group will receive PV in either the superior or inferior canaliculus of each affected eye on Day 1.

At the Baseline Visit 2/Insertion Visit, in the event that after randomization the insertion of the intracanalicular depot is unsuccessful in the first eye, the subject will be exited from the study. If insertion is unsuccessful in the second eye, the intracanalicular depot from the contralateral eye (if already inserted) will not be removed. The subject will be prescribed IOP-lowering drops at the Investigator's

discretion for the eye that did not receive a depot. The subject will be followed for safety only, and the eye that received a depot will be included in the safety analysis. The study will be supplemented with additional subjects to account for these subjects in order to ensure that the necessary number of subjects (490) who received a depot bilaterally are followed through the 12 Week Visit for efficacy and safety. If neither insertion is successful the End of Study eCRF will be completed for the subject and the subject will be exited from the study. Unsuccessful punctal dilation of either eye (if needed) or if the punctum of either eye is too small to allow transient dilation to 0.7 mm prior for insertion of OTX-TP or PV is considered a Procedural Exclusion Criterion and the subject will be exited as a screen failure.

All subjects will undergo follow-up visits at 2, 4, 6, 8, 10, and 12 Weeks. If at any visit, the Investigator deems it necessary to initiate IOP-lowering drops as rescue therapy due to an increase in IOP, the subject will be considered an efficacy failure. and will be followed through the remainder of the study for safety. If still present, the intracanalicular depot will not be removed. IOP measurements taken through the remainder of the study will be excluded from the efficacy analyses.

For any subject, if at any point the intracanalicular depot is removed bilaterally by the Investigator for an adverse event or subject discomfort, the subject will be exited from the study at that visit. If the intracanalicular depot needs to be removed from only one eye, the depot from the contralateral eye will not be removed and the subject will be followed per the study schedule for safety.

Intracanalicular depots that are removed due to subject withdrawal or an undesired reaction at any point in the study will not be replaced.

For subjects with Early Loss of Intracanalicular Depot Prior to the 6 Week Visit:

At any visit prior to the 6 Week Visit, if the intracanalicular depot is not visualized in one or both eyes by the Investigator, the Investigator will insert a new intracanalicular depot in the respective eye(s) after confirming patency. For any depot replacements, IOP assessments should be completed prior to replacement. The subject will continue to return for follow-up visits per the study schedule through the 12 Week Visit. The number of depot replacements will be tracked and documented on the appropriate electronic Case Report Form (eCRF).

For subjects with Early Loss of Intracanalicular depot from the 6 Week Visit prior to the 12 Week Visit:

At any visit from the 6 Week Visit prior to the 12 Week Visit, if the intracanalicular depot is not visualized in one or both eyes by the Investigator, the Investigator will insert a new intracanalicular depot in the respective eye(s) after confirming patency. For any depot replacements, IOP assessments should be completed prior to replacement. The subject will return for follow-up visits through the 12 Week Visit and then at the 20 Week Visit. Depots replaced between the 6 Week Visit and the 12 Week Visit will not be

removed at the 12 Week Visit. The first attempt to remove these depots will be at the 20 Week Visit. The number of depot replacements will be tracked and documented on the appropriate eCRF.

12 Week Visit:

If the intracanalicular depot(s) is/are still present at the 12 Week Visit, the Investigator will attempt to remove the depot(s). If removal is successful bilaterally, the subject will be exited from the study upon confirmation of the bilateral absence of the intracanalicular depot. If the intracanalicular depot are not present bilaterally at the 12 Week Visit, the subject will be exited at the end of that visit.

If removal is unsuccessful in one or both eyes at the 12 Week Visit, the subject will return at the 20 Week Visit. The subject may be prescribed IOP-lowering drops if necessary at the 12 Week Visit at the Investigator's discretion.

20 Week Visit:

At the 20 Week Visit, the Investigator will attempt removal of the intracanalicular depot(s), if still present. If removal at the 20 Week Visit is successful bilaterally, the subject will be exited from the study upon confirmation of the bilateral absence of the intracanalicular depot.

If removal at the 20 Week Visit is not successful in one or both eyes, the subject will be required to return to the clinic every 30 (\pm 10) days until the intracanalicular depot is confirmed to be no longer present or removal of the intracanalicular depot is successful for the respective eye(s). Removal will be attempted at every visit until the intracanalicular depot is no longer present.

The subject may be prescribed IOP-lowering drops if necessary at the 20 Week Visit at the Investigator's discretion.

Schedule of Visits and Assessments

The schematic of the study schedule is presented in Table 1, Table 2, and Table 3, respectively for: Stratum A, Stratum B, and Stratum C.



Table 1: Study Schedule for subjects on prostaglandin treatment at the time of the Screening Visit (Stratum A)

Study Parameter	Follow-Up Assessments												
	Screening	Baseline Visit 1 6 weeks (-2 days/ +3 days) after Screening	Baseline Visit 2/ Insertion Visit	2 Week (Day 15 ±3 days)	4 Week (Day 29 ±3 days)	6 Week (Day 43 ±3 days)	8 Week (Day 57 ±3 days)	10 Week (Day 71 ±3 days)	12 Week (Day 85 ±3 days)	20 Week (Day 141 ± 7 days)			
	8AM	8AM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	8AM	10AM	4PM	8AM
Informed Consent	X												
Determine Eligibility	X	X	X										
Iris Color	X									X			
Medical/Ophthalmic and Medication	X												
Demographic Information	X												
Urine Pregnancy Test (if applicable)	X												
Automated Perimetry	X												
Gonioscopy	X												
Dilated Fundus Exam	X												X
Pachymetry	X												
Punctum Size Assessment	X												
Assessment of BCVA	X		X			X			X		X		X
Slit Lamp Biomicroscopy	X	X	X			X			X		X		X
Assess/Grade Hyperemia	X		X			X			X		X		X
Punctum Exam	X		X			X			X		X		X
IOP Measurement	X (8AM)	X	X	X	X	X	X	X	X	X	X	X	X
Subject Ocular Comfort			X			X			X		X		X
Randomize													
Punctum Size													
Pre/Post Dilatation			X										
Intracanalicular Depot Insertion			X										
Intracanalicular Depot Presence						X			X		X		X
Assessment of Ocular Complaints						X			X		X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Study Schedule for subjects who are treatment-naïve at the time of the Screening Visit (Stratum B)

Study Parameter	Follow-Up Assessments																									
	Screening		Run-in		Baseline Visit 1		Baseline Visit 2/ Insertion Visit		2 Week (Day 15 ±3 days)		4 Week (Day 29 ±3 days)		6 Week (Day 43 ±3 days)		8 Week (Day 57 ±3 days)		10 Week (Day 71 ±3 days)		12 Week (Day 85 ±3 days)		20 Week (Day 141 ±7 days)					
	8AM	8AM	Visit 1 (Day 2 +3 days)	Visit 2 (Day 11 +3 days)	8AM	8 Weeks (-2 days/+3 days) after Screening	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	
Informed Consent	X																									
Determine Eligibility	X				X		X																			
Iris Color	X																									
Medical/Ophthalmic and Medication History	X																									
Demographic Information	X																									
Urine Pregnancy Test (if applicable)	X																									
Automated Perimetry	X																									
Gonioscopy	X																									
Dilated Fundus Exam	X																									
Pachymetry	X																									
Punctum Size Assessment	X																									
Assessment of BCVA	X																									
Slit Lamp	X																									
Biomicroscopy	X																									
Assess/Grade Hyperemia	X																									
Punctum Exam	X																									
IOP Measurement	X (8AM)																									
Subject Ocular Comfort																										
Randomize																										
Punctum Size Pre/Post Dilation																										
Intracanalicular Depot Insertion																										
Intracanalicular Depot Presence																										
Assessment of Ocular Complaints																										
Adverse Events	X																									
Record Medications	X																									



Table 3: Study Schedule for Subjects who have exited from a prior ophthalmic investigational research study within 8 weeks of the Screening Visit and have written approval from the Medical Monitor to be allowed to participate in the current study without additional exposure to prostaglandin (Stratum C)*

Study Parameter	Screening	IOP Confirmation	Baseline Visit 1	Baseline Visit 2/ Insertion Visit		Follow-Up Assessments											
				Day 1	Day 2	2 Week (Day 15 ±3 days)	4 Week (Day 29 ±3 days)	6 Week (Day 43 ±3 days)	8 Week (Day 57 ±3 days)	10 Week (Day 71 ±3 days)	12 Week (Day 85 ±3 days)	20 Week (Day 141 ±7 days)					
Informed Consent	X																
Determine Eligibility	X		X	X	X												
Iris Color	X											X					
Medical/Ophthalmic and Medication History	X																
Demographic Information	X																
Urine Pregnancy Test (if applicable)	X																
Automated Perimetry	X																
Gonioscopy	X																
Dilated Fundus Exam	X																X
Paachymetry	X																
Punctum Size Assessment	X																
Assessment of BCVA	X				X				X			X			X		X
Slit Lamp Biomicroscopy	X			X					X			X			X		X
Assess/Grade Hyperemia	X			X					X			X			X		X
Punctum Exam	X			X					X			X			X		X
IOP Measurement	X (8AM)		X	X		X			X			X			X		X
Subject Ocular Comfort	X (8AM)		X						X			X			X		X
Randomize																	
Punctum Size Pre/Post Dilatation				X													
Intracanalicular Depot Insertion				X													
Intracanalicular Depot Presence					X				X			X			X		X
Assessment of Ocular Complaints				X					X			X			X		X
Adverse Events	X		X	X		X			X			X			X		X
Record Medications	X		X		X				X			X			X		X

* For information on which study schedule should be followed after the IOP Confirmation Visit, please refer to Appendix A to determine whether the subject is in Stratum A, B, or C.

5. Study Treatments

There are two study treatments, OTX-TP intracanalicular depot and PV intracanalicular depot, which are explained below.

OTX-TP Intracanalicular Depot

The OTX-TP drug product is a fluorescent dried polyethylene glycol based, rod-shaped hydrogel intracanalicular depot designed to be placed in the superior or inferior canaliculus. The hydrogel swells on contact with moisture to occlude the lumen, thus holding the OTX-PV in place. Once OTX-TP swells to fill the canaliculus, it is contained in the canaliculus until the hydrogel is resorbed. OTX-TP contains conjugated fluorescein to serve as a visualization aid through the use of a blue light source and yellow filter to confirm product presence.

Placebo Vehicle Intracanalicular Depot

The PV consists of the same components as OTX-TP, except that it does not contain travoprost. The PV will be provided in the same packaging as OTX-TP to maintain masking for the clinical trial.

Method of Assigning Subjects to Treatment Groups

Prior to the initiation of the study, a treatment randomization scheme will be generated using a 3:2 ratio (Active Treatment to Placebo Control) approximately 330 subjects in the OTX-TP arm and 220 in the PV arm. The study will be supplemented with additional subjects for whom bilateral depot insertion is successful in order to ensure that at least 490 subjects who receive a depot bilaterally are followed through the 12 Week Visit for safety and efficacy.

Once it is determined that the subject continues to meet eligibility for the study at Baseline Visit 2, the subject will be randomized into the study through assigning the next sequential kit within the kits corresponding to the subjects previous ocular anti-hypertensive therapy category. Both eyes will be provided with the same assigned treatment, OTX-TP or PV. Randomization will be stratified by investigational site (i.e., one randomization schema per study site) and previous ocular anti-hypertensive therapy with three stratum levels below:

Stratum A: Subjects who were on prostaglandin treatment at the time of the Screening Visit and have shown an adequate IOP rise after a 6-week washout (interval from Screening to Baseline Visit 1 is 6 weeks).

Stratum B: Subjects who were treatment-naïve at Screening and have shown an adequate prostaglandin response after a 2-week Run-in period on prostaglandin treatment followed by a 6-week washout (interval from Screening to Baseline Visit 1 is 8 weeks).

Stratum C: Subjects who have recently exited from a prior ophthalmic investigational research study and have written approval from the Medical Monitor to be allowed to participate in the current study without additional exposure to prostaglandin.

A site may randomize up to a maximum of 55 subjects.

The randomization number will be an alpha-numeric code using the following scheme: RnnX-*nnn* with R in the first place followed by the 2-digit site ID and one letter X corresponding to the stratum (A, B or C). Then a hyphen will separate the first alpha-numeric section and be followed by a three-digit number increasing in sequential order within each site and starting with 001.

Masking and Unmasking

The Investigator and the subject will be masked to the treatment assignment throughout the duration of therapy. The sponsor and study team (with the exception of the Investigators/investigative site staff) will be unmasked at the time of the interim analysis (i.e., the final analysis of the primary endpoint).

OTX-TP and the PV are identical in appearance, and will be supplied in identical packages so they cannot be distinguished by the user. If it is medically necessary to identify the product used, the Investigator will contact the Sponsor with the details of the emergency unmasking request. Ocular Therapeutix will make the final determination if the unmasking request will be granted. If granted, the Investigator will be permitted to use the unmasking instructions available on site.

6. Sample Size and Power Considerations

Assuming a common standard deviation of 3.75 mmHg within a treatment group, a mean difference of 1.5 mmHg or greater between treatment groups at each of the 3 time points of each of the 3 visits, and a 3:2 randomization ratio, 294 subjects in the OTX-TP arm and 196 subjects in the PV arm yield > 90% power to conclude superiority of OTX-TP to PV in mean IOP at all of the 9 time points using a 2-sided alpha = 0.05 and assuming independence among time points. The power increases with increasing positive correlation among time points.

To account for 10% of subjects discontinuing before the 12 Week Visit, approximately 330 subjects will be randomized into the OTX-TP arm and 220 subjects will be randomized into the PV arm.

7. Data Preparation

All reported study data will be recorded on eCRFs using the iMedNet electronic data capture (EDC) system. All authorized personnel will have access to the EDC system; however, only the site study personnel assigned to have the role of a Research Coordinator will have data entry user rights.

Ocular Therapeutix (OTX) is responsible for validating the OTX-16-002 study database, maintaining the study data, and cleaning and reviewing the data prior to database lock. OTX data management will prepare the edit check specifications document as well as the Business Logic Documents for review and approval. These documents are maintained in the trial master file. After data are entered into the clinical study database, electronic edit checks and data review will be performed. When the database has been declared to be complete, the following activities will take place to prepare for database lock:

- All clinical data are entered, source verified, and approved in the clinical database
- All discrepancies are resolved and applied to the database
- Dictionary coding (by SDC) is complete and Final AE Coding Approval Form is signed
- SAE reconciliation is complete
- Any DMP amendments are signed by the appropriate team members

Additionally, for the final database lock and analysis, all analyses outlined in this document will be carried out only after the following have occurred:

- Protocol deviations have been identified and status defined (major/important vs minor deviations)
- Analysis populations have been determined
- Randomized treatment codes have been unmasked

In the event that the database must be unlocked, unlocking procedures fall under OTX processes and operating procedures.

For the interim analysis, the database will not be locked but relevant enrollment, randomization demographics, baseline characteristics, protocol deviation, and efficacy eCRFs for IOP data will be marked as DM reviewed, ensuring the data are complete and clean with no outstanding queries. Datasets will be downloaded and exported using the *Datasets on Demand* functionality. At the time of interim and final analyses, OTX DM will communicate timing of the dataset downloads and release to Statistics & Data Corporation (SDC).

8. Analysis Populations

Subjects will be considered enrolled once they have signed informed consent. Once randomized and treated, subjects will fall into at least one of the following analysis populations.

Full Analysis Set

The Full Analysis Set (FAS) population will include all randomized subjects with depots inserted in both eyes. Analysis on the data for the primary study eye in the FAS will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.

Per Protocol Population

The Per Protocol (PP) population will include all FAS subjects who do not deviate from the protocol in any way likely to seriously affect the efficacy outcomes of the study. Analysis on the PP population will be used as secondary efficacy analysis and will be performed for select efficacy endpoints, analyzing subjects under the treatment actually received. Important protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be identified

prior to the data cut-off date for the interim analysis. The primary efficacy analysis will be conducted using the PP population as a sensitivity analysis of the primary outcome.

Safety Population

The Safety population will include all subjects who received any investigational study treatment (OTX-TP or PV). Analyses performed on the Safety population will be according to the treatment the subjects actually received. All safety analyses will be based on the Safety population.

