A prospective, multi-center, randomized, parallel-group, controlled study to evaluate the efficacy and safety of OTX-TIC (traverso) intracameral implant in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT)

Statistical Analysis Plan

OTX-TIC-2020-201

Version 1.0

Version Date: 26 January 2024

Sponsor

Ocular Therapeutix, Inc.
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CONFIDENTIALITY STATEMENT

SIGNATURE PAGE

I acknowledge that I have read the document and approve of the planned statistical analyses described herein by signing this document. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AS-OTC	Anterior Segment Optical Coherence Tomography
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best-Corrected Visual Acuity
BMI	Body Mass Index
C/D	Cup to Disk
CRC	Central Reading Center
CS	Clinically Significant
dB	Decibels
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter of Mercury
NCS	Not Clinically Significant
NFL	Nerve Fiber Layer
NSE	Non-study eye
OAG	Open-angle glaucoma
OCT	Optical Coherence Tomography
OD	Oculus Dextrus (right eye)
OHT	Ocular Hypertension
OTX-TIC	OTX-TIC (travoprost) Intracameral Implant
PDF	Portable Document Format
[redacted]	[redacted]
PGA	Prostaglandin
PLA	Polylactide
PSD	Pattern standard deviation
PT	Preferred Term
RNFL	Retinal Nerve Fiber Layer
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Study Eye
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VFI	Visual Field Index
WHO DDE	World Health Organization Drug Dictionary Enhanced

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol OTX-TIC-2020-201, Version 05, dated 22JAN2024.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (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.

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 clinical study report.

3 STUDY DESIGN

3.1 Description of Study

3.1.1 Description of Main Study

This is a prospective, multi-center, randomized, parallel-group, double masked, phase 2 clinical study designed to evaluate the efficacy, and safety of OTX-TIC (travoprost) intracameral implant in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT). Approximately 86 subjects will be enrolled in this study at approximately 25 sites in the United States (US). Subjects will be a randomized to one of three treatment groups as noted in Table 1.

Subject can have only one eye treated with OTX-TIC or Durysta™ as part of this study; that eye will be designated as the Study Eye (SE). If both eyes qualify for study entry the SE will be selected on the basis of the eye with the highest IOP after the protocol washout period. If both eyes have the same IOP after the washout period, the right eye will be chosen as the SE. Non-study eyes (NSE) will be treated with the PGA, if not contraindicated.

Table 1.Treatment Assignment Paradigm

Treatment Group	Number of Subjects	Study Eye (SE) Treatment	Non-Study Eye (NSE) treatment *
Group 1: OTX-TIC 5 µg (travoprost) Intracameral Implant	~16+	Dose strength: 5µg	Eye-drops: PGA QD
Group 2: OTX-TIC 26 µg (travoprost) Intracameral Implant	35	Dose strength: 26µg	Eye-drops: PGA QD

Group 3: Active Control	35	Durysta™	Eye-drops: PGA QD

QD= once daily

* The non-study eye, if needed, should be treated with prostaglandin analogues (PGA, if not contraindicated) QD in the evening, every effort should be made to endure the dose and frequency remain unchanged for the duration of the study.

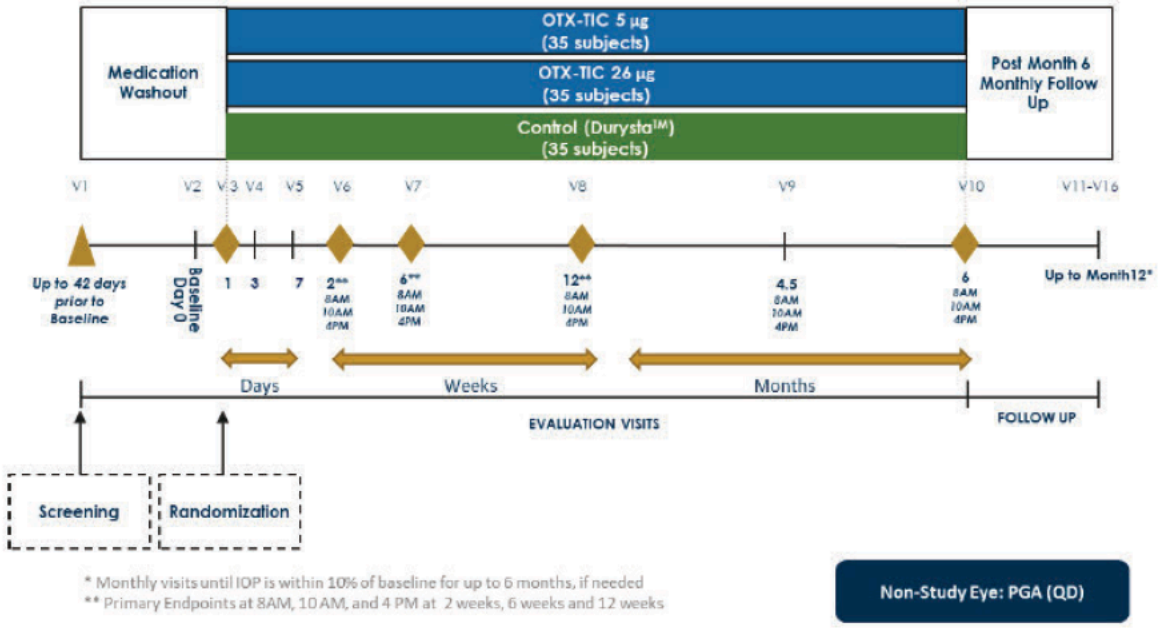
[redacted]

This study is intended to last for approximately 6 months from the time of injection of OTX-TIC or Durysta™. It consists of a **Screening Visit (Visit 1)** that should take place within approximately 56 days prior to the baseline visit, which includes a washout period of glaucoma medications, if needed.

Study participants will return after the washout period to the **Baseline Visit (Visit 2)** to confirm they meet eligibility criteria including IOP. Eligible subjects will then return for the **Injection Day Visit (Visit 3)** where they will be randomly assigned to one of 3 treatment groups (OTX-TIC implant 5 µg, OTX-TIC implant 26 µg, or Durysta™ implant). [redacted] Subjects will return for follow-up visits **2 days (Visit 4), and 6 days (Visit 5) post-injection** for safety evaluations and IOP check. Subjects will return for follow-up visits post-injection at **Week 2 (Visit 6), Week 6 (Visit 7)**, **Week 12 (Visit 8)**, and **Month 4.5 (Visit 9)**, when diurnal IOP will be checked, and safety evaluations will be performed. Following that, subjects will return at **Month 6 (Visit 10)** for evaluations, and eligibility for the repeat dosing sub-study.

For subjects that do not qualify or are not willing to participate in the repeat dose sub-study, they can be discharged from the main study, unless biological activity is noted per Investigator's discretion, (e.g., including but not limited to the case when the decrease of IOP at 8 AM is greater than or equal to 10% compared to the baseline measurement) or the [redacted] For all visits beyond Month 6, the same schedule of assessments should be followed as delineated for the Post Month 6 Monthly Follow-Up, and the Final Study Visit should follow the Post Month 6 Exit visit. The main study will be conducted per the schedule shown in Figure 1.

Figure 1. Study Schematic for Main Study (Initial Dose)



3.1.2 Description of Repeat Dose Sub-Study

This sub-study is intended to last for approximately 6-12 months from the time of repeat injection with OTX-TIC 26µg or Sham. Only OTX-TIC 26µg or Durysta™ subjects that have not required Rescue Therapy prior to Visit 10 will be asked to participate. Subjects may choose not to participate in the sub-study. For subjects who qualify and consent to participate in the repeat dosing sub-study, **Screening/Baseline** will be completed in conjunction with the **Visit 10 Month 6 Follow-up Visit**. Subjects that qualify will return for **Visit 11R (Injection/Day 1-R)** eligibility will be confirmed and subjects who are eligible will be assigned to one of three masked treatment groups. Subjects will be a randomized to one of three treatment groups as noted in Table 2.

- For subjects that received an initial dose of OTX-TIC 26 µg:
  [redacted]
- For subjects that received an initial dose of Durysta:
  - Sham Only

Table 2. Treatment Assignment Paradigm Repeat Dose Sub-Study

Treatment Group	Number of Subjects	Study Eye (SE) Treatment	Non-Study Eye (NSE) treatment *
Group 1: Sham injection + OTX-TIC 26 µg (travoprost) Intracameral	< 18	Dose strength: 26µg	Eye-drops: PGA QD

[redacted]			
Group 2: OTX-TIC 26 µg (travoprost) Intracameral [redacted]	< 18	Dose strength: 26µg	Eye-drops: PGA QD
Group 3: Sham injection	< 35	Sham injection	Eye-drops: PGA QD

* The number of subjects for group 1 and group 2 are dependent on the outcome of hydrogel resorption status at Visit 10 (Month 6) and therefore are unpredictable, however the total (group1+group2) is <=35

** The non-study eye, if needed, should be treated with prostaglandin analogues (PGA, if not contraindicated) QD in the evening, every effort should be made to endure the dose and frequency remain unchanged for the duration of the study.