9. General Statistical Considerations

Unit of Analysis

The unit of analysis in this study will be the primary study eye for all efficacy summaries and any eye that received a depot for ocular safety summaries. The primary study eye will be defined as the study eligible eye with ocular hypertension or open angle glaucoma that meets the IOP enrollment criteria and has an intracanalicular depot successfully inserted. If a subject has both eyes eligible, then the primary study eye will be the eye with the highest IOP at 8AM on Baseline Visit 2 (Day 1) and the other eye will be considered to be the secondary study eye; if both eyes are eligible and have the same IOP at 8AM on Baseline Visit 2 (Day 1), the right eye will be the study eye and the left eye will be considered the secondary study eye. Ocular adverse events will be presented at the eye and subject level and non-ocular adverse events will be presented at the subject level.

Missing Data and Imputation Methods

The primary analyses of efficacy data (IOP) will employ multiple imputation (MI) methods using the Markov Chain Monte Carlo (MCMC) approach to impute missing data and using the last time-consistent observation carried forward (LOCF) to impute data for time points after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy.

Sensitivity analyses, to determine robustness of results, will be performed using the MCMC approach to impute non-monotone missing information and pattern mixture models control-based pattern imputation for monotone missing information (including data for subjects who drop out prior to the 12 Week Visit and data for time points after a subject's primary study eye is prescribed IOP-lowering drops), LOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops, baseline time-consistent observation carried forward (BOCF) to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops and using observed data only (excluding data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy). Additionally, sensitivity analyses will be performed on the PP population using observed data only (excluding data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy).

For time-consistent imputations, IOP values missing at an 8AM time point will only be imputed with the IOP value from a previous 8AM time point (last or baseline). Imputations at 10AM and 4PM will be performed similarly.

Definition of Baseline

For IOP, the baseline measure will be defined as the last non-missing time-consistent measure prior to initiation of investigational treatment and after washout of previous IOP medication. In most cases this will be the measure of IOP at Baseline Visit 2. For all other variables, baseline will be defined as the last non-missing measure prior to initiation of investigational treatment. Change from baseline will be calculated as follow-up visit – baseline visit.

Data Analysis Conventions

An interim analysis is planned after all subjects attend the 12 Week Visit. As this interim analysis will be the final analysis for efficacy:

- 1) All efficacy data will be cleaned and monitored prior to unmasking and conducting the interim analysis
- 2) Protocol deviations will be assigned major/minor status to determine the Per Protocol population prior to the data cutoff date for the interim
- 3) No alpha adjustments for multiplicity will be made

At this interim analysis, the study team with the exception of the Investigator/investigative site staff and the subjects will be unmasked.

All data analysis will be performed by SDC at the interim and after the study is completed and the database has been locked. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in RTF format for tables and PDF format for tables, listings, and figures using landscape orientation. All study data will be listed by subject, actual treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, standard deviations and medians will be presented to one additional decimal place than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between treatment groups will be calculated as OTX-TP minus PV and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence.

All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as “< 0.0001”; p-values greater than 0.9999 will be presented as “> 0.9999”.

All efficacy summaries will be presented for the primary study eye. Additional efficacy analyses will be reported for secondary study eyes. Ocular AEs will be summarized at the eye level for any treated eye and subject level, and non-ocular AEs by subject level. All other safety variables will be assessed by primary study eye and secondary study eye, separately.

Adjustments for Multiplicity

In order to maintain the overall Type I error for the primary analyses, all 9 time points must show statistical significance for the study to be successful: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits. No other adjustments for multiplicity are necessary as there are no other sources of multiplicity for the primary analyses.

Unscheduled Visits

For Unscheduled Visits, the reason for the visit should be clearly documented on the appropriate eCRF, including findings from all evaluations that are completed.

Data from unscheduled visits up to the 12 Week Visit will be integrated into subject listings and summary tables. If unscheduled data is available within window of a scheduled Visit with missing data, the unscheduled data will be used. If more than one set of unscheduled data falls within a window for an efficacy assessment, the earliest unscheduled visit in that visit window will be used. If more than one set of unscheduled data falls within a window for a safety assessment, the worst case observation will be used.

10. Disposition of Subjects

Subject disposition of all enrolled subjects will be presented in terms of the numbers and percentages of subjects who were screened, randomized, completed the study, discontinued from the study and /or experienced protocol deviations. Number of subjects exiting the study prior to Week 12, at Week 12, at Week 20 and beyond Week 20 will also be summarized. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects. Reasons for subject discontinuation at various decision time points will be summarized.

Subjects who are enrolled but determined to be ineligible during the screening assessment, Run-in visits, IOP confirmation visit, or baseline visits prior to randomization will be considered screen failures, will be withdrawn from the study, and will not require additional study follow-up visits but will be entered in the EDC system with the reason for screen failure delineated. The total number of screened subjects with the number and percentage of screen failure subjects will be presented. The reasons for screen failure will be displayed with the percentages calculated using total number of screen failures as the denominator.

The number of subjects in each of the analysis populations (FAS, PP and Safety) will be displayed by treatment and percentages will be calculated using randomized subjects as the denominator. A subject listing of analysis populations will be provided including reasons for exclusion from the PP and/or Safety populations. In addition, a subject listing of randomization, including randomization strata assignment, will be provided.

The number and percentage of subjects with major protocol deviations will be summarized by treatment group for all randomized subjects. The protocol deviations will be summarized by deviation codes.

A subject listing will be provided that includes the date of the deviation, the deviation description and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include informed consent date, and inclusion and exclusion criteria violations. Procedural exclusion criteria will be presented in the same listing as study inclusion and exclusion criteria.

11. Demographic and Pretreatment Variables

Demographic Variables

The demographic variables collected at Screening in this study include date of birth, sex, race, ethnicity, height, weight and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the FAS population

Age at informed consent (years), height, weight and BMI will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years. Age will be reported in years and calculated using the following formula:

$$\text{Age} = (\text{informed consent date} - \text{date of birth}) / 365.25 \text{ truncated as an integer}$$

BMI is calculated using the following formula:

$$\text{BMI (kg/m}^2\text{)} = (\text{Weight (lb)} / [\text{Height (in)} * \text{Height (in)}]) * 703 \text{ rounded to the nearest tenth.}$$

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity and iris color.

A subject listing that includes all demographic variables will be provided. Note that iris color will be reassessed at the 12 Week Visit and these results will be listed along with a flag indicating any changes from baseline.

Pretreatment Variables

Female subjects of child-bearing potential will have urine pregnancy test at the Screening Visit. A subject listing of child-bearing status and pregnancy test results will be provided.

Summary statistics will be provided for the baseline characteristic variables, which include mean IOP for both the primary study eye and the secondary study eye at screening (pre-washout) and at Baseline Visit 2, mean deviation in visual fields (dB), central corneal thickness (μm), and cup to disc ratio. Counts and frequencies for current diagnosis of OHT or OAG, and gonioscopy results (including the following categories: Grade 4 [45° to 35° angle wide open], Grade 3 [35° to 20° angle wide open], Grade 2 [20° angle narrow], Grade 1 [$\leq 10^\circ$ angle extremely narrow], and Slit [0° angle narrowed to slit] will also be provided.

A subject listing that includes all pretreatment variables will be provided.

Punctum Size Assessment Prior to Insertion

Punctum size will also be assessed prior to insertion of the depot. At the 4PM time point on Baseline Visit 2 the Investigator will use a standard punctum gauge to assess the size of the punctum. If the punctum measures < 0.4 mm or > 0.9 mm, the subject will be screen failed and will not be randomized. The Investigator will utilize a commercially available dilator probe from standard practice or as provided by Sponsor to dilate the punctum to 0.7 mm, as required for proper insertion of the intracanalicular depot. If the Investigator determines that the punctum cannot be dilated to approximately 0.7 mm, the subject will be screen failed and will not be randomized. If the subject remains eligible for the study, the Investigator will randomize the subject and insert OTX-TP or PV into the superior or inferior canaliculus of the subject's eyes. Punctum size, both prior to and after dilation, will be recorded and provided in a subject listing.

12. Medical History and Concomitant Medications

Medical History

Medical history will be collected at the Screening Visit and coded using MedDRA 20.0.

Non-ocular and ocular medical history will be summarized for the Safety Population using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the FAS. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

Listings of medical history will be generated separately for ocular and non-ocular data.

Concomitant Medications

Starting at the Screening Visit through the end of the study, the use of any concurrent ophthalmic medications and systemic medications, prescription or over-the-counter, from up to 3 years prior to the Screening Visit, is to be recorded on the subject's source document form and corresponding electronic case report form along with the reason the medication was taken. The use of any herbal or vitamin

supplements and any dilation and other Standard of Care drops used for the ophthalmic assessments including IOP measurement and the insertion procedure will not be required to be recorded.

Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) March 2017 and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and preferred name (generic drug name).

Concomitant medications are defined as those medications listed as having been taken 1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or 2) at any time following the first administration of study drug.

Ocular and non-ocular concomitant medications will be summarized using the FAS. Medications will be tabulated for each treatment group using frequencies and percentages. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data. Additionally, a table summarizing the subset of IOP-lowering medications and a summary table of IOP-lowering medication by visit will be produced. IOP-lowering medications will be designated on the listing of ocular medications using the eCRF indication "Lack of IOP control".

13. Dosing Compliance and Treatment Exposure

Dosing compliance and treatment exposure will be assessed using visualization of the intracanalicular depot by the investigator, intracanalicular depot removal and the number of intracanalicular depots required in each eye for the 12 week period per subject. These analyses will be performed on the Safety Population. No statistical inference testing will be performed.

Intracanalicular Depot Visualization by the Investigator

The intracanalicular depot will be assessed for presence and ease of visualization at the time of insertion time point as well as the 8AM time point at each post-baseline visit. The number of subjects with a intracanalicular depot present will be summarized by visit and treatment, and this number will be used as the denominator for the ease of visualization responses. Ease of visualization will be recorded as Easy, Moderate, or Difficult by the investigator. Responses will be summarized by count and percentage at each visit by treatment group. A subject listing, reported separately by primary and secondary study eyes, will also be provided.

Intracanalicular Depot Removal

When an intracanalicular depot is removed the reason for removal (removed per protocol, AE, other), the success of the removal (yes vs no), the ease of removal (easy, moderate, difficult) and the method of removal (saline irrigation, application of manual pressure) will be recorded. The responses will be

summarized by count and percentage at each visit by treatment group. A subject listing, reported separately by primary and secondary study eyes, will also be provided.

Number of Replacements

The number of intracanalicular depots required in each eye for the 12 week period per subject will be reported and listed. For subjects with confirmed depots beyond 12 weeks, summaries will also be provided indicating the length of the depot being present in the canaliculus and the number of depots required and the number of patency checks performed.

Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

$$\text{Total Exposure (days)} = (\text{Date of last investigator visualization of a depot in either eye [that is not subsequently replaced]} - \text{Date of first insertion of a depot in either eye}) + 1$$

Date of first insertion of depot in either eye will in most cases be Baseline Visit 2 [Day 1]. Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

$$\text{Total Exposure (days)} = (\text{Date of last recorded visit} - \text{Date of first insertion of a depot in either eye}) + 1$$

Total treatment exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group and for all subjects, using the Safety population. A subject listing of treatment exposure will also be produced.

14. Efficacy Analyses

Primary Analysis

The primary analysis of the primary efficacy outcome will employ a linear model of IOP in the primary study eye of subjects in the FAS. The response variable will be IOP at the given visit (2 Week, 6 Week, and 12 Week) and time point (8AM, 10AM, and 4PM), time point specific baseline IOP will be used as a covariate, and treatment will be the main effect factor. Each time point within each visit will be modeled separately.

IOP refers to the single result from the following procedure. IOP will be assessed by two qualified independent study site personnel at each visit and time point using a Goldmann applanation tonometer affixed to a slit lamp with the subject seated. Two measurements should be performed, and if the IOP is within 1 mm Hg, the average of the first two measurements should be recorded. If the IOP from the first two readings shows a greater than 1 mm Hg difference, a third reading should be taken and the average of all three readings recorded. Averages of readings are calculated within the clinical database.

For the primary analysis, MI methods will use the MCMC approach for any data missing from these visits/time points, after LOCF has been used to impute data for time points after the subject's primary study eye is prescribed IOP-lowering drops. Example MCMC imputation code which will be implemented after IOP after LOCF has been applied (SAS version 9.4) is shown here:

```
PROC MI DATA = indata SEED = 7436892 OUT = outdata NIMPUTE=20;
  BY TMPTN;
  MCMC INITIAL = EM;
  VAR trt baseline WV2 WV4 WV6 WV8 WV10 WV12;
  RUN;
```

where

- *indata* is the name of the input dataset;
- *outdata* is the name of the output dataset;
- *nimpute* is the number of imputations;
- *tmptn* is the time point of assessment, 8AM, 10AM, or 4PM;
- *trt* is the name of the treatment group variable in numeric format;
- *baseline* is the average IOP at baseline for the *ith* time point
- *WV2* is the IOP value for the 2 Week visit;
- *WV4* is the IOP value for the 4 Week visit;
- *WV6* is the IOP value for the 6 Week visit;
- *WV8* is the IOP value for the 8 Week visit;
- *WV10* is the IOP value for the 10 Week visit;
- *WV12* is the IOP value for the 12 Week visit.

Twenty complete data sets for each time point will be generated from the above code. The data will be transposed to have a vertical structure with one record per subject, imputation, visit, and time point. Each complete data set will be used to compute the mean IOP and analyze using the linear model with time point specific baseline IOP used as a covariate, and treatment as the main effect factor. Then, the SAS procedure MIANALYZE will be used to analyze the results from the 20 complete data sets to generate a combined inference. The following SAS code will be used:

```
ODS OUTPUT LSMEANS = outdataB;
PROC MIXED DATA = outdataA;
  CLASS trt;
  MODEL IOP=trt baseline;
  BY visitn tmptn _IMPUTATION_;
  LSMEANS trt/PDIFF CL;
  RUN;
```


where

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmptn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *outdataA* is the transposed dataset containing the 20 “complete” datasets from the imputation.

```

ODS OUTPUT PARAMETERESTIMATES = outdataC;
PROC MIANALYZE DATA = outdataB;
MODELEFFECTS ESTIMATE;
STDERR;
BY visitn tmptn;
RUN;

```

where

- *outdataB* is the name of the output dataset that contains the statistical results of the difference between treatment groups from the MIXED procedure that is run on each of the twenty imputation datasets;
- *outdataC* is the name of the output dataset that contains all the information needed for the table.

After imputation the least squares mean differences (OTX-TP minus PV) will be presented along with 2-sided 95% confidence intervals (CIs) around the difference and 2-sided p-values testing the difference equal to 0. Inference will be made on the 2-sided p-value at a 2-sided alpha = 0.05 at each time point and visit. The study will be considered a success if the 2-sided p-value < 0.05 (demonstrating statistical superiority) and the point estimate of the difference is < 0 at all time points over the three visits.

Two-sample t-test p-values and two-sided 95% CI's will also be computed around the difference (OTX-TP minus PV) in IOP between treatment groups at each time point and visit for the primary analysis data (FAS employing MI methods using MCMC approach to impute missing data and using LOCF to impute data for time points after a subject's study eye is prescribed IOP-lowering drops as rescue therapy). The following SAS code will be used for the t-test:

```

ODS OUTPUT STATISTICS = outdataB;
PROC TTEST DATA = outdataA;
CLASS trt;
VAR IOP;
BY visitn tmptn _Imputation_;

```

RUN;

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmpn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *outdataA* is the transposed dataset containing the 20 “complete” datasets from the imputation.

Then, as with the PROC MIXED results, the SAS procedure MIANALYZE will be used to analyze the results from the 20 complete data sets to generate a combined inference.

```
ODS OUTPUT PARAMETERESTIMATES = outdataC;
PROC MIANALYZE DATA = outdataB;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
BY visitn tmpn;
RUN;
```

where

- *outdataB* is the name of the output dataset that contains the statistical results of the difference between treatment groups from the MIXED procedure that is run on each of the twenty imputation datasets;
- *outdataC* is the name of the output dataset that contains all the information needed for the table.