[redacted]

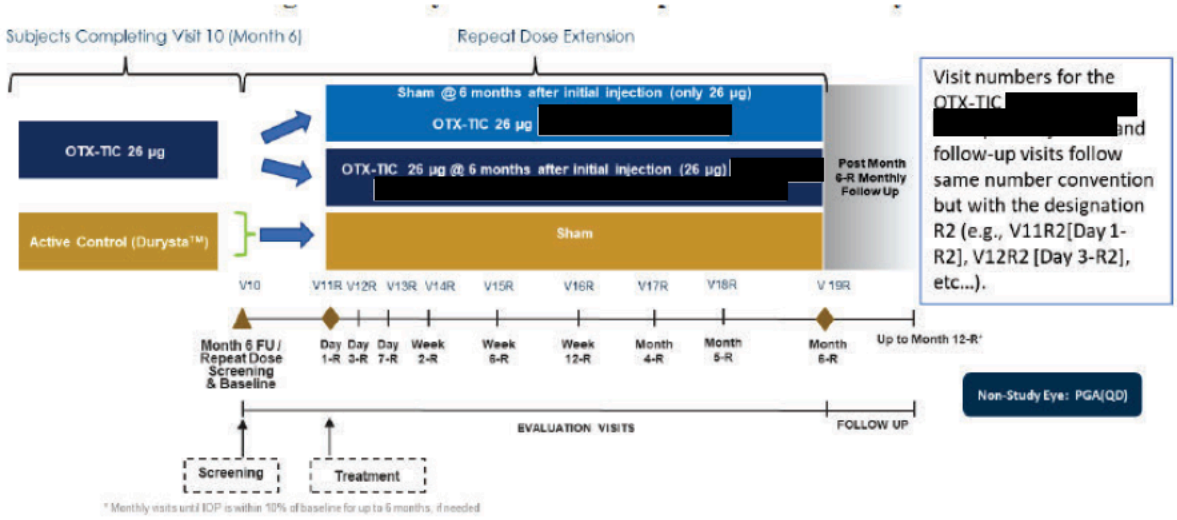
The NSE should continue to be treated with PGA (if not contraindicated) QD in the evening; every effort should be made to ensure the dose and frequency remain unchanged for the duration of the study. The treatment follow-up visits will occur on Day 2-R (Visit 12R), Day 7-R (Visit 13R), Week 2-R (Visit 14R), Week 6-R (Visit 15R), Week 12-R (Visit 16R), Month 4-R (Visit 17R), and Month 5-R (Visit 18R) for IOP checks, and safety evaluations will also be performed. Following that, subjects will return at Month 6-R (Visit 19R) for final evaluations, and discharge from the study.

If biological activity is noted per Investigator's discretion, (e.g., including but not limited to the case when the decrease of IOP at 8 AM is lower by at least 10% compared to the baseline measurement) or the implant is present at the Month 6-R visit, subjects will be followed monthly, until no biological activity is present and/or until the Investigator believes the subject is clinically stable despite the presence of the implant remnants in the anterior chamber. For all visits beyond Month 6-R, the same schedule of assessments should be followed as delineated for the Post Month 6-R Monthly Follow-Up, and the Post Month 6-R Exit visit.

Subjects in the Sham/OTX-TIC 26 µg group will receive their OTX-TIC 26 µg injection at the first visit after [redacted] At that time the subjects will restart their visit schedule at Day 1-R2 (Visit 11R2). All visits after this OTX-TIC 26 µg injection will have the designation R2 as well (including post 6-month follow-up should either biological activity continue, or the implant continue to be visualized).

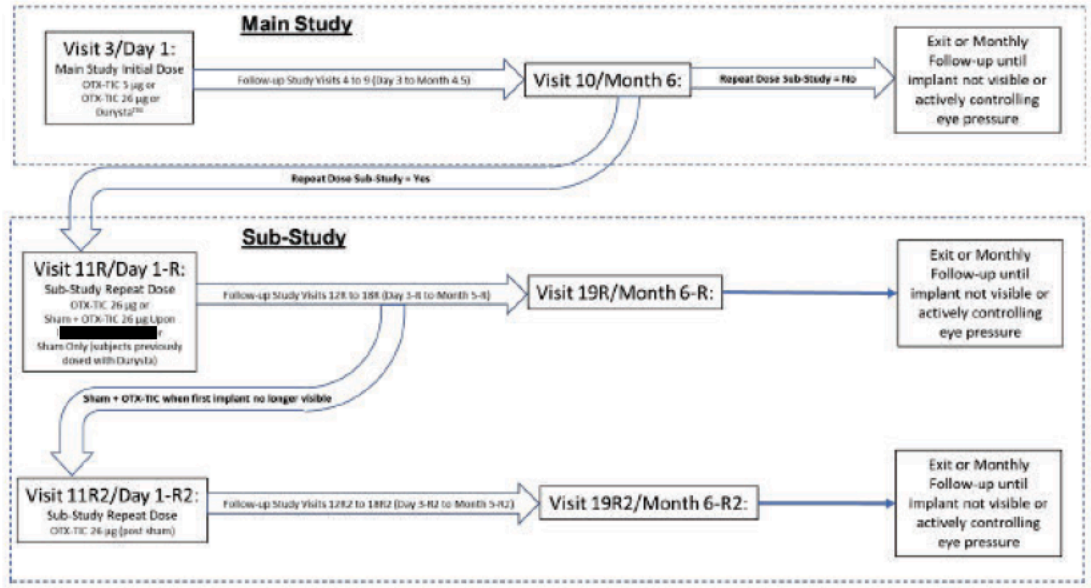
The repeat dosing sub-study will be conducted per the schedule shown in Figure 2.

Figure 2. Study Schematic for Repeat Dose Sub-Study



The schematic showing subject flow through the main study and repeat dosing sub-study is shown in Figure 3.

Figure 3. Schematic of Subject Flow Through the Main Study and Repeat Dose Sub-Study



3.2 Study Objectives

3.2.1 Main Study (Initial Dose)

The objectives of the trial are to assess the intraocular pressure (IOP) lowering efficacy, and safety of a single sustained release dose of the OTX-TIC drug product (2 dose strengths*) compared to a single injection Durysta™ in subjects with OAG or OHT.

[redacted]

3.2.2 Repeat Dose Sub-Study

The objectives of the sub-study are to explore the preliminary safety of a repeat sustained release dose of the OTX-TIC using 26 µg drug product in small sub-set of subjects with OAG or OHT previously treated with OTX-TIC 26 µg.

3.3 Randomization, Non-Randomized Treatment Assignment and Masking

3.3.1 Main Study (Initial Dose)

Subjects will be randomized to treatment assignment and the study will be double masked. The study personnel who collect efficacy data, and subjects will be masked to the treatment. If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data to individuals that are not involved in the study conduct or directly by the investigator if required in an emergency.

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme prior to unmasking. Unless the subject's safety requires otherwise, the decision to unmask a treatment assignment is to be made jointly by the Investigator and Sponsor's medical monitor.

Randomization schedules will be computer-generated by a qualified biostatistician independent of the study conduct or project team and uploaded into the Interactive Response Technology (IRT) system. The IRT system will be used for randomization and unmasking.

Subjects were randomized to be administered OTX-TIC 5µg, OTX-TIC 26µg or Durysta™ implant in a 1:1:1 ratio after qualifying for randomization, [redacted]. Enrollment continues in the OTX-TIC 26µg or Durysta™ treatment groups in a 1:1 ratio after qualifying for randomization. Non-study eyes will be treated with PGA drops, if not contraindicated. Investigators and their staff will be masked to the identity of treatment until the final database is locked. The Sponsor's personnel involved with the conduct and monitoring of the study will remain masked until completion of the study and database lock.

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme prior to unmasking. Unless the subject's safety requires otherwise, the decision to unmask a treatment assignment is to be made jointly by the Investigator and Sponsor's medical monitor.

A listing for randomization will be presented.

3.3.2 Repeat Dose Sub-Study

OTX-TIC 26µg or Durysta™ subjects that have not required rescue therapy prior to the Month 6 visit (Visit 10) and have consented to participate in the repeat dosing sub-study and met the repeat dosing eligibility will be assigned to a treatment group (not randomized) based on the criteria below.