Sensitivity analyses for the primary efficacy endpoint include both linear models of IOP and 2-sample t-tests presented on the FAS population using (1) MI approach using MCMC to impute non-monotone missing information and a pattern mixture model control-based pattern imputation for monotone missing information to impute both missing data and data after a subject’s primary study eye is prescribed IOP-lowering drops as rescue therapy, (2) using LOCF to impute both missing data and data after a subject’s primary study eye is prescribed IOP-lowering drops as rescue therapy, (3) using BOCF to impute both missing data and data after a subject’s primary study eye is prescribed IOP-lowering drops as rescue therapy, and these analyses using observed data only (excluding data after a primary study eye is prescribed rescue therapy) for the (4) FAS and (5) per protocol populations.

For multiple imputations using a control-based pattern-mixture model, a process will be used that is similar to multiple imputations using MCMC. Twenty “complete” (imputed) datasets will be produced and analyzed. Results from the analyses on the twenty “complete” datasets will be combined for presentation through the use of SAS PROC MIANALYZE. Time point specific baseline IOP will be used as a covariate, and treatment will be the main effect factor. A separate model will be fit for each visit/time point combination. Monotone missing information refers to data missing from any visits beyond a

subject's final visit (at which IOP is assessed) up to and including the 12 Week Visit. Non-monotone missing information refers to data from missed visits between any two visits at which IOP is assessed. First LOCF will be used to impute data for time points after a subject's primary study eye is prescribed IOP-lowering drops. Then MCMC will be employed to impute any non-monotone missing information using the code:

```
PROC MI DATA = indata SEED = 3335891 OUT = mondata NIMPUTE=1;
BY TMPTN;
MCMC INITIAL = EM IMPUTE = MONOTONE;
VAR trt baseline WV2 WV4 WV6 WV8 WV10 WV12;
RUN;
```

where

- *indata_i* is the name of the input dataset for the *i*th time point (*i* in {8, 10, 4} for 2, 6 and 12 Week visits, *i* = 8 for 4,8 and 10 Week visits);
- *mondata_i* is the name of the output dataset for the *i*th time point;
- *nimpute* is the number of imputations;
- *trt* is the name of the treatment group variable in numeric format;
- *baseline* is the average IOP at baseline for the *i*th time point
- *WV2* is the IOP value for the 2 Week visit;
- *WV4* is the IOP value for the 4 Week visit;
- *WV6* is the IOP value for the 6 Week visit;
- *WV8* is the IOP value for the 8 Week visit;
- *WV10* is the IOP value for the 10 Week visit;
- *WV12* is the IOP value for the 12 Week visit.

Then the following SAS code will be used to produce twenty "complete" datasets for each time point, imputing monotone missing data using a control-based pattern mixture model:

```
PROC MI DATA = mondatai SEED = 48670 NIMPUTE = 20 OUT = outdatai
MINIMUM = . . 0 MAXIMUM = . . 70 ROUND = . . 0.25;
BY visitn tmpn;
CLASS trt;
MONOTONE REG(WV2_8 WV4_8 WV6_8 WV8_8 WV10_8 WV12_8 = baseline /
details);
MNAR model(WV2_8 WV4_8 WV6_8 WV8_8 WV10_8 WV12_8/ MODELOBS =
(TREATMENT="2"));
VAR trt baseline WV2_8 WV4_8 WV6_8 WV8_8 WV10_8 WV12_8;
RUN;
```

After obtaining twenty complete datasets, the data from the two MI procedures will be combined and will then be transposed to have a vertical structure with one record per subject, imputation, visit, and time point. SAS code similar to what is previously described for multiple imputations in the primary analysis will then be employed to run the model on each dataset and combine results across imputations.

In the case that there is no missing data for a given visit and time point, observed data will be analyzed. Analyses on observed data and without MI methods will use the following statistical models:

```
ODS OUTPUT LSMEANS = outdata;
PROC MIXED DATA = indata;
CLASS trt;
MODEL IOP=trt baseline;
BY visitn tmpn;
LSMEANS trt/PDIFF CL;
RUN;
```

where

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmpn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *indata* is the dataset containing only observed data.

and

```
ODS OUTPUT STATISTICS = outdata;
PROC TTEST DATA = indata;
CLASS trt;
VAR IOP;
BY visitn tmpn;
RUN;
```

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmpn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *indata* is the dataset containing only observed data.

Secondary Analysis

Mean change from baseline IOP and mean percent change from baseline IOP will be analyzed similarly to the primary endpoint analysis, including all sensitivity analyses. As described above, these analyses involve linear models of the response variables on the FAS population using various combinations of imputation methods [(a) MCMC for missing data, LOCF for timepoints after rescue therapy has been initiated; (b) MCMC for non-monotone missing, pattern mixture models for monotone missing; (c) LOCF for both missing and “rescue” time points; and (d) BOCF for both missing and “rescue” time points] as well as inference on observed data confined to the FAS and Per Protocol populations.

Additional Analyses

14.1.1 ADDITIONAL EFFICACY ANALYSES

IOP measures, mean change from baseline, and mean percent change from baseline IOP measures from non-primary visits (4 Week, 8 Week, 10 Week Visits) will be also analyzed similarly to the primary endpoint analysis.

Additionally, to further understand efficacy within each previous ocular anti-hypertensive therapy category, the primary analysis strategy (linear model of IOP Markov Chain Monte Carlo (MCMC) approach to impute missing data and using the last time-consistent observation carried forward (LOCF) to impute data for time points after a subject’s primary study eye is prescribed IOP-lowering drops as rescue therapy) will be completed separately for the subgroups (i.e. stratum) of subjects within each previous ocular anti-hypertensive therapy category. The FAS will be used for these subgroup analyses.

All analyses will be presented in summary tables by treatment group. Subject level listings will also show IOP by treatment, time point and visit where appropriate.

14.1.2 PUNCTUM EXAMINATION

At Screening, prior to insertion at Baseline Visit 2, and at the 8AM time point of each subsequent post-baseline visit investigators will assess punctal appearance, lid apposition, tear meniscus recording results as normal, abnormal NCS or abnormal CS for each eye. The responses will be summarized by count and percentage at each visit by treatment group and for all subjects. Shifts from Baseline to the evaluation visit will also be presented as frequencies and percentages. A subject listing, reported separately by primary and secondary study eyes, will also be provided.

14.1.3 INSERTION RESULTS AND EASE OF INSERTION

The results of insertion will be summarized for insertion location (superior vs inferior punctum), success of insertion (yes vs no), ease of insertion (easy, moderate, difficult), the number of packages opened, number of depots used to attempt insertion in each eye and the reason(s) depots were not utilized (swelling of depot prior to insertion, depot not present in foam package, depot dropped prior to insertion, failed insertion in initial punctum, or other). Product malfunctions during the insertion will also be

recorded. Summaries based on the Safety Population will be presented for Baseline Visit 2 and any Replacement or Re-insertion visits, and Replacement/Re-insertion visits within the initial 12 Week period by treatment group and overall. Summaries will be separated by primary and secondary study eyes. A subject listing, reported separately by primary and secondary study eyes, will also be provided.

14.1.4 OCULAR COMPLAINTS

In order to assess tolerability, ocular complaints are evaluated after insertion at Baseline Visit 2, and at the 8AM time point of each subsequent post-baseline visit. Complaint categories include Excessive Tearing, Foreign Body Sensation, Itching, Stinging/Burning, and Other Ocular Complaints. Within each category, a subject is required to answer yes or no as to whether the issue occurred, and the investigator responds as to whether or not the issue was within clinical expectations as well as whether or not any action was taken.

Counts and percentages of study eyes and subjects experiencing each complaint category will be summarized by visit and treatment group using the number of assessments performed within each treatment group as the denominator. For expectedness and actions, counts and frequencies of yes and no responses will also be summarized, using the number of subjects having the complaint category as the denominator. Summaries at the study eye level will be split up by primary and secondary study eyes. For subject level summaries, the worse result between the two eyes will be summarized (ie, a response of yes to the ocular complaint). A subject listing, reported separately by primary and secondary study eyes, will also be provided.

Graphical Outputs

In addition to the tabular output, graphs will be provided of the mean (averaged over subjects) and standard error of IOP values for the primary study eye and changes from baseline values by treatment, visit and time point in the FAS with imputed data per the primary endpoint imputation strategy. In addition, figures will be created showing the difference between OTX-TP and PV mean IOP values along with their 95% CIs for each visit and time point using the FAS with imputed data per the primary endpoint imputation strategy and for observed data. Reference lines will be included at ± 1 mmHg and ± 1.5 mmHg. Figures using observed data for the PP population will also be presented.

15. Safety Analyses

Ocular and Non-Ocular Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. If adverse events occur, the first concern will be the safety and welfare of the subject. Appropriate medical intervention will be undertaken. Any adverse events observed by the Investigator or reported by the subjects, whether or not ascribed to the study treatment, will be recorded on the subject's Adverse Event Case Report Form.

Documentation regarding the adverse event will be made as to the nature, date of onset, end date, severity, and relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning. All AEs will be coded using the MedDRA version 16.1.

AEs will be reported from the point subjects sign informed consent. The AE and treatment emergent adverse event (TEAE) reporting period ends upon study exit for new AEs. Existing AEs and TEAEs will be followed until:

- Resolution (return to baseline status or to 'normal')
 - AEs may be determined to have resolved (completely) or resolved with sequelae.
- Principal Investigator determines, for events that do not end (i.e., metastasis), the condition to be chronic. The event can be determined to be resolved or resolved with sequelae.
- Stabilization of the event has occurred (no worsening expected by the investigator)

Adverse Event (or Adverse Experience, AE)

An AE is any untoward medical occurrence, which does not necessarily have to have a causal relationship with the treatment.

Adverse Ocular Event

An adverse ocular event is an AE that affects ocular tissues, the nasolacrimal duct, sinuses or vision. All adverse ocular events are a subset of adverse events.

Note: Subjects will be queried for the presence or absence of the following ocular complaints: excessive tearing, foreign body sensation, stinging/burning, and itching. Positive responses to these standardized ocular complaint inquiries should be reported as ocular complaints and not adverse ocular events unless the complaint: meets the criteria of a specific event as listed, and/or is: outside of normal limits, associated with clinical sequelae (e.g., adverse slit lamp examination findings), and requires an intervention to be resolved.

Treatment Emergent Adverse Ocular Event (or TEAOE)

An adverse ocular event will be considered a treatment emergent AE if it occurs or worsens (based on severity: mild, moderate or severe) on or after the initiation of the intracanalicular depot insertion.

Treatment Emergent Adverse Event (or TEAE)

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the initiation of the intracanalicular depot insertion, whether ocular or non-ocular in nature. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

Adverse Reaction (or Related Adverse Event or Adverse Effect)

An adverse reaction is any noxious and unintended response to the treatment.

Unexpected Adverse Reaction (Unanticipated Adverse Effect)

An unexpected adverse reaction is an adverse reaction, the nature (including specificity and outcome) or severity of which is not consistent with the applicable product information. For this study, the study protocol; Investigator's Brochure; and prescribing information for the registered formulation of travoprost (Travatan®) will be used to assess events for unexpectedness.

Anticipated (as specified in the protocol) adverse ocular events that may be associated with OTX-TP or PV include, but are not necessarily limited to:

- Ocular hyperemia should be considered as an AE only if the subject complains of it or if the subject is discontinued because of ocular hyperemia
- Prostaglandin Associated Orbitopathy
- Iris discoloration
- Blepharitis
- Worsening in BCVA defined as ≥ 3 lines (≥ 15 letters)
- Subconjunctival hemorrhage
- Cataract
- Macular edema
- Conjunctivitis
- Keratitis
- Perforation of or trauma to the punctum and/or surrounding tissues
- Allergic reaction
- Chemosis
- Inflammatory reaction
- Epiphora, defined as clinically significant excessive tearing outside of normal limits
- Dacryocystitis
- Tearing with mucopurulent discharge
- Stenosis of the punctum
- Infection*

*Note: In the unlikely event of infection, the organism will be identified.

Serious Adverse Event (Serious Adverse Experience)

A serious adverse event (SAE) (experience) or reaction is any untoward medical occurrence that:

- results in death

- is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the subject 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.)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is sight threatening

Medical and scientific judgment will be exercised in deciding whether expedited 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- Mild: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject’s daily activities.
- Moderate: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject’s daily activities.
- Severe: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject’s daily activities.¹

¹The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations. (Severity of all adverse events, ocular and non-ocular, will be reported according to the terminology defined in the protocol.)

Relationship to OTX-TP or PV

The following table will be used by the investigator as a guide when assessing the causal relationship of an AE to the intracanalicular depot and the insertion procedure.

NO RELATIONSHIP SUSPECTED	This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
---------------------------	--

RELATIONSHIP SUSPECTED	<p>The following criteria should be applied in considering inclusion of an AE in this category:</p> <ol style="list-style-type: none"> 1) It bears a reasonable temporal relationship to the insertion procedure or the presence of the intracanalicular depot. 2) It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. 3) It disappears or decreases on removal of the intracanalicular depot.
UNABLE TO DETERMINE*	<p>The Investigator is unable to assess the relationship of the event to the insertion procedure or the intracanalicular depot.</p>
<p>*Where the causal relationship of the AE to the insertion procedure or the intracanalicular depot has not been determined or is unknown, the AE will be treated as if a relationship is suspected for the purposes of regulatory reporting.</p>	

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the study drug caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and the AE. Types of evidence that would suggest a causal relationship between the study drug and the adverse event include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure; one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. For TEAEs not suspected to be related to study product, a most likely cause will be selected from the following categories: Concomitant Medication(s), Pre-existing Condition(s), Insertion Process, Other.

Expected AEs

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- Unexpected: An AE or adverse reaction that is not listed in the study protocol, Investigator’s brochure, or prescribing information for the registered formulation of travoprost (Travatan®) or is not listed at the specificity or severity that has been observed.
- Expected: An AE that is listed in the Investigator’s brochure at the specificity and severity that has been observed.

AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

The Investigator should initially classify the expectedness of an adverse event, but the final classification is subject to the Medical Monitor's determination.

AE Summaries

All AEs and TEAEs will be coded using MedDRA 20.0. AEs will be summarized in listings and tables for overall and ocular TEAEs by treatment group.

An overall summary will be presented that includes the number of AEs, TEAEs and the number and percentage of subjects who experienced at least one AE or TEAE, by treatment group and for all subjects. This summary will also include breakdowns of TEAEs further categorized as ocular (primary study eye and secondary study eye separately) or non-ocular, serious AEs (SAEs), ocular TEAEs by maximum severity, non-ocular TEAEs by maximum severity, related TEAEs, TEAEs leading to early discontinuation, and deaths.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE and will be presented by SOC and PT. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject level for both eyes and for primary study and secondary study eyes separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries will be provided for the following categories of AEs:

- Ocular TEAEs in the primary study eye
- Ocular TEAEs in the secondary study eye
- Non-ocular TEAEs
- Expected TEAEs
- Unexpected TEAEs
- Treatment related ocular TEAEs
- Treatment related non-ocular TEAEs
- Serious AEs
- TEAEs by Maximum Severity
- Non-related TEAEs by Most Likely Cause

- Non-related SAEs by Most Likely Cause

All TEAEs, SAEs and TEAEs leading to early discontinuation will be presented in subject listing separately for ocular and non-ocular events.

Best Corrected Visual Acuity (BCVA)

The logarithm of the minimum angle of resolution (logMAR) visual acuity is assessed at each visit using an EDTRS chart at a viewing distance of 4 meters. BCVA will be measured without refraction using a pinhole or while the subject is wearing his/her glasses, if the subject normally wears glasses or contact lenses. Subjects are required to read the chart from the top to the bottom until 2 letters are misread on the line. The visual score is to be calculated based on an assigned value of 0.02 logMAR per letter. If visual acuity is so poor that the subject cannot read any of the largest letters at 4 meters, then acuity is to be measured at 2 meters and the appropriate conversions made.

If visual acuity is so poor that the subject cannot read any of the largest letters at 2 meters, the subject should be checked for the ability to count fingers or see hand motion or light perception as appropriate.

BCVA will be measured at screening, at 8AM on Baseline Visit 2 and as well as the 8AM time point at each post-baseline visit. The baseline measurement will be the last assessment prior to insertion of the depot.

The observed and change from baseline BCVA will be summarized for the primary study eye and secondary study eye using continuous descriptive statistics by visit for each treatment group and for all actively treated subjects. Additionally, discrete summaries of the worst change from baseline will be presented for both the primary study eye and the secondary study eye with the following groupings based on the logMAR scores: 0 or less, >0 to +0.09, +0.10 to +0.19, +0.20 to 0.29, +0.30 or more.

Visual acuity scores will also be presented in data listings. Subjects who lost three or more lines (equivalent to change from baseline of 0.30 logMAR or more) will be presented in an additional listing. This additional listing will also include subjects for whom vision worsened to the extent that the subject's vision is measured by finger count, hand motion or light perception.

Slit Lamp Biomicroscopy Examination

A slit lamp biomicroscopy examination of the eyelid, conjunctiva, iris, cornea, anterior chamber, lens, and vitreous will be performed at each visit (except the Run-in Visits for Stratum B subjects) at the 8AM time point. The results will be graded as normal, abnormal NCS or abnormal CS.

The results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye (primary study eye and secondary study eye). Percentages will be based on the number of subjects in each treatment group with responses. Shift

tables for the slit lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline. A subject listing of the slit lamp biomicroscopy parameters will also be produced.

Dilated Fundoscopy Examination

A dilated funduscopy examination of the macula, peripheral retina, and optic nerve will be performed at Screening, and the 12 Week Visit. The results will be graded as normal, abnormal NCS or abnormal CS. The cup to disc (C/D) ratio will also be measured. Explanation/comment should be provided on the case report form for any abnormal findings.

The results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye (primary study eye and secondary study eye). Percentages will be based on the number of subjects in each treatment group with responses. For the cup to disc ratio, a continuous summary, including change from baseline, will be provided for each eye. Shift tables for the dilated funduscopy parameters will also be provided comparing the 12 Week Visit results for each subject to the Screening results. A subject listing of the dilated funduscopy parameters (including C/D ratio) will also be produced.

Ocular Hyperemia

Ocular hyperemia will be graded every visit at 8AM (except the 1st baseline measurement, Visit 1) on the following scale: 0 (None), 1 (Mild), 2 (Moderate), 3 (Severe), and 0.5 increments may be used if the subject's hyperemia is between two grades. Frequencies and percentages will be summarized for each visit and treatment group. Shifts from baseline to post-baseline visits will be summarized categorically as ≤ 0 (no change or decrease), +0.5, +1, +1.5, +2, +2.5, +3.

A subject listing of ocular hyperemia will also be produced.

Ocular Comfort Assessment

The subject comfort level will be assessed prior to insertion of the OTX-TP or PV, and again at each post-baseline visit. Subjects will be asked to grade their comfort level by asking them the following question:

“On a scale of 0 to 10, 0 being very comfortable and 10 being very uncomfortable, how comfortable does your eye feel?”

Descriptive summary statistics of the comfort scores will be presented for each day which the question is asked. Changes from baseline will also be calculated and summarized alongside the observed values. Subject comfort scores will be listed, along with the Investigator's response to the expectedness of the score and any action taken to alleviate discomfort.

Observed IOP Results

A summary and listing of observed IOP data with no imputation, based on the Safety Population, will also be provided.

16. Interim Analyses

An interim analysis is planned after all subjects attend the 12 Week Visit. As this interim analysis will be the final analysis for efficacy:

- 1) All efficacy data will be cleaned and monitored prior to unmasking and conducting the interim analysis
- 2) Protocol deviations will be assigned major/minor status to determine the Per Protocol population prior to the data cutoff date for the interim

At this interim analysis, the study team will be unmasked and the Investigator/investigative site staff and the subjects will remain masked.

Once all subjects have completed the study (all intracanalicular depot removed or absence confirmed) the final safety data summaries will be created.

17. Pharmacokinetic Analyses

No pharmacokinetic data will be collected for this study.

18. Pharmacodynamic Analyses

No pharmacodynamic data will be collected for this study.

19. Quality of Life

No Quality of Life data will be collected for this study.

20. Changes from Protocol-Stated Analyses

This SAP differs from the protocol-stated analysis in three respects:

- (1) The statement, “Intent-to-Treat (ITT): The ITT population will include all randomized subjects with a primary study eye in which an intracanalicular depot was inserted. Analysis on the ITT population will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized” in the protocol has been changed to “The Full Analysis Set (FAS) will include all randomized subjects with depots inserted in both eyes. Analysis on the data for the primary study eye in the FAS will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.
- (2) No subject visualization of depots are required.
- (3) The protocol (5.6) states, “At the conclusion of the 12 Week visit, if both eyes no longer have the depot present or depots have been removed bilaterally, the Investigator may be unmasked to the treatment assignment of the subjects who were assigned to OTX-TP or PV as those subjects may require IOP-lowering drops.” Due to the logistics involved and the potential for bias, the sponsor has determined that investigators and investigative site staff will not be unmasked until the end of the study.

Any changes to the planned analyses after the interim analysis and unblinding will be described in the clinical study report.

21. References

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)

22. Revision History

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

23. Tables

Tables that will be included in the topline delivery are shown in boldface font. Tables that will be included in the interim analysis are shown in italicized font.

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Table 14.1.3	Demographic and Baseline Characteristics	Full Analysis Set
<i>Table 14.1.4</i>	<i>Baseline Disease Characteristics</i>	<i>Full Analysis Set</i>
Table 14.1.5.1	Non-Ocular Medical History	Safety Population
Table 14.1.5.2	Ocular Medical History	Safety Population
Table 14.1.6.1	Non-Ocular Concomitant Medications	Safety Population
Table 14.1.6.2	Ocular Concomitant Medications	Safety Population
<i>Table 14.1.6.3</i>	<i>IOP-Lowering Ocular Medications</i>	<i>Safety Population</i>
<i>Table 14.1.6.4</i>	<i>Rescue Medication Use (IOP-Lowering Drops) by Visit</i>	<i>Full Analysis Set</i>
Table 14.2.1.1	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point MCMC Analysis – Primary Time Points	Full Analysis Set
<i>Table 14.2.1.2</i>	<i>Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point MCMC Analysis – Non-Primary Time Points</i>	<i>Full Analysis Set</i>
<i>Table 14.2.1.3</i>	<i>Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point Pattern Mixture Analysis</i>	<i>Full Analysis Set</i>
<i>Table 14.2.1.4</i>	<i>Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point LOCF Analysis</i>	<i>Full Analysis Set</i>
<i>Table 14.2.1.5</i>	<i>Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point BOCF Analysis</i>	<i>Full Analysis Set</i>
<i>Table 14.2.1.6</i>	<i>Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point Observed Data Analysis</i>	<i>Full Analysis Set</i>

Table Number	Title	Population
Table 14.2.1.7	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point Observed Data Analysis	Per Protocol Population
Table 14.2.1.8	Mean Observed, Change, and Percent Change from Baseline in Secondary Study Eye IOP by Time Point Observed Data Analysis	Full Analysis Set
Table 14.2.1.9	Mean Observed, Change, and Percent Change from Baseline in Secondary Study Eye IOP by Time Point Observed Data Analysis	Per Protocol Population
Table 14.2.2.1	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point and Strata MCMC Analysis	Full Analysis Set
Table 14.2.4.1	Insertion Results and Ease of Insertion	Safety Population
Table 14.2.4.2	Summary of Replacements	Safety Population
Table 14.2.4.3	Removal of Intracanalicular Depot	Safety Population
Table 14.2.5	Ocular Complaints by Study Eye	Safety Population
Table 14.2.6	Investigator Visualization of Intracanalicular Depot and Patency Check (Post Insertion Visit)	Safety Population
Table 14.2.7	Punctum Examination Results	Safety Population
Table 14.3.1	Study Treatment Exposure	Safety Population
Table 14.3.2.1	Overall Summary of Adverse Events	Safety Population
Table 14.3.2.2.1	Non-Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.2	Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.3	Primary Study Eye Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.4	Secondary Study Eye Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
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Table 14.3.2.2.6	Treatment Related Non-Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.7	Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.8	Treatment Emergent Adverse Events Leading to Subject Withdrawal by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
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Table 14.3.4.2	Shifts from Baseline in Slit Lamp Biomicroscopy by Visit and Eye	Safety Population
Table 14.3.5.1	Dilated Fundoscopy Examination by Visit and Eye	Safety Population
Table 14.3.5.2	Shifts from Screening to 12 Week Visit in Dilated Fundoscopy Examination by Visit and Eye	Safety Population

Table Number	Title	Population
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24. Listings

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Listing 16.2.1	Subject Disposition	All Enrolled Subjects
Listing 16.2.2.1	Protocol Deviations	All Randomized Subjects
<i>Listing 16.2.2.2</i>	<i>Inclusion, Exclusion, and Procedural Exclusion Criteria</i>	<i>All Enrolled Subjects</i>
<i>Listing 16.2.3</i>	<i>Subjects Excluded from the Per Protocol Population</i>	<i>All Randomized Subjects</i>
<i>Listing 16.2.4.1</i>	<i>Demographics</i>	<i>All Randomized Subjects</i>
<i>Listing 16.2.4.2</i>	<i>Baseline Characteristics: Study Condition, Gonioscopy, Punctum Size, Cup to Disc Ratio and Intraocular Pressure</i>	<i>Full Analysis Set</i>
<i>Listing 16.2.4.3</i>	<i>Pre-Treatment Perimetry</i>	<i>All Randomized Subjects</i>
<i>Listing 16.2.4.4</i>	<i>Pre-Treatment Pachymetry</i>	<i>All Randomized Subjects</i>
Listing 16.2.4.5	Non-Ocular Medical History	Safety Population
Listing 16.2.4.6	Ocular Medical History	Safety Population
Listing 16.2.4.7	Prior and Concomitant Non-Ocular Medications	Safety Population
Listing 16.2.4.8	Prior and Concomitant Ocular Medications	Safety Population
Listing 16.2.4.9	Pregnancy Test Results	Safety Population
<i>Listing 16.2.5.2</i>	<i>Insertion of Intracanalicular Depot</i>	<i>All Randomized Subjects</i>
Listing 16.2.5.3	Investigator Intracanalicular Depot Visualization and Patency Check	Safety Population
Listing 16.2.5.4	Removal of Intracanalicular Depot	Safety Population
<i>Listing 16.2.6.1</i>	<i>Intraocular Pressure</i>	<i>Full Analysis Set</i>
Listing 16.2.6.2	Ocular Complaints	Safety Population
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Listing 16.2.8.2	Serious Ocular Adverse Events	Safety Population
Listing 16.2.8.3	Ocular Adverse Events Leading to Subject Withdrawal	Safety Population
Listing 16.2.8.4	Non-Ocular Adverse Events	Safety Population
Listing 16.2.8.5	Serious Non-Ocular Adverse Events	Safety Population
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Listing 16.2.9.2	Visual Acuity (logMAR) for Subjects Who Lost Three or More Lines	Safety Population
Listing 16.2.9.3	Slit Lamp Biomicroscopy	Safety Population
Listing 16.2.9.4	Dilated Fundus Examination and Cup to Disc Ratio	Safety Population

Table Number	Title	Population
Listing 16.2.9.5	Punctum Examination Results	Safety Population
Listing 16.2.9.6	Punctum Size at Insertion	All Randomized Subjects
Listing 16.2.9.7	Slit Lamp Ocular Hyperemia and Ocular Comfort Assessment	Safety Population

25. Figures

All figures will be produced as final for the interim analysis.

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Figure 14.2.2	Mean Primary Study Eye IOP by Time Point and Treatment	Per Protocol Population
Figure 14.2.3	Mean Change from Baseline in Primary Study Eye IOP by Time Point and Treatment (MCMC)	Full Analysis Set
Figure 14.2.4	Mean Change from Baseline in Primary Study Eye IOP by Time Point and Treatment	Per Protocol Population
Figure 14.2.5	Mean Difference in Primary Study Eye IOP by Time Point (MCMC)	Full Analysis Set
Figure 14.2.6	Mean Difference in Primary Study Eye IOP by Time Point	Per Protocol Population
Figure 14.2.7	Mean Primary Study Eye IOP by Time Point and Treatment (Observed Data)	Full Analysis Set
Figure 14.2.8	Mean Change from Baseline in Primary Study Eye IOP by Time Point and Treatment (Observed Data)	Full Analysis Set
Figure 14.2.9	Mean Difference in Primary Study Eye IOP by Time Point (Observed Data)	Full Analysis Set

STATISTICAL ANALYSIS PLAN

A Prospective, Multicenter, Randomized, Parallel-Arm, Double Masked, Vehicle Controlled Phase 3a Study Evaluating the Safety and Efficacy of OTX-TP in the Treatment of Subjects with Open-Angle Glaucoma or Ocular Hypertension

Sponsor: Ocular Therapeutix, Inc
34 Crosby Drive, Suite 105
Bedford, MA 01730 USA

Protocol Number: OTX-16-002

Author: Elizabeth Kumm
Principal Biostatistician
Statistics & Data Corporation

Date: 27 February 2019

Version: Version 2.0

A Prospective, Multicenter, Randomized, Parallel-Arm, Double Masked, Vehicle Controlled Phase 3a Study Evaluating the Safety and Efficacy of OTX-TP in the Treatment of Subjects with Open-Angle Glaucoma or Ocular Hypertension

Protocol Number: OTX-16-002
Version: Version 2.0
Date: 27 February 2019

Statistical Analysis Plan Approval

Prepared by: Elizabeth Kumm 27 Feb 2019
Elizabeth Kumm
Principal Biostatistician
Statistics & Data Corporation

Reviewed by: Kirk Bateman 27 FEB 2019
Kirk Bateman
Date
Director, Biostatistics
Statistics & Data Corporation

Approved by: Swati Sane 27 Feb 2019
Swati Sane
Date
Director, Data Management and Biostatistics
Ocular Therapeutix, Inc.

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best Corrected Visual Acuity
BOCF	Baseline Time-Consistent Observation Carried Forward
CI	Confidence intervals
C/D	Cup to Disc
CS	Clinically Significant
CSR	Clinical Study Report
dB	Decibel
DMP	Data Management Plan
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCS	Not Clinically Significant
OTX	Ocular Therapeutix, Inc
OTX-TP	Sustained Release Travoprost Intracanalicular Depot
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
PV	Placebo Vehicle Intracanalicular Depot
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO DDE	World Health Organization Drug Dictionary Enhanced

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol OTX-16-002, Revision E dated 02May2017

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the CSR.

2. Study Objectives

The objective of this study is to evaluate the safety and intraocular pressure (IOP)-lowering efficacy of OTX-TP, a sustained release travoprost drug product, placed in the canaliculus of the eye in the treatment of subjects with open-angle glaucoma or ocular hypertension.

3. Study Variables

Primary Variable

The primary efficacy variable is mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.

Secondary Variables

The secondary efficacy variables include the following:

- Mean change from baseline IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.
- Mean percent change from baseline IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.

Other Variables

Additional variables on which data will be collected include the following:

- Ocular complaints
- Visualization of intracanalicular depot by the Investigator at each time point
- Ease of insertion of intracanalicular depot
- Number of intracanalicular depots required in each eye for the 12 week period per subject.

Safety Variables

The safety variables include the following:

- BCVA
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Subject ocular comfort assessment
- Dilated fundus exam
- Adverse events

Statistical Hypotheses

The null and alternative hypotheses, based on the primary variables, are as follows:

- H_0 : The difference between study eyes that received sustained release travoprost (OTX-TP) and study eyes that received Placebo Vehicle (PV) (calculated as OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is ≥ 0 mmHg for at least one time point over all visits.
- H_1 : The difference between study eyes that received OTX-TP and study eyes that received PV (calculated as OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is < 0 mmHg for all time points over all visits.

4. Study Design and Procedures

General Study Design

This is a prospective, multicenter, randomized, parallel-arm, double masked, placebo vehicle controlled Phase 3a trial to evaluate the safety and IOP-lowering efficacy of OTX-TP, a sustained release drug product placed in the canaliculus of the eyelid in subjects with open-angle glaucoma or ocular hypertension. A total of up to 550 subjects (1100 eyes) with a clinical diagnosis of open-angle glaucoma or ocular hypertension in both eyes will receive either OTX-TP or PV to evaluate the safety and efficacy of OTX-TP.