- For subjects that received an initial dose of OTX-TIC 26 µg:
  [redacted]
- For subjects that received an initial dose of Durysta:
  - Sham Only

Non-study eyes will continue to be treated with PGA drops, if not contraindicated. The Sponsor's personnel involved with the conduct and monitoring of the study will remain masked until completion of the main study database lock for the interim analysis (once all subjects complete Month 6, Visit 10).

A listing for non-randomization treatment assignment will be presented.

3.3.3 Site Activities/Assessments by Masking Requirement

Masked Site Staff:

- IOP Measurement by applanation tonometry (Goldmann)
- BCVA
- Subject Ocular Comfort Score
- Patient Reported Outcome: Implant Acceptability Questionnaire
- AE assessment (as it is feasible)
- Concomitant Medication evaluation (as it is feasible)
- Pachymetry

Unmasked Site Staff:

- Slit Lamp Biomicroscopy including External Eye Exam
- Fundus exam (dilated and undilated)
- Specular Microscopy
- Anterior Segment (AS)-OCT
- OCT Optic nerve and RNFL
- Gonioscopy
- Implant assessment [redacted]
- Injection
- Randomization
- IP Management

Shared (can be completed by either masked or unmasked site staff):

- Informed Consent
- Urine Pregnancy Test
- Visual Field

3.4 Study Endpoints

3.4.1 Efficacy Endpoints

3.4.1.1 Primary Efficacy Endpoints

IOP changes from baseline at 8AM, 10AM, and 4PM at Week 2, Week 6, and Week 12 in the study eye.

3.4.1.2 Secondary Efficacy Endpoints

- Mean diurnal IOP changes from baseline at Week 2, Week 6, and Week 12 in the study and non-study eye.
- IOP changes from baseline at all other study visits (except those listed in the primary efficacy evaluations) in the study eye.
- IOP changes from baseline at all study visits in the non-study eye.
- Proportion of subjects who are well-controlled (mean diurnal IOP <=21 mmHg) on fewer, the same, and more number of topical IOP-lowering medications at all assessment visits compared to screening in the study and non-study eye.
- Mean time to rescue therapy in the study and non-study eyes.
- Mean number of rescue medications in the study and non-study eyes.

3.4.2 Ocular Safety Endpoints

- Incidence of adverse event reporting
- [redacted]
- Changes from baseline in subject ocular comfort assessment
- Changes from baseline in BCVA
- Changes from baseline in slit lamp biomicroscopy parameters
- Changes in gonioscopy parameters
- Changes from baseline fundus exam parameters
- Mean endothelial cell counts with specular microscopy
- Changes from baseline in endothelial cell counts with specular microscopy
- Mean central corneal thickness with Pachymetry
- Changes from baseline in central corneal thickness with Pachymetry
- Changes from baseline in Anterior segment (AS)-OCT parameters
- Changes from baseline in Automatic Visual Field parameters
- Changes from baseline in OCT Optic nerve and Retinal Nerve Fiber Layer (RNFL)
- Changes from baseline in Posterior Segment (PS)-OCT

3.4.3 Repeat Dosing Sub-Study Endpoints

- Changes from baseline in endothelial cell counts with specular microscopy in the study eye and non-study eye.
- Changes from baseline in central corneal thickness with Pachymetry in the study eye and non-study eye.
- IOP changes from baseline at all repeat dosing post injection Visits in the study eye and non-study eye.
- Mean diurnal IOP changes from baseline at Week 2-R/R2, Week 6-R/R2, and Week 12-R/R2 in the study and non-study eye.
- Proportion of subjects who are well-controlled (mean diurnal IOP <=21 mmHg) on fewer, the same, and more number of topical IOP-lowering medications at all repeat dosing sub-study assessment visits in the repeat dose sub-study compared to screening in the study eye and non-study eye.
- All other ocular safety evaluations in the main study.

3.4.4 Patient Reported Outcome Evaluations

- Implant Acceptability Questionnaire at 12 weeks and 6 months for the main study.

3.5 Study Treatment

3.5.1 Main Study (Initial Dose)

- OTX-TIC (travoprost) 5 µg Intracameral Implant*
- OTX-TIC (travoprost) 26 µg Intracameral Implant

[redacted]

Active Control:

- Durysta™ (Bimatoprost Implant)

3.5.2 Repeat Dose Sub-Study

- For subjects that received an initial dose of OTX-TIC 26 µg:

  [redacted]

- For subjects that received an initial dose of Durysta:
  - Sham Only

3.6 Study Duration

An individual subject's participation in the main trial will last approximately 6 Months after treatment. For subjects that qualify and consent to participation on the repeat dosing sub-study, participation would approximately be a total of 12 months for the OTX-TIC 26 µg and Sham

(initially dosed with Durysta) groups or 18 months for the Sham [redacted]

For any subjects that do not move into the repeat dose sub-study at Month 6 or complete 6 months of follow-up after the repeat dose and have evidence of biological activity as noted per Investigator's discretion, (e.g., including but not limited to the case when the decrease of IOP at 8 AM is lower by at least 10% compared to the baseline measurement) or implant is still present at Month 6/Month 6-R or Month 6-R2 visit, subjects will be followed monthly, until no biological activity present and/or until the Investigator believes the subject is clinically stable despite the presence of the implant remnants in the anterior chamber.

For a schematic showing subject flow through the main study and repeat dosing sub-study, see Figure 3. After the study, subjects will be treated per the standard of care, at the discretion of their physician.

Ongoing clinical investigational data will be reviewed by the Medical Monitor. The clinical investigation may be suspended if the Medical Monitor, upon review and evaluation of the clinical data, finds the severity or incidence of adverse events or complications unacceptable for continuation of the investigation.

3.7 Central Reading Center

A central reading center (CRC) will evaluate endothelial cell count (specular microscopy) and determine eligibility of both or one eye. The CRC will also evaluate AS-OCT, and OCT optic nerve and RNFL. Photographers and equipment must be certified by the Central Reading Center before imaging of any study subjects. Imaging will follow a standard protocol. Instructions for these procedures will be provided in a separate imaging manual.

4 ANALYSIS POPULATIONS

4.1 Main Study (Initial Dose)

Modified Intent-to-Treat (mITT): The mITT population will include all subjects who received an implant, investigational product (OTX-TIC or Durysta) in the study eye. The mITT population will be used as the primary efficacy analysis population and will also be used for all efficacy endpoints. Analyses performed on the mITT population will be according to the treatment received.

Per Protocol (PP): The Per-Protocol (PP) population is a subset of the mITT population and includes the subjects with no major protocol violations that would significantly impact the safety and efficacy evaluation of the drug. This population will be analyzed as treated using observed data only for confirmatory analyses. The Per Protocol population will be analyzed as treated.

Safety: The Safety population includes all randomized subjects who received an implant, investigational product (OTX-TIC or Durysta). The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

All Screened Subjects: All screened subjects will include all subjects who signed informed consent. Subject disposition and eligibility listings will be performed on all screened subjects.

4.2 Repeat Dose Sub-Study

Repeat Dosing Sub-Study Population: The Repeat Dosing Sub-Study Population includes subjects who were initially treated with OTX-TIC 26µg or Durysta in the main study and have consented and qualified to the repeat dose sub-study at the Month 6 (Visit 10) follow up visit in the main study and received any of sub-study treatments. The Repeat Dosing Sub-Study Population will be analyzed as treated.

5 STATISTICAL METHODS

5.1 Sample Size Justification

No formal sample size calculations were performed. This study is not powered to show statistical significance but will provide initial estimates and trends of the endpoints for use in future trial designs. The sample size will allow for safety information to be obtained, while still limiting the number of subjects exposed to the IP.

5.2 General Statistical Methods and Data Handling

5.2.1 General Methods

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 and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values.

Summaries for discrete variables will include frequencies and percentages. All percentages will be rounded to one decimal place.

Graphic approach such as line plots will be employed for efficacy variables when appropriate (e.g., IOP, IOP change from baseline).

All safety and efficacy summaries will be presented by treatment group and overall, where appropriate, for each study visit.

Listings will be sorted by treatment group, subject number, study visit, and parameter, as applicable.

5.2.2 Definition of Baseline

5.2.2.1 Main Study (Initial Dose)

For IOP, baseline will refer to the time-relevant last non-missing measure prior to injection of study treatment for main study (e.g., IOP at 8 AM at Visit 2 Baseline visit prior to injection). For all other variables, baseline will be defined as the last non-missing measure prior to initiation of investigational treatment. Differences between treatment groups will be calculated as OTX-TIC minus control and change from baseline will be calculated as follow-up visit minus baseline values.