The subjects enrolled in this parallel-arm study will be randomized to receive either OTX-TP intracanalicular depot (OTX-TP) or PV intracanalicular depot (PV), respectively. Subjects randomized to the treatment group will receive OTX-TP in either the superior or inferior canaliculus of each affected eye on Day 1. Subjects randomized to the control group will receive PV in either the superior or inferior canaliculus of each affected eye on Day 1.

At the Baseline Visit 2/Insertion Visit, in the event that after randomization the insertion of the intracanalicular depot is unsuccessful in the first eye, the subject will be exited from the study. If insertion is unsuccessful in the second eye, the intracanalicular depot from the contralateral eye (if already inserted) will not be removed. The subject will be prescribed IOP-lowering drops at the Investigator's

discretion for the eye that did not receive a depot. The subject will be followed for safety only, and the eye that received a depot will be included in the safety analysis. The study will be supplemented with additional subjects to account for these subjects in order to ensure that the necessary number of subjects (490) who received a depot bilaterally are followed through the 12 Week Visit for efficacy and safety. If neither insertion is successful the End of Study eCRF will be completed for the subject and the subject will be exited from the study. Unsuccessful punctal dilation of either eye (if needed) or if the punctum of either eye is too small to allow transient dilation to 0.7 mm prior for insertion of OTX-TP or PV is considered a Procedural Exclusion Criterion and the subject will be exited as a screen failure.

All subjects will undergo follow-up visits at 2, 4, 6, 8, 10, and 12 Weeks. If at any visit, the Investigator deems it necessary to initiate IOP-lowering drops as rescue therapy due to an increase in IOP, the subject will be considered an efficacy failure and will be followed through the remainder of the study for safety. If still present, the intracanalicular depot will not be removed. IOP measurements taken through the remainder of the study will be excluded from the efficacy analyses.

For any subject, if at any point the intracanalicular depot is removed bilaterally by the Investigator for an adverse event or subject discomfort, the subject will be exited from the study at that visit. If the intracanalicular depot needs to be removed from only one eye, the depot from the contralateral eye will not be removed and the subject will be followed per the study schedule for safety.

Intracanalicular depots that are removed due to subject withdrawal or an undesired reaction at any point in the study will not be replaced.

For subjects with Early Loss of Intracanalicular Depot Prior to the 6 Week Visit:

At any visit prior to the 6 Week Visit, if the intracanalicular depot is not visualized in one or both eyes by the Investigator, the Investigator will insert a new intracanalicular depot in the respective eye(s) after confirming patency. For any depot replacements, IOP assessments should be completed prior to replacement. The subject will continue to return for follow-up visits per the study schedule through the 12 Week Visit. The number of depot replacements will be tracked and documented on the appropriate electronic Case Report Form (eCRF).

For subjects with Early Loss of Intracanalicular depot from the 6 Week Visit prior to the 12 Week Visit:

At any visit from the 6 Week Visit prior to the 12 Week Visit, if the intracanalicular depot is not visualized in one or both eyes by the Investigator, the Investigator will insert a new intracanalicular depot in the respective eye(s) after confirming patency. For any depot replacements, IOP assessments should be completed prior to replacement. The subject will return for follow-up visits through the 12 Week Visit and then at the 20 Week Visit. Depots replaced between the 6 Week Visit and the 12 Week Visit will not be

removed at the 12 Week Visit. The first attempt to remove these depots will be at the 20 Week Visit. The number of depot replacements will be tracked and documented on the appropriate eCRF.

12 Week Visit:

If the intracanalicular depot(s) is/are still present at the 12 Week Visit, the Investigator will attempt to remove the depot(s). If removal is successful bilaterally, the subject will be exited from the study upon confirmation of the bilateral absence of the intracanalicular depot. If the intracanalicular depot are not present bilaterally at the 12 Week Visit, the subject will be exited at the end of that visit.

If removal is unsuccessful in one or both eyes at the 12 Week Visit, the subject will return at the 20 Week Visit. The subject may be prescribed IOP-lowering drops if necessary at the 12 Week Visit at the Investigator's discretion.

20 Week Visit:

At the 20 Week Visit, the Investigator will attempt removal of the intracanalicular depot(s), if still present. If removal at the 20 Week Visit is successful bilaterally, the subject will be exited from the study upon confirmation of the bilateral absence of the intracanalicular depot.

If removal at the 20 Week Visit is not successful in one or both eyes, the subject will be required to return to the clinic every 30 (\pm 10) days until the intracanalicular depot is confirmed to be no longer present or removal of the intracanalicular depot is successful for the respective eye(s). Removal will be attempted at every visit until the intracanalicular depot is no longer present.

The subject may be prescribed IOP-lowering drops if necessary at the 20 Week Visit at the Investigator's discretion.

Schedule of Visits and Assessments

The schematic of the study schedule is presented in Table 1, Table 2, and Table 3, respectively for: Stratum A, Stratum B, and Stratum C.

Table 1: Study Schedule for subjects on prostaglandin treatment at the time of the Screening Visit (Stratum A)

Study Parameter	Screening	Baseline Visit 1		Baseline Visit 2/ Insertion Visit		Follow-Up Assessments																
		6 weeks (-2 days/ +3 days) after Screening		2 days [+2 days] after Baseline Visit 1)		2 Week (Day 15 ±3 days)		4 Week (Day 29 ±3 days)		6 Week (Day 43 ±3 days)		8 Week (Day 57 ±3 days)		10 Week (Day 71 ±3 days)		12 Week (Day 85 ±3 days)		20 Week (Day 141 ± 7 days)				
		8AM	8AM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	8AM	10AM	4PM	8AM	8AM	10AM	4PM	8AM	8AM	10AM	4PM	
Informed Consent	X																					
Determine Eligibility	X	X		X																		
Iris Color	X																					
Medical/Ophthalmic and Medication	X																					
Demographic Information	X																					
Urine Pregnancy Test (if applicable)	X																					
Automated Perimetry	X																					
Gonioscopy	X																					
Dilated Fundus Exam	X																					
Pachymetry	X																					
Punctum Size Assessment	X																					
Assessment of BCVA	X																					
Slit Lamp Biomicroscopy	X	X																				
Assess/Grade Hyperemia	X																					
Punctum Exam	X																					
IOP Measurement	X (8AM)	X		X																		
Subject Ocular Comfort																						
Randomize																						
Punctum Size																						
Pre/Post Dilatation																						
Intracanalicular Depot Insertion																						
Intracanalicular Depot Presence																						
Assessment of Ocular Complaints																						
Adverse Events	X	X		X																		
Record Medications	X	X		X																		

Table 2: Study Schedule for subjects who are treatment-naïve at the time of the Screening Visit (Stratum B)

Study Parameter	Follow-up Assessments																								
	Screening		Run-in		Baseline Visit 1		Baseline Visit 2/ Insertion Visit		2 Week (Day 15 ±3 days)		4 Week (Day 29 ±3 days)		6 Week (Day 43 ±3 days)		8 Week (Day 57 ±3 days)		10 Week (Day 71 ±3 days)		12 Week (Day 85 ±3 days)		20 Week (Day 141 ±7 days)				
	8AM		Visit 1 (Day 2 +3 days)	8AM	Visit 2 (Day 11 +3 days)	8AM	8 Weeks (- 2 days/ +3 days) after Screening	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
Informed Consent	X																								
Determine Eligibility	X					X		X																	
Iris Color	X																								
Medical/Ophthalmic and Medication History	X																								
Demographic Information	X																								
Urine Pregnancy Test (if applicable)	X																								
Automated Perimetry	X																								
Gonioscopy	X																								
Dilated Fundus Exam	X																								
Pachymetry	X																								
Punctum Size Assessment	X																								
Assessment of BCVA	X							X		X				X						X					X
Slit Lamp	X							X		X				X						X					X
Biomicroscopy	X																								
Assess/Grade Hyperemia	X							X						X						X					X
Punctum Exam	X													X						X					X
IOP Measurement	X (8AM)							X		X				X						X					X
Subject Ocular Comfort														X						X					X
Randomize														X											
Punctum Size Pre/Post Dilution														X											
Intracanalicular Depot Insertion																									
Intracanalicular Depot Presence														X						X					X
Assessment of Ocular Complaints														X						X					X
Adverse Events	X							X		X				X						X					X
Record Medications	X							X		X				X						X					X

5. Study Treatments

There are two study treatments, OTX-TP intracanalicular depot and PV intracanalicular depot, which are explained below.

OTX-TP Intracanalicular Depot

The OTX-TP drug product is a fluorescent dried polyethylene glycol based, rod-shaped hydrogel intracanalicular depot designed to be placed in the superior or inferior canaliculus. The hydrogel swells on contact with moisture to occlude the lumen, thus holding the OTX-PV in place. Once OTX-TP swells to fill the canaliculus, it is contained in the canaliculus until the hydrogel is resorbed. OTX-TP contains conjugated fluorescein to serve as a visualization aid through the use of a blue light source and yellow filter to confirm product presence.

Placebo Vehicle Intracanalicular Depot

The PV consists of the same components as OTX-TP, except that it does not contain travoprost. The PV will be provided in the same packaging as OTX-TP to maintain masking for the clinical trial.

Method of Assigning Subjects to Treatment Groups

Prior to the initiation of the study, a treatment randomization scheme will be generated using a 3:2 ratio (Active Treatment to Placebo Control) approximately 330 subjects in the OTX-TP arm and 220 in the PV arm. The study will be supplemented with additional subjects for whom bilateral depot insertion is successful in order to ensure that at least 490 subjects who receive a depot bilaterally are followed through the 12 Week Visit for safety and efficacy.

Once it is determined that the subject continues to meet eligibility for the study at Baseline Visit 2, the subject will be randomized into the study through assigning the next sequential kit within the kits corresponding to the subject's previous ocular anti-hypertensive therapy category. Both eyes will be provided with the same assigned treatment, OTX-TP or PV. Randomization will be stratified by investigational site (i.e., one randomization schema per study site) and previous ocular anti-hypertensive therapy with three stratum levels below:

Stratum A: Subjects who were on prostaglandin treatment at the time of the Screening Visit and have shown an adequate IOP rise after a 6-week washout (interval from Screening to Baseline Visit 1 is 6 weeks).

Stratum B: Subjects who were treatment-naïve at Screening and have shown an adequate prostaglandin response after a 2-week Run-in period on prostaglandin treatment followed by a 6-week washout (interval from Screening to Baseline Visit 1 is 8 weeks).

Stratum C: Subjects who have recently exited from a prior ophthalmic investigational research study and have written approval from the Medical Monitor to be allowed to participate in the current study without additional exposure to prostaglandin.

A site may randomize up to a maximum of 55 subjects.

The randomization number will be an alpha-numeric code using the following scheme: RnnX-*nnn* with R in the first place followed by the 2-digit site ID and one letter X corresponding to the stratum (A, B or C). Then a hyphen will separate the first alpha-numeric section and be followed by a three-digit number increasing in sequential order within each site and starting with 001.

Masking and Unmasking

The Investigator and the subject will be masked to the treatment assignment throughout the duration of therapy.

OTX-TP and the PV are identical in appearance, and will be supplied in identical packages so they cannot be distinguished by the user. If it is medically necessary to identify the product used, the Investigator will contact the Sponsor with the details of the emergency unmasking request. Ocular Therapeutix will make the final determination if the unmasking request will be granted. If granted, the Investigator will be permitted to use the unmasking instructions available on site.

6. Sample Size and Power Considerations

Assuming a common standard deviation of 3.75 mmHg within a treatment group, a mean difference of 1.5 mmHg or greater between treatment groups at each of the 3 time points of each of the 3 visits, and a 3:2 randomization ratio, 294 subjects in the OTX-TP arm and 196 subjects in the PV arm yield > 90% power to conclude superiority of OTX-TP to PV in mean IOP at all of the 9 time points using a 2-sided alpha = 0.05 and assuming independence among time points. The power increases with increasing positive correlation among time points.

To account for 10% of subjects discontinuing before the 12 Week Visit, approximately 330 subjects will be randomized into the OTX-TP arm and 220 subjects will be randomized into the PV arm.

7. Data Preparation

All reported study data will be recorded on eCRFs using the iMedNet electronic data capture (EDC) system. All authorized personnel will have access to the EDC system; however, only the site study personnel assigned to have the role of a Research Coordinator will have data entry user rights.

Ocular Therapeutix (OTX) is responsible for validating the OTX-16-002 study database, maintaining the study data, and cleaning and reviewing the data prior to database lock. OTX data management will prepare the edit check specifications document as well as the Business Logic Documents for review and approval. These documents are maintained in the trial master file. After data are entered into the clinical study database, electronic edit checks and data review will be performed. When the database has been declared to be complete, the following activities will take place to prepare for database lock:

- All clinical data are entered, source verified, and approved in the clinical database

- All discrepancies are resolved and applied to the database
- Dictionary coding (by SDC) is complete and Final AE Coding Approval Form is signed
- SAE reconciliation is complete
- Any DMP amendments are signed by the appropriate team members

Additionally, for the final database lock and analysis, all analyses outlined in this document will be carried out only after the following have occurred:

- Protocol deviations have been identified and status defined (major/important vs minor deviations)
- Analysis populations have been determined
- Randomized treatment codes have been unmasked

In the event that the database must be unlocked, unlocking procedures fall under OTX processes and operating procedures.

8. Analysis Populations

Subjects will be considered enrolled once they have signed informed consent. Once randomized and treated, subjects will fall into at least one of the following analysis populations.

Full Analysis Set

The Full Analysis Set (FAS) population will include all randomized subjects with depots inserted in both eyes. Analysis on the data for the primary study eye in the FAS will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.

Per Protocol Population

The Per Protocol (PP) population will include all FAS subjects who do not deviate from the protocol in any way likely to seriously affect the efficacy outcomes of the study. Analysis on the PP population will be used as secondary efficacy analysis and will be performed for select efficacy endpoints, analyzing subjects under the treatment actually received. Important protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be identified prior to the database lock. The primary efficacy analysis will be conducted using the PP population as a sensitivity analysis of the primary outcome.

Safety Population

The Safety population will include all subjects who received any investigational study treatment (OTX-TP or PV). Analyses performed on the Safety population will be according to the treatment the subjects actually received. All safety analyses will be based on the Safety population.

9. General Statistical Considerations

Unit of Analysis

The unit of analysis in this study will be the primary study eye for all efficacy summaries and any eye that received a depot for ocular safety summaries. The primary study eye will be defined as the study eligible eye with ocular hypertension or open angle glaucoma that meets the IOP enrollment criteria and has an intracanalicular depot successfully inserted. If a subject has both eyes eligible and treated, then the primary study eye will be the eye with the highest IOP at 8AM on Baseline Visit 2 (Day 1) and the other eye will be considered to be the secondary study eye; if both eyes are eligible, treated, and have the same IOP at 8AM on Baseline Visit 2 (Day 1), the right eye will be the study eye and the left eye will be considered the secondary study eye. If both eyes are eligible but only one eye receives a depot, the eye with the depot inserted will be considered the primary study eye (for safety evaluations), and no secondary eye will be designated for this subject.

Ocular adverse events will be presented at the eye and subject level and non-ocular adverse events will be presented at the subject level.

Missing Data and Imputation Methods

The primary analyses of efficacy data (IOP) will employ multiple imputation (MI) methods using the Markov Chain Monte Carlo (MCMC) approach to impute missing data and using the last time-consistent observation carried forward (LOCF) to impute data for time points after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy.

Sensitivity analyses, to determine robustness of results, will be performed using the MCMC approach to impute non-monotone missing information and pattern mixture models control-based pattern imputation for monotone missing information (including data for subjects who drop out prior to the 12 Week Visit and data for time points after a subject's primary study eye is prescribed IOP-lowering drops), LOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops, baseline time-consistent observation carried forward (BOCF) to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops and using observed data only (excluding data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy). Additionally, sensitivity analyses will be performed on the PP population using observed data only (excluding data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy).

For time-consistent imputations, IOP values missing at an 8AM time point will only be imputed with the IOP value from a previous 8AM time point (last or baseline). Imputations at 10AM and 4PM will be performed similarly.

Definition of Baseline

For IOP, the baseline measure will be defined as the last non-missing time-consistent measure prior to initiation of investigational treatment and after washout of previous IOP medication. In most cases this will be the measure of IOP at Baseline Visit 2. For all other variables, baseline will be defined as the last non-missing measure prior to initiation of investigational treatment. Change from baseline will be calculated as follow-up visit – baseline visit.

Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in RTF format for tables and PDF format for tables, listings, and figures using landscape orientation. All study data will be listed by subject, actual treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, standard deviations and medians will be presented to one additional decimal place than reported in the raw values. (Height and weight which are collected in inches and pounds are converted to metric units and presented with 2 decimal places.) Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between treatment groups will be calculated as OTX-TP minus PV and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as “< 0.0001”; p-values greater than 0.9999 will be presented as “> 0.9999”.

All efficacy summaries will be presented for the primary study eye. Additional efficacy analyses will be reported for secondary study eyes. Ocular AEs will be summarized at the eye level for any treated eye and subject level, and non-ocular AEs by subject level. All other safety variables will be assessed by primary study eye and secondary study eye, separately.

Adjustments for Multiplicity

In order to maintain the overall Type I error for the primary analyses, all 9 time points must show statistical significance for the study to be successful: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits. No other adjustments for multiplicity are necessary as there are no other sources of multiplicity for the primary analyses.

Unscheduled Visits

For Unscheduled Visits, the reason for the visit should be clearly documented on the appropriate eCRF, including findings from all evaluations that are completed.

Data from unscheduled visits up to the 12 Week Visit will be integrated into subject listings and summary tables. All unscheduled data is presented in listings. Tables will incorporate unscheduled data according to the following rules. If unscheduled data is available within window of a scheduled Visit with missing data, the unscheduled data will be used. If scheduled Visit data is not missing, unscheduled data will not be used. If more than one set of unscheduled data falls within a window for an efficacy assessment, the earliest unscheduled visit in that visit window will be used. If more than one set of unscheduled data falls within a window for a safety assessment, the worst case observation will be used. "Within window" is calculated based on Visit name rather than Visit date.

10. Disposition of Subjects

Subject disposition of all enrolled subjects will be presented in terms of the numbers and percentages of subjects who were screened, screened but not randomized, randomized, completed the study, discontinued from the study and/or experienced protocol deviations. Number of subjects exiting the study prior to Week 12, at Week 12, at Week 20 and beyond Week 20 will also be summarized. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects. Reasons for subject discontinuation at various decision time points will be summarized.

Subjects who are enrolled but determined to be ineligible during the screening assessment, Run-in visits, IOP confirmation visit, or baseline visits prior to randomization will be considered screen failures, will be withdrawn from the study, and will not require additional study follow-up visits but will be entered in the EDC system with the reason for screen failure delineated. The total number of screened subjects with the number and percentage of screen failure subjects will be presented. The reasons for screen failure will be displayed with the percentages calculated using total number of screen failures as the denominator.

The number of subjects in each of the analysis populations (FAS, PP and Safety) will be displayed by treatment and percentages will be calculated using randomized subjects as the denominator. A subject listing of analysis populations will be provided including reasons for exclusion from the PP and/or Safety populations. In addition, a subject listing of stratum assignment, randomization, including site records of whether randomization and kit choice were correct, and a listing of all subject visit dates, including reasons for unscheduled visits, will be provided.

The number and percentage of subjects with major protocol deviations will be summarized by treatment group for all randomized subjects. The protocol deviations will be summarized by deviation codes.

A subject listing will be provided that includes the date of the deviation, the deviation description and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include informed consent date, and inclusion and exclusion criteria violations. Procedural exclusion criteria will be presented in the same listing as study inclusion and exclusion criteria.

11. Demographic and Pretreatment Variables

Demographic Variables

The demographic variables collected at Screening in this study include date of birth, sex, race, ethnicity, height, weight and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the FAS population.

Age at informed consent (years), height, weight and BMI will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years. Age will be reported in years and calculated using the following formula:

$$\text{Age} = (\text{informed consent date} - \text{date of birth}) / 365.25 \text{ truncated as an integer}$$

BMI is calculated in the database.

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity and iris color.

A subject listing that includes all demographic variables will be provided. Note that iris color will be reassessed at the 12 Week Visit (or the Early Termination Visit if subject discontinues the study prior to the 12 Week Visit) and these results will be listed along with a flag indicating any changes from baseline.

Pretreatment Variables

Female subjects of child-bearing potential will have urine pregnancy test at the Screening Visit. A subject listing of child-bearing status and pregnancy test results will be provided.

Summary statistics will be provided for the baseline characteristic variables, which include mean IOP for both the primary study eye and the secondary study eye at screening (pre-washout) and at Baseline Visit 2, mean deviation in visual fields (dB), central corneal thickness (μm), and cup to disc ratio. Counts and frequencies for current diagnosis of OHT or OAG, and gonioscopy results (including the following categories: Grade 4 [45° to 35° angle wide open], Grade 3 [35° to 20° angle wide open], Grade 2 [20° angle narrow], Grade 1 [≤10° angle extremely narrow], and Slit [0° angle narrowed to slit] will also be provided.

A subject listing that includes all pretreatment variables will be provided.

Punctum Size Assessment Prior to Insertion

Punctum size will also be assessed prior to insertion of the depot. At the 4PM time point on Baseline Visit 2 the Investigator will use a standard punctum gauge to assess the size of the punctum. If the punctum measures < 0.4 mm or > 0.9 mm, the subject will be screen failed and will not be randomized. The Investigator will utilize a commercially available dilator probe from standard practice or as provided by Sponsor to dilate the punctum to 0.7 mm, as required for proper insertion of the intracanalicular depot. If the Investigator determines that the punctum cannot be dilated to approximately 0.7 mm, the subject will be screen failed and will not be randomized. If the subject remains eligible for the study, the Investigator will randomize the subject and insert OTX-TP or PV into the superior or inferior canaliculus of the subject's eyes. Punctum size, both prior to and after dilation, will be recorded and provided in a subject listing.

12. Medical History and Concomitant Medications

Medical History

Medical history will be collected at the Screening Visit and coded using MedDRA 20.0.

Non-ocular and ocular medical history will be summarized for the Safety Population using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT). If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

Listings of medical history will be generated separately for ocular and non-ocular data.

Concomitant Medications

Starting at the Screening Visit through the end of the study, the use of any concurrent ophthalmic medications and systemic medications, prescription or over-the-counter, from up to 3 years prior to the Screening Visit, is to be recorded on the subject's source document form and corresponding electronic case report form along with the reason the medication was taken. The use of any herbal or vitamin supplements and any dilation and other Standard of Care drops used for the ophthalmic assessments including IOP measurement and the insertion procedure will not be required to be recorded.

Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) March 2017 and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and preferred name (generic drug name).

Concomitant medications are defined as those medications listed as having been taken 1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or 2) at any time following the first administration of study drug.

Ocular and non-ocular concomitant medications will be summarized using the Safety Population. Medications will be tabulated for each treatment group using frequencies and percentages. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data. Additionally, a table summarizing the subset of IOP-lowering medications used in the primary study eye and a summary table of IOP-lowering medication used in the primary study eye by visit will be produced, as well as a listing of FAS subjects with IOP-lowering medications with start dates after Baseline Visit 2 and prior to 12 Week Visit. IOP-lowering medications (rescue medications) are determined by the eCRF indication “Lack of IOP control” in the primary study eye.

Dosing Compliance and Treatment Exposure

Dosing compliance and treatment exposure will be assessed using visualization of the intracanalicular depot by the investigator, intracanalicular depot removal and the number of intracanalicular depots required in each eye for the 12 week period per subject. These analyses will be performed on the Safety Population. No statistical inference testing will be performed.

Intracanalicular Depot Visualization by the Investigator

The intracanalicular depot will be assessed for presence and ease of visualization at the time of insertion time point as well as the 8AM time point at each post-baseline visit. The number of subjects with a intracanalicular depot present will be summarized by visit and treatment, and this number will be used as the denominator for the ease of visualization responses. Ease of visualization will be recorded as Easy, Moderate, or Difficult by the investigator. Responses will be summarized by count and percentage at each visit by treatment group. A subject listing, reported separately by right and left eyes, will also be provided.

Intracanalicular Depot Removal

When an intracanalicular depot is removed the reason for removal (removed per protocol, AE, other), the success of the removal (yes vs no), the ease of removal (easy, moderate, difficult) and the method of removal (saline irrigation, application of manual pressure) will be recorded. The responses will be summarized by count and percentage at each visit by treatment group. A subject listing, reported separately by right and left eyes, will also be provided.

Number of Replacements

The number of intracanalicular depots required in each eye for the 12 week period per subject will be reported and listed. For subjects with confirmed depots beyond 12 weeks, summaries will also be provided indicating the length of the depot being present in the canaliculus and the number of depots required and the number of patency checks performed.

Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

$$\text{Total Exposure (days)} = (\text{Date of last investigator visualization of a depot in either eye [that is not subsequently replaced]} - \text{Date of first insertion of a depot in either eye}) + 1$$

Date of first insertion of depot in either eye will in most cases be Baseline Visit 2 [Day 1]. Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

$$\text{Total Exposure (days)} = (\text{Date of last recorded visit} - \text{Date of first insertion of a depot in either eye}) + 1$$

Total treatment exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group and for all subjects, using the Safety population. A subject listing of treatment exposure will also be produced.

13. Efficacy Analyses

Primary Analysis

The primary analysis of the primary efficacy outcome will employ a linear model of IOP in the primary study eye of subjects in the FAS. The response variable will be IOP at the given visit (2 Week, 6 Week, and 12 Week) and time point (8AM, 10AM, and 4PM), time point specific baseline IOP will be used as a covariate, and treatment will be the main effect factor. Each time point within each visit will be modeled separately.

IOP refers to the single result from the following procedure. IOP will be assessed by two qualified independent study site personnel at each visit and time point using a Goldmann applanation tonometer affixed to a slit lamp with the subject seated. Two measurements should be performed, and if the IOP is within 1 mm Hg, the average of the first two measurements should be recorded. If the IOP from the first two readings shows a greater than 1 mm Hg difference, a third reading should be taken and the average of all three readings recorded. Averages of readings are calculated within the clinical database.

For the primary analysis, MI methods will use the MCMC approach for any data missing from these visits/time points, after LOCF has been used to impute data for time points after the subject's primary study eye is prescribed IOP-lowering drops. Example MCMC imputation code which will be implemented after LOCF has been applied (SAS® version 9.4) is shown here:

```
PROC MI DATA = indata SEED = 7436892 OUT = outdata NIMPUTE=20;
BY TMPTN;
MCMC INITIAL = EM;
VAR trt baseline WV2 WV4 WV6 WV8 WV10 WV12;
```

RUN;

where

- *indata* is the name of the input dataset;
- *outdata* is the name of the output dataset;
- *nimpute* is the number of imputations;
- *tmpn* is the time point of assessment, 8AM, 10AM, or 4PM;
- *trt* is the name of the treatment group variable in numeric format;
- *baseline* is the average IOP at baseline
- *WV2* is the IOP value for the 2 Week visit;
- *WV4* is the IOP value for the 4 Week visit;
- *WV6* is the IOP value for the 6 Week visit;
- *WV8* is the IOP value for the 8 Week visit;
- *WV10* is the IOP value for the 10 Week visit;
- *WV12* is the IOP value for the 12 Week visit.

Twenty complete data sets for each time point will be generated from the above code. The data will be transposed to have a vertical structure with one record per subject, imputation, visit, and time point. Each complete data set will be used to compute the mean IOP and analyze using the linear model with time point specific baseline IOP used as a covariate, and treatment as the main effect factor. A separate model will be fit for each visit/time point combination. Then, the SAS® procedure MIANALYZE will be used to analyze the results from the 20 complete data sets to generate a combined inference. The following SAS® code will be used:

```

ODS OUTPUT LSMEANS = outdataB;
PROC MIXED DATA = outdataA;
CLASS trt;
MODEL IOP = trt baseline;
BY visitn tmpn _IMPUTATION_;
LSMEANS trt/PDIFF CL;
RUN;

```

where

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmpn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *outdataA* is the transposed dataset containing the 20 “complete” datasets from the imputation.

```

ODS OUTPUT PARAMETERESTIMATES = outdataC;
PROC MIANALYZE DATA = outdataB;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
BY visitn tmpn;
RUN;

```

where

- *outdataB* is the name of the output dataset that contains the statistical results of the difference between treatment groups from the MIXED procedure that is run on each of the twenty imputation datasets;
- *outdataC* is the name of the output dataset that contains all the information needed for the table.

After imputation the least squares mean differences (OTX-TP minus PV) will be presented along with 2-sided 95% confidence intervals (CIs) around the difference and 2-sided p-values testing the difference equal to 0. Inference will be made on the 2-sided p-value at a 2-sided alpha = 0.05 at each time point and visit. The study will be considered a success if the 2-sided p-value < 0.05 (demonstrating statistical superiority) and the point estimate of the difference is < 0 at all time points over the three visits.

Two-sample t-test p-values and two-sided 95% CI's will also be computed around the difference (OTX-TP minus PV) in IOP between treatment groups at each time point and visit for the primary analysis data (FAS employing MI methods using MCMC approach to impute missing data and using LOCF to impute data for time points after a subject's study eye is prescribed IOP-lowering drops as rescue therapy). The following SAS® code will be used for the t-test:

```

ODS OUTPUT STATISTICS = outdataB;
PROC TTEST DATA = outdataA;
CLASS trt;
VAR IOP;
BY visitn tmpn _Imputation_;
RUN;

```

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmpn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *outdataA* is the transposed dataset containing the 20 "complete" datasets from the imputation.

Then, as with the PROC MIXED results, the SAS® procedure MIANALYZE will be used to analyze the results from the 20 complete data sets to generate a combined inference.

```
ODS OUTPUT PARAMETERESTIMATES = outdataC;  
PROC MIANALYZE DATA = outdataB;  
MODELEFFECTS ESTIMATE;  
STDERR STDERR;  
BY visitn tmptn;  
RUN;
```

where

- *outdataB* is the name of the output dataset that contains the statistical results of the difference between treatment groups from the MIXED procedure that is run on each of the twenty imputation datasets;
- *outdataC* is the name of the output dataset that contains all the information needed for the table.

Sensitivity analyses for the primary efficacy endpoint include both linear models of IOP and 2-sample t-tests presented on the FAS population using (1) MI approach using MCMC to impute non-monotone missing information and a pattern mixture model control-based pattern imputation for monotone missing information to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy, (2) using LOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy, (3) using BOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy, and these analyses using observed data only (excluding data after a primary study eye is prescribed rescue therapy) for the (4) FAS and (5) per protocol populations.

For multiple imputations using a control-based pattern-mixture model, a process will be used that is similar to multiple imputations using MCMC. Twenty "complete" (imputed) datasets will be produced and analyzed. Results from the analyses on the twenty "complete" datasets will be combined for presentation through the use of SAS® PROC MIANALYZE. Time point specific baseline IOP will be used as a covariate, and treatment will be the main effect factor. A separate model will be fit for each visit/time point combination. Monotone missing information refers to data missing from any visits beyond a subject's final visit (at which IOP is assessed) up to and including the 12 Week Visit. Non-monotone missing information refers to data from missed visits between any two visits at which IOP is assessed. First LOCF will be used to impute data for time points after a subject's primary study eye is prescribed IOP-lowering drops. Then MCMC will be employed to impute any non-monotone missing information using the code:

```
PROC MI DATA = indata SEED = 3335891 OUT = mondata NIMPUTE=1;  
BY TMPTN;
```

```
MCMC INITIAL = EM IMPUTE = MONOTONE;
VAR trt baseline WV2 WV4 WV6 WV8 WV10 WV12;
RUN;
```

where

- *indata* is the name of the input dataset;
- *mondata* is the name of the output dataset;
- *nimpute* is the number of imputations;
- *trt* is the name of the treatment group variable in numeric format;
- *baseline* is the average IOP at baseline;
- *WV2* is the IOP value for the 2 Week visit;
- *WV4* is the IOP value for the 4 Week visit;
- *WV6* is the IOP value for the 6 Week visit;
- *WV8* is the IOP value for the 8 Week visit;
- *WV10* is the IOP value for the 10 Week visit;
- *WV12* is the IOP value for the 12 Week visit.