5.2.2.2 **Repeat Dose Sub-Study**

The baseline in the main study [redacted] will be used f or the baseline of repeat dose sub-study.

5.2.3 **Unit of Analysis**

Efficacy and safety summaries will be presented for the study eye, and non-study eye if applicable. All summaries will be presented by treatment group and visit, where appropriate.

5.2.4 **Statistical Significance**

This study is not designed to show statistical significance, therefore, there will be no formal statistical testing. All summaries will be descriptive.

5.2.5 **Adjustments for Multiplicity**

No multiplicity adjustments will be made since there are no formal hypothesis tests.

5.2.6 **Computing Environment**

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coding using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 (or higher version). Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODRUG) GLOBAL B3 March 2022 (or higher version).

5.2.7 **Subpopulations**

No analyses of subgroups of subjects are planned.

5.2.8 **Withdrawals, Dropouts, Loss to Follow-up**

All subjects treated in the study will be required to adhere to the follow-up schedule as described in this protocol.

Subjects may withdraw from the clinical study at any time for any reason without jeopardy or prejudice and without compromising their clinical care by the Investigator. The Investigator also has the right to withdraw subjects from the study in the event of an intercurrent illness, AE, protocol violation and/or administrative reason.

For any subject who withdraws their consent following treatment, to the extent possible, the reason(s) for withdrawal will be documented on the End of Study eCRF.

If the withdrawal from the study is a result of an AE, or death, an AE Form will also be completed. If a subject is withdrawn from the study as a result of an AE, every attempt should be made by the Investigator to follow the subject until the AE has resolved or stabilized.

Every attempt will be made to contact subjects who are non-compliant or lost to follow-up and such attempts will be documented in the subject's study record.

Subjects who withdraw from the study after receiving the investigational product will not be replaced. Subjects who did not receive the implant will be replaced.

5.2.9 Missing or Inconclusive Data Handling

In general, there will be no imputation of missing data other than for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month
- Dates with both day and month missing will be imputed as 31 Dec
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the end of study date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.
- The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

5.2.10 Visit Windows

Visit windows will be calculated based on the Schedule of Assessments in Appendix 1. Any visits or procedures performed outside the scheduled visits will be documented in the Unscheduled Visit page of the eCRF. All ocular examinations need to be performed on both eyes. Although there is a visit window around the expected visit date, nominal visits will be used for the per-visit analyses. Data from unscheduled visit will be presented in subject listings. In addition, the subject listing of implant removal on unscheduled visit will also be presented.

6 SUBJECT DISPOSITION

6.1 Disposition

Subject disposition will be summarized by treatment group and overall.

6.1.1 Main study (Initial Dose)

The disposition will include the numbers of subjects who were screened, screened not randomized, randomized, randomized not treated, treated, in mITT population, in PP population, in safety population, completed Visit 6 (follow-up Week 2 visit), completed Visit 7 (follow-up Week 6 visit), completed Visit 8 (follow-up Week 12 visit), completed Visit 10 (follow-up Month 6 visit), completed the main study, and discontinued from the main study. Percentages of subjects who completed Visit 6 (follow-up Week 2 visit), completed Visit 7 (follow-up Week 6 visit), completed Visit 8 (follow-up Week 12 visit), completed Visit 10 (follow-up Month 6 visit), completed the main study, exited the main study, participated the repeat dose sub-study, and discontinued from the main study will be presented. The percentages will be calculated using the number of subjects treated with any investigational product (OTX-TIC or Durysta) as the denominator, unless otherwise noted.

Reasons for screen failure and discontinuation will also be summarized.

- The reasons for screen failure include adverse event, death, failure to meet eligibility criteria, unsuccessful intracameral injection, lost to follow-up, subject withdrawal of consent and other. Percentages will be calculated using screen failure subjects as the denominator.
- The reasons for discontinuation include adverse event, death, investigator decision, lost to follow-up, pregnancy, significant protocol deviation, study terminated by sponsor, subject withdrawal of consent and other. Percentages will be calculated using the number of subjects who discontinued from the main study as the denominator.

Subject disposition data will be presented in a listing.

6.1.2 Repeat Dose Sub-Study

The disposition will include the numbers of subjects who plan to continue to repeat-dose sub-study, meet all sub-study eligibility, signed the informed consent, qualified and consented, assigned to treatment, assigned to treatment but not treated, treated at visit 11R, treated at visit 11R2, in the Repeat Dosing Sub-Study Population, completed Visit 19R/Visit 19R2 (follow up Month 6-R/Month 6-R2), completed the sub-study, and discontinued from the sub-study. Percentages of subjects who completed Visit 19R/Visit 19R2 (Follow up Month 6-R/Month 6-R2), completed the sub-study, and discontinued from the sub-study will be presented. The percentages will be calculated using the number of subjects who were assigned to each treatment as the denominator, unless otherwise noted.

6.2 Protocol Deviations

6.2.1 Main study (Initial Dose)

Protocol deviation will be reviewed by the sponsor at on-going basis. Major protocol deviations are determined by a review of the data prior to the conduct of statistical analyses may result in the removal of a subject's data from the PP Population. This file will include a description of the protocol deviations, classification of major or minor, as well as which protocol deviations that warrant exclusion from PP population. The file will be finalized prior to hard database lock. Major

and minor protocol deviations will be summarized by treatment groups and overall using mITT population in the main study.

Protocol deviations, including both major and minor deviations, will be presented in a listing.

6.2.2 Repeat Dose Sub-Study

Protocol Deviations will be summarized and listed in a similar way to the main study using the Repeat Dosing Sub-Study Population in the repeat dose sub-study.

7 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

7.1 Main study (Initial Dose)

7.1.1 Demographics

The summary of demographics and baseline characteristics will be based on mITT population in the main study. Summary statistics (e.g., number of subjects, mean, SD, median, minimum, and maximum) will be generated for the continuous variable age and age grouping (years), by treatment group and for all subjects. Age will also be categorized as follows: < 65 years and ≥ 65 years.
The number and percentage of subjects in each class of qualitative demographic variable (age, age grouping, gender, ethnicity, race, specific Asian sub-category, and iris color) will be tabulated by treatment group and for all subjects.

7.1.2 Baseline Characteristics

Baseline characteristics will be summarized for study eye and non-study eye separately.

Duration of since diagnosis of either OAG (primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT, Intraocular Pressure (IOP), Central Corneal Thickness by Pachymetry, Endothelial Cell Count, OCT average RNFL thickness, Visual Field including mean deviation, pattern standard deviation and visual field index and the number of glaucoma medications will be summarized using descriptive statistics as continuous endpoints for mITT population in the main study by treatment group and overall. The number and percentage of subjects who use glaucoma medication/s will be categorized as follows: 1 medication, 2 medications, and >2 medications and will be tabulated by treatment group and for all subjects.

Subject demographics and baseline characteristics will be presented in a listing. Other baseline characteristics, e.g., BCVA, slit lamp biomicroscopy and fundus examinations, will also be summarized; see each respective section below.

7.2 Repeat Dose Sub-Study

The summary of demographics and baseline characteristics will be based on Repeat Dosing Sub-Study Population in the repeat dose sub-study. Demographics and baseline characteristics will be summarized and listed in a similar way to the main study.

8 MEDICAL HISTORY, MEDICATIONS AND MEDICAL PROCEDURES

8.1 Main study (Initial Dose)

8.1.1 Medical history

Medical history, including ocular medical history, will be coded using MedDRA Version 25.1 (or a later version if updated during the study). Medical history will be presented separately for ocular and non-ocular histories. Non-ocular medical history will be summarized in the mITT population by system organ class (SOC) and preferred term (PT) by treatment group and overall. SOC will be sorted alphabetically. PT will be sorted by descending frequency overall within each SOC. Subjects with a particular medical history event or medical history class will be counted once at the PT level and once at the SOC level. Ocular medical history will be summarized using discrete summary statistics and presented separately for study eye and non-study eye. Non-ocular medical history will be similarly summarized but at the subject level for the mITT population.

Data listings will be provided for medical history as well.

8.1.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG) GLOBAL B3 (Version September 2022 [or a later version if updated during the study]) and summarized by therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 3 classification) and preferred name. Subjects are counted only once under each therapeutic class or preferred name (generic drug name) for which they have at least one concomitant medication. If the ATC3 classification is not provided, then the next lowest classification that is provided in the coding dictionary will be used.

Concomitant medications are medications which started 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 during the study period. Prior medications are medications which are started before the first administration of study drug.

Ocular prior and concomitant medications will be summarized using discrete summary statistics and presented separately for study eye and non-study eye using Safety population. Non-ocular prior and concomitant medications will be similarly summarized but at the subject level.