Then the following SAS® code will be used to produce twenty “complete” datasets for each time point, imputing monotone missing data using a control-based pattern mixture model:

```
PROC MI DATA = mondata SEED = 48670 NIMPUTE = 20 OUT = outdata
MINIMUM = . . 0 MAXIMUM = . . 70 ROUND = . . 0.25;
BY visitn tmpntn;
CLASS trt;
MONOTONE REG(WV2_8 WV4_8 WV6_8 WV8_8 WV10_8 WV12_8 = baseline /
details);
MNAR model(WV2_8 WV4_8 WV6_8 WV8_8 WV10_8 WV12_8/ MODELOBS =
(TREATMENT="2"));
VAR trt baseline WV2_8 WV4_8 WV6_8 WV8_8 WV10_8 WV12_8;
RUN;
```

After obtaining twenty complete datasets, the data from the two MI procedures will be combined and will then be transposed to have a vertical structure with one record per subject, imputation, visit, and time point. SAS® code similar to what is previously described for multiple imputations in the primary analysis will then be employed to run the model on each dataset and combine results across imputations.

In the case that there is no missing data for a given visit and time point, observed data will be analyzed. Analyses on observed data and without MI methods will use the following statistical models:

```
ODS OUTPUT LSMEANS = outdata;
PROC MIXED DATA = indata;
```

```

CLASS trt;
MODEL IOP=trt baseline;
BY visitn tmptn
LSMEANS trt/PDIFF CL;
RUN;
    
```

where

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmptn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *indata* is the dataset containing only observed data.

and

```

ODS OUTPUT STATISTICS = outdata;
PROC TTEST DATA = indata;
CLASS trt;
VAR IOP;
BY visitn tmptn;
RUN;
    
```

- *IOP* is the IOP for each visit and time point;
- *visitn* is the visit number variable in numeric format;
- *tmptn* is the time point variable in numeric format;
- *baseline* is the average IOP at baseline, matched by time point;
- *trt* is the name of the treatment group variable in numeric format;
- *indata* is the dataset containing only observed data.

Secondary Analysis

Mean change from baseline IOP and mean percent change from baseline IOP will be analyzed similarly to the primary endpoint analysis, including all sensitivity analyses. (If a subject is missing a baseline IOP value, or if Baseline Visit 2: 4PM IOP is measured after insertion, change from baseline and percent change from baseline are not calculated.) As described above, these analyses involve linear models of the response variables on the FAS population using various combinations of imputation methods [(a) MCMC for missing data, LOCF for timepoints after rescue therapy has been initiated; (b) MCMC for non-monotone missing, pattern mixture models for monotone missing; (c) LOCF for both missing and “rescue” time points; and (d) BOCF for both missing and “rescue” time points] as well as inference on observed data confined to the FAS and Per Protocol populations.

Additional Analyses

13.1.1 ADDITIONAL EFFICACY ANALYSES

IOP measures, mean change from baseline, and mean percent change from baseline IOP measures from non-primary visits (4 Week, 8 Week, 10 Week Visits) will be also analyzed similarly to the primary endpoint analysis.

Additionally, to further understand efficacy within each previous ocular anti-hypertensive therapy category, the primary analysis strategy (linear model of IOP Markov Chain Monte Carlo (MCMC) approach to impute missing data and using the last time-consistent observation carried forward (LOCF) to impute data for time points after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy) will be completed separately for the subgroups (i.e. stratum) of subjects within each previous ocular anti-hypertensive therapy category. The FAS will be used for these subgroup analyses.

All analyses will be presented in summary tables by treatment group. Subject level listings will also show IOP by treatment, time point and visit where appropriate.

13.1.2 PUNCTUM EXAMINATION

At Screening, prior to insertion at Baseline Visit 2, and at the 8AM time point of each subsequent post-baseline visit investigators will assess punctal appearance, lid apposition, tear meniscus recording results as normal, abnormal NCS or abnormal CS for each eye. The responses will be summarized by count and percentage at each visit by treatment group and for all subjects. Shifts from Baseline to the evaluation visit will also be presented as frequencies and percentages. A subject listing, reported separately by right and left eyes, will also be provided.

13.1.3 INSERTION RESULTS AND EASE OF INSERTION

The results of insertion will be summarized for insertion location (superior vs inferior punctum), success of insertion (yes vs no), ease of insertion (easy, moderate, difficult), the number of packages opened, number of depots used to attempt insertion in each eye and the reason(s) depots were not utilized (swelling of depot prior to insertion, depot not present in foam package, depot dropped prior to insertion, failed insertion in initial punctum, or other). Product malfunctions during the insertion will also be recorded. Summaries based on the Safety Population will be presented for Baseline Visit 2 and any Replacement or Re-insertion visits, and Replacement/Re-insertion visits within the initial 12 Week period by treatment group and overall. Summaries will be separated by primary and secondary study eyes. A subject listing, reported separately by primary and secondary study eyes, will also be provided.

13.1.4 OCULAR COMPLAINTS

In order to assess tolerability, ocular complaints are evaluated after insertion at Baseline Visit 2, and at the 8AM time point of each subsequent post-baseline visit. Complaint categories include Excessive Tearing, Foreign Body Sensation, Itching, Stinging/Burning, and Other Ocular Complaints. Within each

category, a subject is required to answer yes or no as to whether the issue occurred, and the investigator responds as to whether or not the issue was within clinical expectations as well as whether or not any action was taken.

Counts and percentages of study eyes and subjects experiencing each complaint category will be summarized by visit and treatment group using the number of assessments performed within each treatment group as the denominator. For expectedness and actions, counts and frequencies of yes and no responses will also be summarized, using the number of subjects having the complaint category as the denominator. Summaries at the study eye level will be split up by primary and secondary study eyes. For subject level summaries, the worse result between the two eyes will be summarized (ie, a response of yes to the ocular complaint). A subject listing, reported separately by primary and secondary study eyes, will also be provided.

Graphical Outputs

In addition to the tabular output, graphs will be provided of the mean (averaged over subjects) and standard error of IOP values for the primary study eye and changes from baseline values by treatment, visit and time point in the FAS with imputed data per the primary endpoint imputation strategy. In addition, figures will be created showing the difference between OTX-TP and PV mean IOP values along with their 95% CIs for each visit and time point using the FAS with imputed data per the primary endpoint imputation strategy and for observed data. Reference lines will be included at ± 1 mmHg and ± 1.5 mmHg. Figures using observed data for the PP population will also be presented.

14. Safety Analyses

Ocular and Non-Ocular Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. If adverse events occur, the first concern will be the safety and welfare of the subject. Appropriate medical intervention will be undertaken. Any adverse events observed by the Investigator or reported by the subjects, whether or not ascribed to the study treatment, will be recorded on the subject's Adverse Event Case Report Form.

Documentation regarding the adverse event will be made as to the nature, date of onset, end date, severity, and relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning. All AEs will be coded using the MedDRA version 16.1.

AEs will be reported from the point subjects sign informed consent. The AE and treatment emergent adverse event (TEAE) reporting period ends upon study exit for new AEs. Existing AEs and TEAEs will be followed until:

- Resolution (return to baseline status or to 'normal')

- AEs may be determined to have resolved (completely) or resolved with sequelae.
- Principal Investigator determines, for events that do not end (i.e., metastasis), the condition to be chronic. The event can be determined to be resolved or resolved with sequelae.
- Stabilization of the event has occurred (no worsening expected by the investigator)

Adverse Event (or Adverse Experience, AE)

An AE is any untoward medical occurrence, which does not necessarily have to have a causal relationship with the treatment.

Adverse Ocular Event

An adverse ocular event is an AE that affects ocular tissues, the nasolacrimal duct, sinuses or vision. All adverse ocular events are a subset of adverse events.

Note: Subjects will be queried for the presence or absence of the following ocular complaints: excessive tearing, foreign body sensation, stinging/burning, and itching. Positive responses to these standardized ocular complaint inquiries should be reported as ocular complaints and not adverse ocular events unless the complaint: meets the criteria of a specific event as listed, and/or is: outside of normal limits, associated with clinical sequelae (e.g., adverse slit lamp examination findings), and requires an intervention to be resolved.

Treatment Emergent Adverse Ocular Event (or TEAOE)

An adverse ocular event will be considered a treatment emergent AE if it occurs or worsens (based on severity: mild, moderate or severe) on or after the initiation of the intracanalicular depot insertion.

Treatment Emergent Adverse Event (or TEAE)

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the initiation of the intracanalicular depot insertion, whether ocular or non-ocular in nature. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

Adverse Reaction (or Related Adverse Event or Adverse Effect)

An adverse reaction is any noxious and unintended response to the treatment.

Unexpected Adverse Reaction (Unanticipated Adverse Effect)

An unexpected adverse reaction is an adverse reaction, the nature (including specificity and outcome) or severity of which is not consistent with the applicable product information. For this study, the study protocol; Investigator's Brochure; and prescribing information for the registered formulation of travoprost (Travatan®) will be used to assess events for unexpectedness.

Anticipated (as specified in the protocol) adverse ocular events that may be associated with OTX-TP or PV include, but are not necessarily limited to:

- Ocular hyperemia should be considered as an AE only if the subject complains of it or if the subject is discontinued because of ocular hyperemia
- Prostaglandin Associated Orbitopathy
- Iris discoloration
- Blepharitis
- Worsening in BCVA defined as ≥ 3 lines (≥ 15 letters)
- Subconjunctival hemorrhage
- Cataract
- Macular edema
- Conjunctivitis
- Keratitis
- Perforation of or trauma to the punctum and/or surrounding tissues
- Allergic reaction
- Chemosis
- Inflammatory reaction
- Epiphora, defined as clinically significant excessive tearing outside of normal limits
- Dacryocystitis
- Tearing with mucopurulent discharge
- Stenosis of the punctum
- Infection*

*Note: In the unlikely event of infection, the organism will be identified.

Serious Adverse Event (Serious Adverse Experience)

A serious adverse event (SAE) (experience) or reaction is any untoward medical occurrence that:

- results in death
- is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the subject 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.)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is sight-threatening

Medical and scientific judgment will be exercised in deciding whether expedited 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 subject or may require intervention to prevent

one of the other outcomes listed in the definition above. These should also usually be considered serious.

Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

Mild: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject’s daily activities.

Moderate: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject’s daily activities.

Severe: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject’s daily activities.¹

¹The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations. (Severity of all adverse events, ocular and non-ocular, will be reported according to the terminology defined in the protocol.)

Relationship to OTX-TP or PV

The following table will be used by the investigator as a guide when assessing the causal relationship of an AE to the intracanalicular depot and the insertion procedure.

NO RELATIONSHIP SUSPECTED	This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
RELATIONSHIP SUSPECTED	<p>The following criteria should be applied in considering inclusion of an AE in this category:</p> <ol style="list-style-type: none"> 1) It bears a reasonable temporal relationship to the insertion procedure or the presence of the intracanalicular depot. 2) It could not be reasonably explained by the known characteristics of the subject’s clinical state, environmental or toxic factors or other modes of therapy administered to the subject. 3) It disappears or decreases on removal of the intracanalicular depot. 4) It follows a known pattern of response to the insertion procedure or the intracanalicular depot.

UNABLE TO DETERMINE*	The Investigator is unable to assess the relationship of the event to the insertion procedure or the intracanalicular depot.
*Where the causal relationship of the AE to the insertion procedure or the intracanalicular depot has not been determined or is unknown, the AE will be treated as if a relationship is suspected for the purposes of regulatory reporting.	

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the study drug caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and the AE. Types of evidence that would suggest a causal relationship between the study drug and the adverse event include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure; one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. For TEAEs not suspected to be related to study product, a most likely cause will be selected from the following categories: Concomitant Medication(s), Pre-existing Condition(s), Insertion Process, Other.

Expected AEs

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- Unexpected: An AE or adverse reaction that is not listed in the study protocol, Investigator’s brochure, or prescribing information for the registered formulation of travoprost (Travatan®) or is not listed at the specificity or severity that has been observed.
- Expected: An AE that is listed in the Investigator’s brochure at the specificity and severity that has been observed.

AEs that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

The Investigator should initially classify the expectedness of an adverse event, but the final classification is subject to the Medical Monitor’s determination.

AE Summaries

All AEs and TEAEs will be coded using MedDRA 20.0. AEs will be summarized in listings and tables for overall and ocular TEAEs by treatment group.

An overall summary will be presented that includes the number of AEs, TEAEs and the number and percentage of subjects who experienced at least one AE or TEAE, by treatment group and for all subjects. This summary will also include breakdowns of TEAEs further categorized as ocular (primary study eye and secondary study eye separately) or non-ocular, serious AEs (SAEs), ocular TEAEs by maximum severity, non-ocular TEAEs by maximum severity, related TEAEs, TEAEs leading to subject withdrawal, and deaths.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE and will be presented by SOC and PT. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject level for both eyes and for primary study and secondary study eyes separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries will be provided for the following categories of AEs:

- Ocular TEAEs in the primary study eye
- Ocular TEAEs in the secondary study eye
- Non-ocular TEAEs
- Expected TEAEs
- Unexpected TEAEs
- Treatment related ocular TEAEs
- Treatment related non-ocular TEAEs
- Serious AEs
- TEAEs by Maximum Severity
- Non-related TEAEs by Most Likely Cause
- Non-related SAEs by Most Likely Cause
- Ocular TEAEs of Special Interest

The following Preferred Terms are considered TEAEs of Special Interest:

- Conjunctival hyperaemia
- Ocular hyperaemia
- Iritis
- Cystoid macular oedema
- Eye colour change

- Madarosis
- Eyelash discolouration
- Eyelash hyperpigmentation
- Eyelash injury
- Growth of eyelashes

All TEAEs, SAEs and TEAEs leading to subject withdrawal from the study will be presented in subject listings separately for ocular and non-ocular events.

Best Corrected Visual Acuity (BCVA)

The logarithm of the minimum angle of resolution (logMAR) visual acuity is assessed at each visit using an EDTRS chart at a viewing distance of 4 meters. BCVA will be measured without refraction using a pinhole or while the subject is wearing his/her glasses, if the subject normally wears glasses or contact lenses. Subjects are required to read the chart from the top to the bottom until 2 letters are misread on the line. The visual score is to be calculated based on an assigned value of 0.02 logMAR per letter. If visual acuity is so poor that the subject cannot read any of the largest letters at 4 meters, then acuity is to be measured at 2 meters and the appropriate conversions made.

If visual acuity is so poor that the subject cannot read any of the largest letters at 2 meters, the subject should be checked for the ability to count fingers or see hand motion or light perception as appropriate.

BCVA will be measured at screening, at 8AM on Baseline Visit 2 and as well as the 8AM time point at each post-baseline visit. The baseline measurement will be the last assessment prior to insertion of the depot.

The observed and change from baseline BCVA will be summarized for the primary study eye and secondary study eye using continuous descriptive statistics by visit for each treatment group and for all actively treated subjects. Additionally, discrete summaries of the worst change from baseline will be presented for both the primary study eye and the secondary study eye with the following groupings based on the logMAR scores: 0 or less, >0 to +0.09, +0.10 to +0.19, +0.20 to 0.29, +0.30 or more.

Visual acuity scores will also be presented in data listings. Subjects who lost three or more lines (equivalent to change from baseline of 0.30 logMAR or more) will be presented in an additional listing. This additional listing will also include subjects for whom vision worsened to the extent that the subject's vision is measured by finger count, hand motion or light perception.

Slit Lamp Biomicroscopy Examination

A slit lamp biomicroscopy examination of the eyelid, conjunctiva, iris, cornea, anterior chamber, lens, and vitreous will be performed at each visit (except the Run-in Visits for Stratum B subjects) at the 8AM time point. The results will be graded as normal, abnormal NCS or abnormal CS.

The results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye (primary study eye and secondary study eye). Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the slit lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline. A subject listing of the slit lamp biomicroscopy parameters will also be produced.

Dilated Fundoscopy Examination

A dilated funduscopy examination of the macula, peripheral retina, and optic nerve will be performed at Screening, and the 12 Week Visit. The results will be graded as normal, abnormal NCS or abnormal CS. The cup to disc (C/D) ratio will also be measured. Explanation/comment should be provided on the case report form for any abnormal findings.