Subject concomitant medications will be presented in separate listings for ocular and non-ocular data. The listings will indicate if medications are prior or concomitant medications.

8.1.3 Prior and Concomitant Procedures

Prior and concomitant procedures will be presented in separate listings for ocular and non-ocular data using Safety population. The listings will indicate if procedures are prior or concomitant procedures.

8.1.4 Rescue Therapy

If at any point in the study the investigator determines that the IOP is not adequately controlled, IOP lowering drops may be provided as rescue therapy at the Investigator’s discretion after

discussion with the Medical Monitor to ensure the subjects' safety. Rescue therapy is the IOP-lowering medication recorded in the eCRF as a concomitant medication with the indication of "Used as a Rescue Medication". Weeks to rescue therapy will be defined as:

Weeks to Rescue Therapy = (Date of receiving first rescue therapy

– Date of successful injection of the implant in the SE + 1) /7

Proportion of subjects receiving rescue medications, proportion of subjects receiving rescue medications by number of medications and the number of rescue medications at all assessment visits will be summarized by treatment group and overall separately for study eye and non-study eye using mITT population.

The median time in weeks to the first rescue therapy will be summarized by treatment group using Kaplan-Meier methods, and the 95% CI will be presented. The rescue therapy survival curve will be estimated by treatment group using Kaplan-Meier product limit estimates. Subjects who exit the study without receiving any rescue therapy will be censored at their last visit date.

A listing will be provided for the rescue medications.

8.2 **Repeat Dose Sub-Study**

Medical history, prior and concomitant medications/procedures for repeat dose sub-study will be summarized and listed in a similar way to the main study using Repeat Dosing Sub-Study Population.

8.2.1 **Rescue Therapy**

Rescue therapy is the IOP-lowering medication recorded in the eCRF as a concomitant medication with the indication of "Used as a Rescue Medication". Weeks to rescue therapy will be defined as:

Weeks to Rescue Therapy = (Date of receiving first rescue therapy

– Date of successful injection of the initial implant in the SE + 1) /7

Proportion of subjects receiving rescue medications, proportion of subjects receiving rescue medications by number of medications and the number of rescue medications at all assessment visits in the repeat dose sub-study will be summarized by treatment group and overall separately for study eye and non-study eye using Repeat Dosing Sub-Study Population.

The median time in weeks to the first rescue therapy will be summarized by treatment group using Kaplan-Meier methods with Repeat Dosing Sub-Study Population, and the 95% CI will be presented. The rescue therapy survival curve will be estimated by treatment group using Kaplan-Meier product limit estimates. Subjects who exit the study without receiving any rescue therapy will be censored at their last visit date.

A listing will be provided for the rescue medications using Repeat Dosing Sub-Study Population.

9 TREATMENT ADMINISTRATION AND EXPOSURE

9.1 Main study (Initial Dose)

9.1.1 Treatment Administration

Subject treatment administration will be summarized using discrete summary statistics by treatment group and overall. The treatment administration will include the numbers of subjects who were administrated by study treatment at visit 3/Day 1 (injection day), the position of implant in the anterior chamber and the method of implant procedure.

A subject listing will also be provided.

9.1.2 Injection Results

The Investigator will provide and grade the level of ease of injection of the intracameral implant as “easy”, “moderate”, or “difficult”. The injection results and ease of injection will be recorded on the appropriate eCRF. Responses will be summarized using discrete summary statistics at visit 3/Injection Day 1 (post-injection) by treatment group. A subject listing will also be provided.

9.1.3 Implant Exposure

Implant exposure will be calculated in weeks using the following:

Implant Exposure (weeks) = Average of (Date of last implant visualization – Date of successful injection of the initial implant in the SE + 1)/7 and (Date of first implant non-visualization after the last implant visualization in the SE – Date of successful injection of the initial implant in the SE + 1)/7

If all records are visualized, last record date will be used as visualization and non-visualization date.

If all records are non-visualized, first record date will be used as visualization and non-visualization date.

For other cases, last visualized date will be determined first, then

- first non-visualized after the last visualized will be determined
- if the last visualized is the last record, then last record date will be used for non-visualized. Implant exposure will be summarized with continuous descriptive statistics for each treatment group using the safety population. A subject listing will also be provided.

9.2 Repeat Dose Sub-Study

9.2.1 Treatment Administration

Subject treatment administration will be summarized using discrete summary statistics by treatment group and overall. The treatment administration will include the numbers of subjects who were administrated by study treatment (OTX-TIC 26 µg/ Sham) at visit 11R/Day 1-R (Repeat Injection Day), the numbers of subjects who were administrated by post-hydrogel resorption treatment at Visit 11R2/Day 1-R2 (for subjects who are assigned to sham+ OTX-TIC 26 µg group in the repeat dose sub-study), duration between 11R/Day 1-R and Visit 11R2/Day 1-R2 (days) for

subjects who are assigned to sham+ OTX-TIC 26 µg group, and the position of implant in the anterior chamber and the method of implant procedure.

A subject listing will also be provided.

9.2.2 **Injection Results**

The Investigator will provide and grade the level of ease of injection of the intracameral implant as “easy”, “moderate”, or “difficult”. The injection results and ease of injection will be recorded on the appropriate eCRF. Responses will be summarized using discrete summary statistics at visit 11R/Day 1-R (post-injection) as well as at Visit 11R2/Day 1-R2 (post-injection) by treatment group. A subject listing will also be provided.

9.2.3 **Implant Exposure**

Implant exposure will be calculated in days using the following:

Implant Exposure (weeks) = Average of (Date of last implant visualization – Date of successful injection of the initial implant in the SE + 1)/7 and (Date of first implant non-visualization after the last implant visualization in the SE – Date of successful injection of the initial implant in the SE + 1)/7

If all records are visualized, last record date will be used as visualization and non-visualization date.

If all records are non-visualized, first record date will be used as visualization and non-visualization date.

For other cases, last visualized date will be determined first, then

- first non-visualized after the last visualized will be determined
- if the last visualized is the last record, then last record date will be used for non-visualized.

Implant exposure will be summarized with continuous descriptive statistics for treatment group using the repeat dosing sub-study population. A subject listing will also be provided.

10 STATISTICAL ANALYSIS

10.1 **Efficacy Analyses – Main Study (Initial Dose)**

The efficacy summaries and analyses will be presented for both study and non-study eyes.
Due to the limited sample size, descriptive summary statistics will be used for the study reporting. No formal statistical hypothesis testing will be performed.

10.1.1 Primary Efficacy Analyses

10.1.1.1 Primary Efficacy Variables

The primary efficacy measurement is IOP. IOP of each eye will be measured using the Goldmann applanation tonometer at 8AM, 10AM and 4PM on each visit (Week 2, Week 6 and Week 12). For each IOP assessment, 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. The IOP value for a given eye will be the median of all measurements.

10.1.1.2 Primary Efficacy Analyses

The primary efficacy analyses of Intraocular Pressure (IOP) changes from baseline at 8AM, 10AM and 4PM at Week 2, Week 6 and Week 12 Visits will be performed on the mITT population. Data collected after the receipt of IOP lowering medication (rescue therapy) will be treated as missing.

In addition, the below two sensitivity analyses will be performed:

Sensitivity Analysis 1: The primary efficacy analysis will be repeated on the PP population.

Sensitivity Analysis 2: The primary efficacy summary will be repeated with all observed data.

IOP observed data will be presented in a listing.

10.1.2 Secondary Efficacy Analyses

Descriptive summary statistics will be used to summarize secondary efficacy endpoints. All secondary efficacy analyses will be performed based on the mITT population. Data collected after the receipt of IOP lowering medication (rescue therapy) will be treated as missing.

The observed mean diurnal IOP and IOP changes from baseline at 8AM, 10AM and 4PM at Week 2, Week 6, Week 12 in the study eye and non-study eye will be summarized using continuous descriptive statistics by visit for each treatment group and over all subjects. Data collected after the receipt of IOP lowering medication (rescue therapy) will be treated as missing. Additional summaries will be repeated with PP population and all observed data.

The observed and mean change from baseline in IOP at Days 1, 3, 7, Months 4.5, Month 6, the Post Month 6 Monthly Follow-Up visits and the Post Month 6 Exit visit in the study eye and non-study eye will be summarized using continuous descriptive statistics by visit for each treatment group and over all subjects. Data collected after the receipt of IOP lowering medication (rescue therapy) will be treated as missing. Additional summaries will be repeated with PP population and all observed data.

Proportion of subjects who are well-controlled receiving fewer, the same, and more number of topical IOP-lowering medications at all assessment visits compared to screening in the study eye

and non-study eye will be summarized for each treatment group and over all subjects. Well-controlled subjects are those who have mean diurnal IOP <=21 mmHg after receiving the investigational product (OTX-TIC or Durysta).

A Scatter plot will be produced to show IOP by treatment group (5 µg OTX-TIC, 26 µg OTX-TIC and Active control (Durysta™)), visit (Week 2, Week 6 and Week 12), and time point (8AM, 10AM and 4PM). Mean change from baseline for each treatment arm will be presented in a similar figure. Both figures will be presented separately for study eye and non-study eye in mITT population using observed data only.

10.2 **Safety Analyses**

All safety analyses will be conducted on the Safety population.

10.2.1 **Adverse Events**

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 (or higher version).

Treatment-emergent adverse events (TEAEs) are defined as any adverse event that occurs or worsens on or after the day that study treatment is initiated.
An overall summary including the number of events, the number and percentage of subjects who experienced at least one TEAE will be presented by treatment group and overall. The overall summary will also include at least one TEAE, at least one ocular TEAE, at least one non-ocular TEAE, treatment-related serious TEAE, treatment-related serious ocular TEAE, treatment-related serious non-ocular TEAE, TEAE leading to insert removal, TEAE leading to subject discontinuation from the study, and TEAE leading to death.

TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). Subjects are counted only once under each SOC or PT for which they have at least one TEAE. Summaries by relationship to study product, by relationship to study procedure and by maximum severity will also be provided. Ocular and non-ocular TEAEs will be summarized separately. Summary of ocular TEAEs will be separated by study eye and non-study eye.

Serious TEAEs will be summarized similarly. This includes summaries of ocular Serious TEAEs for study eye, ocular Serious TEAEs for non-study eye, and non-ocular serious TEAEs. Summaries by SOC and PT, by relationship to study product and by relationship to study procedure and by maximum severity will be provided.

All AEs will be presented in a subject listing with a flag indicating TEAE. TEAEs leading to study treatment discontinuation will be listed separately. In addition, all serious AEs will be presented in a separate listing.

All AEs for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sub-study population for all assessment visits in the main study and repeat dose sub-study.

10.2.2 **Implant Assessments**

The intracameral implant/visualization will be assessed and summarized using discrete summary statistics at each post-injection visit. The summary table will include the number of subjects with the study eye examined using the gonioscopy, the location of the implant, the grade (0-3) of the implant scores, the number of subjects with microparticles present outside the implant and the location of microparticles. A subject listing will be provided.

The pre-injection implant assessment on Visit 11R (Repeat Injection Day 1-R) as well as the Visit 11R2 (post-hydrogel resorption treatment Day 1-R2) and the implant assessment at each post-injection assessment for repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population.

In addition, number of subjects who are assigned in the Sham/OTX-TIC 26 µg group and receive their OTX-TIC 26 µg injection at the first visit after Visit 11R where complete resorption of the initial implant hydrogel is confirmed (Grade 0 on the Implant Assessment) will be summarized using the discrete summary statistics at each assessment visit using repeat doing sun-study population.

10.2.3 **Ocular Comfort Assessment**

The ocular comfort scores will be summarized using continuous descriptive statistics at each visit by treatment group and overall, for the study eye and non-study eye separately. Mean change from Baseline will also be summarized for each post-baseline study visit by treatment group and overall, for the study eye and non-study eye separately.

A subject listing of the ocular comfort assessments, including the Investigator's response to the expectedness of the score and any action taken to alleviate discomfort, will also be produced.

The ocular comfort assessment for repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sub-study population for all assessment visits in the repeat dose sub-study.

10.2.4 **Best Corrected Visual Acuity**

Observed and mean change from baseline (CFB) in BCVA will be summarized using continuous descriptive statistics over all study visits by treatment group and overall for the study eye and non-study eye separately.

In addition, the number and percent of subjects with a decrease of >10, 15 and 30 letters of observed value on compared to baseline will be summarized at each post-baseline visit by treatment group and overall, for the study eye. A subject listing of BCVA will be presented.

BCVA for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.5 **Slit-Lamp Biomicroscopy Examination**

A slit lamp biomicroscopy examination of the external adnexa, Conjunctiva/Sclera, Iris/Pupil, cornea, anterior chamber, and lens, will be performed at scheduled visits (see Appendix 1). The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

The results will be summarized using counts and percentages for each treatment group and study visit for the study eye and non-study eye separately. Percentages will be based on the number of subjects with non-missing results for a given parameter.

In addition to the above assessments, the slip lamp biomicroscopy will be used to evaluate anterior chamber cells and anterior chamber flare; to determine if a hypopyon is present.

The anterior chamber will be examined for the presence of signs of ocular inflammation. Anterior chamber cell count, and flare will be graded using the SUN Working Group grading scheme (see Appendix 2). The results of anterior chamber cells grade and flare grade will be summarized using counts and percentages for each treatment group and study visit for the study eye and non-study eye separately. Percentages will be based on the number of subjects with non-missing results for a given parameter.

The count of anterior chamber cells will be summarized using continuous descriptive statistics for each treatment group and study visit for the study eye and non-study eye separately.

Shift tables for the slit lamp biomicroscopy parameters (external adnexa, Conjunctiva/Sclera, Iris/Pupil, cornea, anterior chamber, lens, anterior chamber cells and anterior chamber flare) will also be provided comparing each post-Baseline visit to Baseline.

Hypopyon and lens status will be summarized using counts and percentages for each treatment group and study visit for the study eye and non-study eye separately. Percentages will be based on the number of subjects with non-missing results for a given parameter.

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

Slit lamp biomicroscopy examination for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.6 **Gonioscopy**

The Gonioscopy is performed using the procedure as described in Appendix 3. Results will be summarized using counts and percentages for each treatment group and study visit for the study eye and non-study eye separately. Percentages will be based on the number of subjects with non-missing results for a given parameter. Shift tables for the gonioscopy parameter (grade) will also be provided comparing each post-Baseline visit to Baseline.

A subject listing of the gonioscopy parameters will be presented.

The gonioscopy parameters for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.7 **Fundus Examination**

Each of the following will be evaluated and documented as normal, abnormal NCS, or abnormal CS: Vitreous, macula, peripheral retina, choroid and optic nerve.

The results will be summarized using counts and percentages for each treatment group and study visit for the study eye and non-study eye separately. Percentages will be based on the number of subjects with non-missing results for a given parameter.

The cup to disc (C/D) ratio, vitreous haze and vitreous cells will also be evaluated. The grading scheme for vitreous haze and vitreous cells are described in Appendix 4.

The cup to disc (C/D) ratio will be summarized for study eye and non-study eye separately using continuous descriptive statistics by study visit for each treatment group and overall.

The vitreous haze (Absent, Trace, 1+,2+,3+, 4+, Not done) and vitreous cells (0, 0.5+,1+,2+,3+,4+, Not done) will be summarized using counts and percentages for each treatment group and study visit for the study eye and non-study eye separately. Percentages will be based on the number of subjects with non-missing results for a given parameter.

Shift tables for the fundus examination parameters (Vitreous, macula, peripheral retina, choroid, optic nerve, vitreous haze scale, and vitreous cells scale) will also be provided comparing each post-Baseline visit to Baseline.

Fundus examination data will be presented in a listing.

All fundus exam parameters for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.8 **Endothelial Cell Count with Specular Microscopy**

Specular microscopy will be used to determine the endothelial cell count at scheduled visits (see Appendix 1). Endothelial cell counts will be determined using an automated and manual method by the CRC based on images sent by the study sites. The observed and mean change from baseline will be summarized for both methods using continuous descriptive statistics by visit at each treatment group and overall for the study eye and non-study eye. In addition, number and percentage of subjects who have 10%, 20% and 30% of endothelial cell loss compared to baseline will also be summarized for both methods at each treatment group and study visit for the study eye and non-study eye separately. Percentages will be based on the number of subjects with non-missing results for a given parameter.

A subject listing of specular microscopy (SM) including the endothelial cell counts as well as other SM parameters will also be presented.

The endothelial cell count for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.9 **Central Corneal Thickness by Pachymetry**

The corneal thickness at scheduled visits (see Appendix 1). In addition, the observed and mean change from baseline for the study eye and non-study eye will be summarized using continuous descriptive statistics by visit for each treatment group and over all subjects. A total of 3 measurements will be made at each scheduled visit with the final result being the mean of the 3 measurements.

A subject listing of the corneal thickness parameters will also be produced.