The results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye (primary study eye and secondary study eye). Percentages will be based on the number of subjects in each treatment group with responses. For the cup to disc ratio, a continuous summary, including change from baseline, will be provided for each eye. Shift tables for the dilated funduscopy parameters will also be provided comparing the 12 Week Visit results for each subject to the Screening results. A subject listing of the dilated funduscopy parameters (including C/D ratio) will also be produced.

Ocular Hyperemia

Ocular hyperemia will be graded every visit at 8AM (except the 1st baseline measurement, Visit 1) on the following scale: 0 (None), 1 (Mild), 2 (Moderate), 3 (Severe), and 0.5 increments may be used if the subject's hyperemia is between two grades. Frequencies and percentages will be summarized for each visit and treatment group. Shifts from baseline to post-baseline visits will be summarized categorically as ≤ 0 (no change or decrease), +0.5, +1, +1.5, +2, +2.5, +3.

A subject listing of ocular hyperemia will also be produced.

Ocular Comfort Assessment

The subject comfort level will be assessed prior to insertion of the OTX-TP or PV, and again at each post-baseline visit. Subjects will be asked to grade their comfort level by asking them the following question:

“On a scale of 0 to 10, 0 being very comfortable and 10 being very uncomfortable, how comfortable does your eye feel?”

Descriptive summary statistics of the comfort scores will be presented for each day which the question is asked. Changes from baseline will also be calculated and summarized alongside the observed values. Subject comfort scores will be listed, along with the Investigator's response to the expectedness of the score and any action taken to alleviate discomfort.

Observed IOP Results

A summary and listing of observed IOP data with no imputation, based on the Safety Population, will also be provided.

15. Interim Analyses

There are no planned interim analyses.

16. Pharmacokinetic Analyses

No pharmacokinetic data will be collected for this study.

17. Pharmacodynamic Analyses

No pharmacodynamic data will be collected for this study.

18. Quality of Life

No Quality of Life data will be collected for this study.

19. Changes from Protocol-Stated Analyses

This SAP differs from the protocol-stated analysis in three respects:

- (1) The statement, “Intent-to-Treat (ITT): The ITT population will include all randomized subjects with a primary study eye in which an intracanalicular depot was inserted. Analysis on the ITT population will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized” in the protocol has been changed to “The Full Analysis Set (FAS) will include all randomized subjects with depots inserted in both eyes. Analysis on the data for the primary study eye in the FAS will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.” The rationale behind this change is that the protocol allows for subjects with successful insertion of a depot in only one eye to be treated with IOP-lowering drops, which may have a systemic effect on both eyes or lead to bilateral treatment with IOP-lowering drops.
- (2) No subject visualization of depots is required.
- (3) The protocol (5.6) states, “At the conclusion of the 12 Week visit, if both eyes no longer have the depot present or depots have been removed bilaterally, the Investigator may be unmasked to the treatment assignment of the subjects who were assigned to OTX-TP or PV as those subjects may require IOP-lowering drops.” Due to the logistics involved and the potential for bias, the sponsor has determined that investigators and investigative site staff will not be unmasked until the end of the study.
- (4) An interim analysis as the primary efficacy analysis was planned as part of the protocol. As the study proceeded, the sponsor determined that the interim would not be necessary as accrual had been sufficient to shorten the time between the interim and final analyses.

Any changes to the planned analyses after unmasking and the final analysis will be described in the clinical study report.

20. References

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)

21. Revision History

Final version 1.0 of this SAP was signed on 02Jan2018. Changes for Version 2.0 are detailed here.

Summary of Changes

Section #	Description of Change	Rationale
Abbreviations	FAS added.	Previously omitted in error.
Section 5 “Masking and Unmasking” subsection	References to interim analysis were removed.	Sponsor determined that interim analysis was not needed.
Section 7 “Data Preparation”	References to interim analysis were removed.	Sponsor determined that interim analysis was not needed.
Section 8 “Per Protocol Population” subsection	References to interim analysis were removed.	Sponsor determined that interim analysis was not needed.
Section 9 “Data Analysis Conventions” subsection	References to interim analysis were removed, and precision for height and weight presentation was clarified.	Sponsor determined that interim analysis was not needed. Details on decimal precision were finalized.
Section 9 “Unit of Analysis” subsection	Clarification was made regarding the focus on bilaterally treated subjects and the classification of primary study eye.	Previous text was incomplete.
Section 9 “Unscheduled Visits” subsection	Clarification was made regarding the used of unscheduled visit data.	Previous text was incomplete.
Section 10 “Subject Disposition”	Descriptions of additional CRF data to be provided in listings was included.	Review of CRFs indicated additional data would be available.

Section 11 "Demographic Variables" subsection	Data on iris color collected at the Early Termination Visit was added.	Previously omitted in error.
Section 12 "Medical History" subsection	Typographical and grammatical errors have been corrected.	Originally in error.
Section 12 "Concomitant Medications" subsection	Criteria for IOP-lowering medications and TLFs presenting these data have clarified.	Final decision on IOP-lowering medications became available.
Section 13 "Intracanalicular Depot Visualization by the Investigator" subsection	References have been changed from primary eye/secondary eye to right eye/left eye	Descriptions of Screening/Baseline assessment listings had previously been described using primary/secondary eye. However, since the CRFs collected these data with respect to right and left eyes and primary eye was not determined until Baseline Visit 2, these were changed to right eye/left eye.
Section 13 "Intracanalicular Depot Removal" subsection	References have been changed from primary eye/secondary eye to right eye/left eye	Descriptions of Screening/Baseline assessment listings had previously been described using primary/secondary eye. However, since the CRFs collected these data with respect to right and left eyes and primary eye was not determined until Baseline Visit 2, these were changed to right eye/left eye.
Section 14 "Primary Analysis" subsection	Typographical and grammatical errors have been corrected.	Originally in error.
Section 14.1.2 "Punctum Examination"	References have been changed from primary eye/secondary eye to right eye/left eye	Descriptions of Screening/Baseline assessment listings had previously been described using primary/secondary eye. However, since the CRFs collected these data with respect to right and left eyes and primary eye was not determined until Baseline Visit 2, these were changed to right eye/left eye.
Section 15 "AE Summaries" subsection	Typographical and grammatical errors have been corrected.	Originally in error.

Section 12 "Concomitant Medications" subsection	The population reference for the summary of ocular and non-ocular concomitant medications has been corrected from FAS to Safety Population	Originally in error.
Section 15 "AE Summaries" subsection	Terminology has been changed to "subject withdrawal"	To match CRF language.
Section 15 "AE Summaries" subsection	AEs of special interest were defined and a summary of AEs of special interest was added.	Sponsor request
Section 16 "Interim Analysis"	References to interim analysis were removed.	Sponsor determined that interim analysis was not needed.
Section 20 "Changes from Protocol- Stated Analyses"	A rationale was added for using FAS rather than ITT for primary analysis.	Further explanation was required.
Headers of Sections 23-25	References to interim analysis were removed.	Sponsor determined that interim analysis was not needed.
Titles of TLFs.	Typographical and grammatical errors have been corrected.	Originally in error.
Section 23 "Tables"	14.1.1, 14.1.6.3, 14.1.6.4 and 14.2.4.2 were added to the top line delivery	Sponsor's request
Section 23 "Tables"	A table for ocular TEAEs of special interest was added.	Sponsor's request
Section 24 "Listings"	A visit date listing was added.	Sponsor's request
Section 24 "Listings"	A rescue medication listing was added.	Sponsor's request
Section 25 "Figures"	Three figures were added.	Completing references from the SAP text

22. Tables

Tables that will be included in the topline delivery are shown in boldface font.

Table Number	Title	Population
Table 14.1.1	Subject Disposition	All Enrolled Subjects
Table 14.1.2	Major Protocol Deviations	Full Analysis Set
Table 14.1.3	Demographic and Baseline Characteristics	Full Analysis Set

Table Number	Title	Population
Table 14.1.4	Baseline Disease Characteristics	Full Analysis Set
Table 14.1.5.1	Non-Ocular Medical History	Safety Population
Table 14.1.5.2	Ocular Medical History	Safety Population
Table 14.1.6.1	Non-Ocular Concomitant Medications	Safety Population
Table 14.1.6.2	Ocular Concomitant Medications	Safety Population
Table 14.1.6.3	IOP-Lowering Ocular Medications	Safety Population
Table 14.1.6.4	Rescue Medication Use (IOP-Lowering Drops) by Visit	Full Analysis Set
Table 14.2.1.1	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point MCMC Analysis – Primary Time Points	Full Analysis Set
Table 14.2.1.2	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point MCMC Analysis – Non-Primary Time Points	Full Analysis Set
Table 14.2.1.3	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point Pattern Mixture Analysis	Full Analysis Set
Table 14.2.1.4	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point LOCF Analysis	Full Analysis Set
Table 14.2.1.5	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point BOCF Analysis	Full Analysis Set
Table 14.2.1.6	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point Observed Data Analysis	Full Analysis Set
Table 14.2.1.7	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point Observed Data Analysis	Per Protocol Population
Table 14.2.1.8	Mean Observed, Change, and Percent Change from Baseline in Secondary Study Eye IOP by Time Point Observed Data Analysis	Full Analysis Set
Table 14.2.1.9	Mean Observed, Change, and Percent Change from Baseline in Secondary Study Eye IOP by Time Point Observed Data Analysis	Per Protocol Population
Table 14.2.2.1	Mean Observed, Change, and Percent Change from Baseline in Primary Study Eye IOP by Time Point and Strata MCMC Analysis	Full Analysis Set
Table 14.2.4.1	Insertion Results and Ease of Insertion	Safety Population
Table 14.2.4.2	Summary of Replacements	Safety Population
Table 14.2.4.3	Removal of Intracanalicular Depot	Safety Population
Table 14.2.5	Ocular Complaints by Study Eye	Safety Population
Table 14.2.6	Investigator Visualization of Intracanalicular Depot	Safety Population
Table 14.2.7	Punctum Examination Results	Safety Population
Table 14.3.1	Study Treatment Exposure	Safety Population
Table 14.3.2.1	Overall Summary of Adverse Events	Safety Population
Table 14.3.2.2.1	Non-Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.2	Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.3	Primary Study Eye Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population

Table Number	Title	Population
Table 14.3.2.2.4	Secondary Study Eye Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.5	Treatment Related Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.6	Treatment Related Non-Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.7	Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.8	Treatment Emergent Adverse Events Leading to Subject Withdrawal by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.9	Ocular Treatment Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.2.4	Non-Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Most Likely Cause	Safety Population
Table 14.3.3.1	Best Corrected Visual Acuity by Time Point and Eye	Safety Population
Table 14.3.3.2	Change from Baseline Category in Best Corrected Visual Acuity by Time Point and Eye	Safety Population
Table 14.3.4.1	Slit Lamp Biomicroscopy by Visit and Eye	Safety Population
Table 14.3.4.2	Shifts from Baseline in Slit Lamp Biomicroscopy by Visit and Eye	Safety Population
Table 14.3.5.1	Dilated Fundoscopy Examination by Visit and Eye	Safety Population
Table 14.3.5.2	Shifts from Screening to 12 Week Visit in Dilated Fundoscopy Examination by Visit and Eye	Safety Population
Table 14.3.6	Mean Observed and Change from Baseline in IOP by Time Point and Eye	Safety Population
Table 14.3.7.1	Slit Lamp Ocular Hyperemia by Visit and Eye	Safety Population
Table 14.3.7.2	Shifts from Baseline to Each Post-Baseline Visit in Ocular Hyperemia by Visit and Eye	Safety Population
Table 14.3.8	Mean Observed and Change from Baseline in Subject Ocular Comfort Assessment by Visit and Eye	Safety Population

23. Listings

Listing Number	Title	Population
Listing 16.1.7	Randomization Schedule	All Enrolled Subjects
Listing 16.2.1	Subject Disposition	All Enrolled Subjects
Listing 16.2.2.1	Protocol Deviations	All Randomized Subjects
Listing 16.2.2.2	Inclusion, Exclusion, and Procedural Exclusion Criteria	All Enrolled Subjects
Listing 16.2.2.3	Subjects Excluded from the Per Protocol Population	All Randomized Subjects
Listing 16.2.3	Visit Dates	All Randomized Subjects
Listing 16.2.4.1	Demographics	All Randomized Subjects
Listing 16.2.4.2	Baseline Characteristics: Current Diagnosis, Gonioscopy, Punctum Size, Cup to Disc Ratio, and Intraocular Pressure	Full Analysis Set
Listing 16.2.4.3	Pre-Treatment Perimetry	All Randomized Subjects

Listing Number	Title	Population
Listing 16.2.4.4	Pre-Treatment Pachymetry	All Randomized Subjects
Listing 16.2.4.5	Non-Ocular Medical History	Safety Population
Listing 16.2.4.6	Ocular Medical History	Safety Population
Listing 16.2.4.7	Prior and Concomitant Non-Ocular Medications	Safety Population
Listing 16.2.4.8	Prior and Concomitant Ocular Medications	Safety Population
Listing 16.2.4.9	Pregnancy Test Results	Safety Population
Listing 16.2.5.2	Insertion of Intracanalicular Depot	All Randomized Subjects
Listing 16.2.5.3	Investigator Intracanalicular Depot Visualization and Patency Check	Safety Population
Listing 16.2.5.4	Removal of Intracanalicular Depot	Safety Population
Listing 16.2.6.1	Intraocular Pressure	Safety Population
Listing 16.2.6.2	Ocular Complaints	Safety Population
Listing 16.2.8.1	Ocular Adverse Events	Safety Population
Listing 16.2.8.2	Serious Ocular Adverse Events	Safety Population
Listing 16.2.8.3	Ocular Adverse Events Leading to Subject Withdrawal	Safety Population
Listing 16.2.8.4	Non-Ocular Adverse Events	Safety Population
Listing 16.2.8.5	Serious Non-Ocular Adverse Events	Safety Population
Listing 16.2.8.6	Non-Ocular Adverse Events Leading to Subject Withdrawal	Safety Population
Listing 16.2.9.1	Best Corrected Visual Acuity (logMAR Scale)	Safety Population
Listing 16.2.9.2	Visual Acuity (logMAR) for Subjects Who Lost Three or More Lines	Safety Population
Listing 16.2.9.3	Slit Lamp Biomicroscopy	Safety Population
Listing 16.2.9.4	Dilated Fundus Examination and Cup to Disc Ratio	Safety Population
Listing 16.2.9.5	Punctum Examination Results	Safety Population
Listing 16.2.9.6	Punctum Size at Insertion	All Randomized Subjects
Listing 16.2.9.7	Slit Lamp Ocular Hyperemia and Ocular Comfort Assessment	Safety Population
Listing 16.2.9.8	Rescue (IOP-Lowering) Ocular Medications	Full Analysis Set

24. Figures

Figure Number	Title	Population
Figure 14.2.1	LSMeans for Primary Study Eye IOP by Time Point and Treatment (MCMC)	Full Analysis Set
Figure 14.2.2	LSMeans for Primary Study Eye IOP by Time Point and Treatment (MCMC)	Per Protocol Population
Figure 14.2.3	LSMeans Change from Baseline in Primary Study Eye IOP by Time Point and Treatment (MCMC)	Full Analysis Set
Figure 14.2.4	LSMeans Change from Baseline in Primary Study Eye IOP by Time Point and Treatment (MCMC)	Per Protocol Population
Figure 14.2.5	LSMeans Difference in Primary Study Eye IOP by Time Point (MCMC)	Full Analysis Set
Figure 14.2.6	LSMeans Difference in Primary Study Eye IOP by Time Point (MCMC)	Per Protocol Population
Figure 14.2.7	LSMeans for Primary Study Eye IOP by Time Point and Treatment (Observed Data)	Full Analysis Set
Figure 14.2.8	LSMeans for Primary Study Eye IOP by Time Point and Treatment (Observed Data)	Per Protocol Population
Figure 14.2.9	LSMeans Change from Baseline in Primary Study Eye IOP by Time Point and Treatment (Observed Data)	Full Analysis Set

Figure Number	Title	Population
Figure 14.2.10	LSMeans Change from Baseline in Primary Study Eye IOP by Time Point and Treatment (Observed Data)	Per Protocol Population
Figure 14.2.11	LSMeans Difference in Primary Study Eye IOP by Time Point (Observed Data)	Full Analysis Set
Figure 14.2.12	LSMeans Difference in Primary Study Eye IOP by Time Point (Observed Data)	Per Protocol Population