The central corneal thickness for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.10**Anterior Segment OCT (AS-OCT)**

The measurement will be made at each scheduled visit (see Appendix 1). The observed value for AS OCT Iridocorneal Angle 6 o'clock and mean change from baseline for the study eye and non-study eye will be summarized using continuous descriptive statistics by visit for each treatment group and all subjects combined.

A subject listing of all AS-OCT will also be produced.

The AS-OCT parameters for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.11**Visual Field**

Visual field examinations will be performed using a Humphrey automated perimetry test at scheduled visits (see Appendix 1). Visual fields will be reported as normal, abnormal clinically significant, or abnormal not clinically significant and the mean deviation will also be recorded in decibels (dB). The visual field classification results will be summarized using counts and percentages for each treatment group and over all subjects at each visit for the study eye and non-study eye. Percentages will be based on the number of subjects in each treatment group with non-missing responses. A continuous summary of the mean deviation, Pattern Standard Deviation (PSD), fixation losses, false positive ratio, false negative ratio and Visual field index (VFI)including mean change from baseline, will be provided for each eye.

A subject listing of the visual field parameters will also be produced.

Visual field measurement for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.12 OCT Optic Nerve and Retinal Nerve Fiber Layer Thickness

The measure of average retinal nerve fiber layer (RNFL) thickness is found using optical coherence tomography at scheduled visits (see Appendix 1) and mean change from baseline for the study eye and non-study eye will be summarized using continuous descriptive statistics by visit for each treatment group and over all subjects.

A subject listing of ON OCT including the RNFL measurements will also be produced.

The RNFL measurements for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.2.13 Posterior Segment (PS)-OCT

The measurement will be made at each scheduled visit (see Appendix 1) and mean change from baseline for the study eye and non-study eye will be summarized using continuous descriptive statistics by visit for each treatment group and all subjects combined.

A subject listing of all PS-OCT will also be produced.

The PS-OCT parameters for the repeat dose sub-study will be summarized and listed in a similar way to the main study using repeat doing sun-study population for all assessment visits in the repeat dose sub-study.

10.3 Repeat Dosing Sub-Study Analyses

The repeat dosing sub-study analyses will be performed on the repeat dosing sub-study population. There will be no formal statistical testing for the repeat dose sub-study. All summaries will be descriptive. In addition, the sham group in the repeat dosing sub-study presented in the summary tables is for masking purpose only and it will not be used to do the comparison with the OTX-TIC treatment groups.

The observed and change from baseline in endothelial cell counts will be summarized for automated and manual methods using continuous descriptive statistics at all repeat dosing sub-study assessment visits by treatment group for the study eye and non-study eye with the observed data only. A subject listing will be provided.

The observed and change from baseline in central corneal thickness with Pachymetry will be summarized using continuous descriptive statistics at all repeat dosing sub-study assessment visits by treatment group for the study eye and non-study eye with the observed data only. A subject listing will be provided.

The observed and change from baseline in IOP will be summarized using continuous descriptive statistics by visit, time, and treatment at all repeat dosing sub-study assessment visits for the study eye and non-study eye. Data collected after the receipt of IOP lowering medication (rescue therapy) will be treated as missing. Additional summaries will be repeated with all observed data. A subject listing will be provided.

The observed mean diurnal IOP and IOP changes from baseline at 8AM and 10AM at Week 2-R/R2, Week 6-R/R2, and Week 12-R/R2 in the study eye and non-study eye will be summarized using continuous descriptive statistics by visit for each treatment group and over all subjects. Data collected after the receipt of IOP lowering medication (rescue therapy) will be treated as missing. Additional summaries will be repeated with all observed data.

Proportion of subjects who are well-controlled receiving fewer, the same, and more number of topical IOP-lowering medications at all repeat dosing sub-study assessment visits compared to screening in the study eye and non-study eye will be summarized for each treatment group and over all subjects. Well-controlled subjects are those who have mean diurnal IOP <=21 mmHg after receiving the investigational product (OTX-TIC or Durysta).

All safety endpoints will be summarized and listed in a similar way to the main study using repeat doing sub-study population. The safety analyses are described in section 0.

10.4 **Patient Reported Outcome Analyses**

The implant Acceptability Questionnaire at 12 weeks, 6 months and unscheduled visits for the main study will be presented in a listing.

The implant Acceptability Questionnaire at Month 6-R and Month 6-R2 for the repeat dose sub-study will be presented in a listing.

11 INTERIM ANALYSES

11.1 **Main Study (Initial Dose)**

An analysis will be conducted when all subjects have reached their Month 6 visit, unless completed an early termination visit. Subjects will continue to be followed per the protocol if they meet criteria to continue beyond Month 6. An end of trial analysis update of data beyond Month 6 will be done after all subjects have exited the study.

11.2 **Repeat Dose Sub-Study**

An analysis will be conducted with all available subjects enrolled in the OTX-TIC 26 µg arm who have reached their Month 6-R/6-R2 visit, when the main study analysis is being done. The sub-study will continue until all subjects have exited the study. Subjects will continue to be followed per the protocol if they meet criteria to continue beyond Month 6-R/6-R2. An analysis update of data will be done after all subject enrolled in the OTX-TIC 26 µg arm have reached their Month 6-R/6-R2 visit, unless completed an early termination visit. A final analysis with the additional beyond Month 6-R/R2 data will be done after all subjects have exited the study.

12 PHARMACOKINETIC EVALUATIONS

PK analysis is not planned in this study.

13 CHANGES TO PLANNED ANALYSES

No changes to planned analyses.

14 REVISION HISTORY

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

15 REFERENCES

International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials. *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials*

International Conference on Harmonisation (ICH) E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports. *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e3-structure-and-content-clinical-study-reports*

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Shaffer RN. Primary glaucomas. Gonioscopy, ophthalmoscopy and perimetry. Trans Am Acad Ophthalmol Otolaryngol, 1960. 64:112– 127.

Appendix 1 Time and Events Schedule

a. Initial Dose and Follow-up

Visit Type	Screening / Washout	Baseline Visit Day 0	Injection Day/ 1 day	Post Injection Follow Up Day 3	Follow-up Day 7	Follow-up Week 2	Follow-up Week 6	Follow-up Week 12	Follow-up Month 4.5	Follow-up Month 6/ ET/Repeat Dose Screening/ Baseline	Post Month 6 Monthly Follow-up[d]	Post Month 6 Exit Visit[d]	Unscheduled Visit[e]
Visit Window	Day -56 from Baseline visit[a]	Day-4 to Day -1 from Day 1	N/A	±1 day	±1 day	±1 day	±2 days	±2 days	±3 days	±3 days	±3 days	±3 days	±3 days
Visit Number	1	2	3	4	5	6	7	8	9	10			UNS
Informed Consent	X									X[g]			
Demographic Information	X												
Medical and Ophthalmic History	X												
Record Medications	X	X	X[b]	X	X	X	X	X	X	X	X	X	X
Record Adverse Events			X[b]	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test (when applicable)		X											
Subject Ocular Comfort Score			X[b]	X	X	X	X	X	X	X	X	X	X
BCVA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Field	X									X		X	X
Endothelial Cell Count (specular microscopy)	X									X		X	X
Anterior segment (AS)-OCT	X									X		X	X
Slit Lamp Biomicroscopy including External Eye Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Implant Assessment			X	X	X	X	X	X	X	X	X	X	X
IOP Measurement by applanation tonometry (Goldmann)	X	X[c]	X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X
Pachymetry	X							X		X		X	X
Gonioscopy	X												

a. Initial Dose and Follow-up

Visit Type	Screening / Washout	Baseline Visit Day 0	Injection Day/ 1 day	Post Injection Follow Up Day 3	Follow-up Day 7	Follow-up Week 2	Follow-up Week 6	Follow-up Week 12	Follow-up Month 4.5	Follow-up Month 6/ ET/Repeat Dose Screening/ Baseline	Post Month 6 Monthly Follow-up[d]	Post Month 6 Exit Visit[d]	Unscheduled Visit[e]
Visit Window	Day -56 from Baseline visit[a]	Day-4 to Day -1 from Day 1	N/A	±1 day	±1 day	±1 day	±2 days	±2 days	±3 days	±3 days	±3 days	±3 days	±3 days
Visit Number	1	2	3	4	5	6	7	8	9	10			UNS
Gonioscopy with Product Visualization and description[f]				X	X	X	X	X	X	X	X	X	X
Dilated Fundus exam	X									X		X	
Undilated Fundus exam		X						X	X		X		X
OCT Optic nerve and RNFL	X									X		X	X
PS OCT	X									X		X	X
Determine Eligibility	X	X	X							X[h]			
Randomization[g]			X										
Intracameral Injection of OTX TIC / Durysta			X										
Implant Acceptability Questionnaire								X		X			
Eligibility for repeat dose confirmed										X[h]			

a: For naïve treatment subjects a minimum of a week (7 days) between the Screening Visit 1 and the Baseline Visit 2 (Day 0).
b: Assessment will be completed prior and post implant placement on Day 1 visit.
c: IOP measurement at 8 a.m. (± 1 hour), 10 a.m. (± 0.5 hour) and 4 p.m. (± 1 hour) at Baseline Visit, Week 2 (Visit 6), Week 6 (Visit 7), Week 12 (Visit 8), Month 4.5 (Visit 9) and Month 6 (Visit 10).
d: Only to be completed for subjects who still have evidence of biological activity or implant presence. For all visits beyond Month 6, the same schedule of assessments should be followed as delineated for the Post Month 6 Monthly Follow-Up, and the Final Study Visit should follow the Post Month 6 Exit visit.
e: Unscheduled Visits: The Investigator determines which assessments need to be performed based on the reason for the unscheduled visit; not all assessment need to be performed.
f: At selected sites only gonioscopy images will be acquired.
g OTX-TIC 26 µg or DurystaTM subjects that have not been rescued prior to the Month-6 follow-up will be presented with the option for participating in a repeat dose in the trial via a second informed consent. Subjects that decline a repeat dose or have been rescued will continue the follow up and exit procedures above for a single dose.

h. Subjects in the OTX-TIC 26 µg and Durysta Treatment Groups that have not been rescued prior to the Month-6 follow-up and consent to participation in the repeat dosing sub-study will have eligibility confirmed based on the Month 6 visit procedures.

b. Repeat Dose and Follow-up

Visit Type	Repeat Injection Day 1-R/R2 day[a]	Follow Up Day 3-R/R2	Follow-up Day 7-R/R2	Follow-up Week 2-R/R2	Follow-up Week 6-R/R2	Follow-up Week 12-R/R2	Follow-up Month 4-R/R2	Follow-up Month 5-R/R2	Follow-up Month 6 or ET-R/R2	Post Month 6-R/R2 Monthly Follow-up[d]	Post Month 6-R/R2 Exit Visit[d]	Unscheduled-R/R2 Visit[e]
Visit Window	Month 6 + 7 days	±1 day	±1 day	±1 day	±2 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Visit Number	11R	12R	13R	14R	15R	16R	17R	18R	19R			UNSR
Record Medications	X[b]	X	X	X	X	X	X	X	X	X	X	X
Record Adverse Events	X[b]	X	X	X	X	X	X	X	X	X	X	X
Subject Ocular Comfort Score	X[b]	X	X	X	X	X			X	X	X	X
BCVA (ETDRS)	X	X	X	X	X	X			X	X	X	X
Visual Field									X		X	X
Endothelial Cell Count (specular microscopy)									X		X	X
Anterior segment (AS)- OCT									X		X	X
Slit Lamp Biomicroscopy including External Eye Exam	X	X	X	X	X	X	X	X	X	X	X	X
Implant Assessment	X	X	X	X	X	X	X	X	X	X	X	X
IOP Measurement by applanation tonometry (Goldmann)	X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X
Pachymetry									X		X	X
Gonioscopy												
Gonioscopy with Product Visualization and description[f]		X	X	X	X	X	X	X	X	X	X	X
Dilated Fundus exam									X		X	
Undilated Fundus exam						X				X		X
OCT Optic nerve and RNFL									X		X	X
PS OCT									X		X	X
Determine Eligibility	X[a]											
Randomization	X											
Intracameral Injection of OTX TIC / Sham	X											
Implant Acceptability Questionnaire									X			

a: Month 6 (Visit 10) is the screening/baseline visit for the repeat dose after which, the injection should be completed within 7 days, upon confirmation of ECC eligibility by Reading Center.
b: Assessment will be completed prior and post implant placement on Day 1-R visit (Visit 11R).

c: IOP measurement at 8 a.m. (± 1 hour) and 10 a.m. (± 0.5 hour) at Week 2-R (Visit 14R), Week 6-R (Visit 15R), Week 12-R (Visit 16R), Month 4-R (Visit 17R), and Month 5-R (Visit 18R).
IOP measurement at 8 a.m. (± 1 hour), 10 a.m. (± 0.5 hour) and 4 p.m. (± 1 hour) at Month 6-R (Visit 19R).
d: Only to be completed for subjects who still have evidence of biological activity or implant presence. For all visits beyond Month 6, the same schedule of assessments should be followed as delineated for the Post Month 6-R Monthly Follow-Up, and the Final Study Visit should follow the Post Month 6-R Exit visit.
e: Unscheduled Visits: The Investigator determines which assessments need to be performed based on the reason for the unscheduled visit; not all assessment need to be performed.
f: At selected sites only gonioscopy images will be acquired

Appendix 2 Slit Lamp Biomicroscopy Examination

To be completed by unmasked site staff.

The slit beam observations should be assessed in a dark room using the highest lamp voltage, an aperture of 0.3 mm, an illumination angle of 30 degrees and a magnification of 16X.

The clinician will use a slit lamp to assess the following as normal, abnormal clinically significant or abnormal not clinically significant:

- External adnexa – Presence or absence of lid erythema, edema or other abnormalities, evaluation of lashes for scurf or other abnormalities
- Conjunctiva – presence or absence of edema, erythema, or other abnormalities
- Iris – presence or absence of stromal or other abnormalities
- Cornea – clarity, presence or absence of superficial punctate keratopathy or other abnormalities asses with fluorescein stain
- Anterior chamber – adequacy of formation depth, cell score and flare count
- Lens

Explanation/comments should be provided on the case report form for any abnormal observations. If a corneal edema is observed, a notation on whether it is *general* or *local* should be added.

ANTERIOR CHAMBER CELLS AND FLARE

Assessment of anterior chamber cells should be performed as follows:

- Low ambient lighting
- 1X1 mm slit beam
- Highest slit lamp voltage
- Illumination angle of 45 degrees
- High magnification

The anterior chamber will be examined for the presence of signs of ocular inflammation. Anterior chamber cell count and flare will be graded using the SUN* Working Group grading scheme: Although an anterior chamber cell grade of “0” is reported as “< 1 cell” in the SUN Working Group grading scheme, it will be characterized as 0 cells in the field for this study.

The anterior chamber cell count will be assessed as the actual number of cells counted within the slit beam of 1.0 mm height and 1.0 mm width described above, if fewer than 16 cells are seen. Only white blood cells will be counted. (Red blood cells and pigment cells are not to be counted). The number of cells counted and the corresponding grade per the below scale will both be recorded in the CRF.

Anterior Chamber Cells	
Grade	**Number of Cells in Field**
0	0 (rare cells, i.e., one cell in a minority of fields)
0.5+	1-5 (trace)
1+	6-15 (cells)
2+	16-25 (cells)
3+	26-50 (cells)
4+	>50 (cells)

Flare	
Grade	**Description**
0	None
1+	Faint
2+	Moderate *iris and lens details clear*
3+	Marked *iris and lens details hazy*
4+	Intense *fibrin or plastic aqueous*

*Standardization of the Uveitis Nomenclature (SUN)

Appendix 3 Gonioscopy

To be completed by unmasked site staff.
The following procedure is recommended for conducting gonioscopy:
Clean and sterilize the front (curved) surface of the goniolens. Apply lubricating fluid to the front surface. Anaesthetize the subject's cornea with topical anesthetic. Prepare the slit lamp for viewing through the goniolens. Gently move the subject's eyelids away from the cornea. Slowly apply the goniolens to the ocular surface, forming suction. Fine-tune the slit lamp to optimize the view. The angle can now be viewed by rotating the lens gently through 360 degrees. Grade the angle based on the Shaffer System (Shaffer 2020) as follows. Subjects with a Grade 2 or lower should be excluded for angle closure glaucoma.
Grade 4 - 45º to 35º angle wide open
Grade 3 - 35º to 20º angle wide open
Grade 2 - 20º angle narrow
Grade 1 - ≤10º angle Extremely narrow
Slit - 0º angle Narrowed to slit

Appendix 4 Grading Scheme for Vitreous Cells and Vitreous Haze

Grading Scheme for Vitreous Cells

Grade	Cells in Field
0	None
0.5+	1-10
1+	11-20
2+	21-30
3+	31-100
4+	>100

Grading Scheme for Vitreous Haze

Grade	Description
0	No Inflammation
0.5+	Trace inflammation (slight blurring of the optic disc margins and/or loss of nerve fiber layer reflex)
1+	Mild blurring of retinal vessels and optic nerve head
2+	Moderate blurring of optic nerve head
3+	Marked blurring of optic nerve head
4+	Optic nerve head not visible

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