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

Investigational Product

OTX-TIC

Version 05

22 Jan 2024

Sponsor

Ocular Therapeutix, Inc.

[redacted]

CONFIDENTIALITY STATEMENT

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

I hereby agree to participate in the clinical investigation of OTX-TIC (travoprost) for intracameral implant use sponsored by Ocular Therapeutix, (hereinafter "Study Sponsor"). I agree to conduct this investigation in accordance with the agreement, the investigational plan, and applicable regulations. I agree to protect the rights, safety, and welfare of subjects under my care; I agree to adhere to the regulations outlined in 21 CFR Part 312, other applicable United States Food and Drug Administration (FDA) regulations, and conditions of approval imposed by the reviewing IRB and the FDA. I agree to supervise all use of the investigational product and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee of the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor. I am also aware that I may be inspected by a representative of the FDA to verify compliance with applicable federal regulations related to clinical research on human subjects. I am aware that my contact for all matters related to this investigation is the Ocular Therapeutix Clinical Department at [redacted]. I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time. In the event that I decide to discontinue my participation as an Investigator in this study, I will notify the Study Sponsor 30 days prior of my intent to discontinue. I understand that I am obligated to complete the follow up of the subjects already participating in the investigation.

Any data generated as a result of this investigation will be the exclusive property of the Study Sponsor who retains all rights of publication. I understand that the Study Sponsor encourages me to pursue independent publications related to my experience with this investigational product with the understanding that Study Sponsor reserves the right of prior review and approval of these publications.

I agree to provide to the Study Sponsor my current curriculum vitae along with the current curriculum vitae of those physicians at this institution who will be using this investigational product or participating in this study as Sub-Investigators under my supervision. These CVs include education, training, and the extent and type of our relevant experience with pertinent dates and locations. I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of a Study Sponsor, an IRB or the FDA.

I understand that this investigation, protocol, and trial results are confidential, and I agree not to disclose any such information to any person other than a representative of the Study Sponsor or FDA without the prior written consent of the Study Sponsor.

I will provide financial information, as indicated in 21 CFR Part 312.64(d) and 21 CFR Part 54.

Accepted by:

Principal Investigator Signature	Date	Printed Name

PROTOCOL REVISION HISTORY

Date	Version	Description of Modifications	Rationale for Modification
03 Aug 2021	01	Original Issue	N/A
19 Nov 2021	02	1. Added language to allow for a possible unmasked interim analysis by an independent group after all subjects complete 12 weeks of follow-up. 2. [redacted] 5. Patient Reported Outcome was modified from COMTOL to a simplified Implant Acceptability Questionnaire. 6. Miscellaneous corrections to address confusing protocol language.	1. To have opportunity to evaluate the data earlier for future trial planning. 2. [redacted] 5. COMTOL may have confused subjects and the revised simplified questionnaire will be easily answered. 6. Updated for clarity.
16 Dec 2022	03	1. [redacted]	1. [redacted]

Date	Version	Description of Modifications	Rationale for Modification
		[redacted]	3. [redacted]
31Jan2023	04	1. Addition of repeat dose sub-study and justifications to section 2, 4.3, 4.5, 5.2, 6.2, 6.33, 6.42, 6.7, 6.9, 7.2, 8.1.2, 8.7, and 11.10. 2. Added new section 8.4 for contact lens use 3. [redacted] 4. [redacted] 5. Miscellaneous corrections (e.g., correct Visit 04 (day 3) visit window from "-1 Day" to "±1 Day", updating OTX phone number on investigator	1. To allow for the collection of preliminary data for repeat dosing with OTX-TIC to assist with the design of a future repeat dosing study to ultimately support product labeling. 2. Added to clarify restrictions on use and requirements for removal prior to visits/assessments. 3. [redacted] 4. [redacted] 5. Updated for clarity.

Date	Version	Description of Modifications	Rationale for Modification
		signature page to [redacted]	
22Jan2024	05	1. Address inconsistent language remaining within text from previous amendment 4. 2. Add new subsection to section 10.8 Procedures for Handling Special Situations [redacted] 3. Update statistical analyses sections to be in alignment with the Statistical Analysis Plan (SAP).	1. Some updates to text were not carried throughout the document during the previous amendment. 2. [redacted] 3. During the drafting of the SAP modifications to the strategy were made that required updates to the protocol statistical sections.

TABLE OF CONTENTS

PROTOCOL REVISION HISTORY 3
1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 11
2 SYNOPSIS....12
3 PRINCIPAL CONTACTS....23
4 BACKGROUND INFORMATION 23
4.1 Overview of Disease (Glaucoma) 23
4.2 Investigational Product Rationale....24
4.3 Nonclinical Findings....26
4.4 Risk-Benefit Analysis 26
4.4.1 Halt of Enrollment of OTX-TIC 5µg arm....29
4.5 Dose and Administration Justification 30
4.6 Compliance....33
4.7 Trial Population....33
5 TRIAL OBJECTIVES 33
5.1 Main Study (Initial Dose)....33
5.2 Repeat Dose Sub-Study....33
6 TRIAL DESIGN 34
6.1 Description of Trial 34
6.2 Description of the Repeat Dosing Sub-Study....35
6.3 Study Endpoints....37
6.3.1 Efficacy Endpoints....37
6.3.1.1 Primary Efficacy Endpoints....37
6.3.1.2 Secondary Efficacy Endpoints....37
6.3.2 Ocular Safety Evaluations 38
6.3.3 Repeat Dosing Sub-Study Evaluations 38
6.3.4 Patient Reported Outcome Evaluations 38
6.4 Randomization, Non-Randomized Treatment Assignment and Masking39
6.4.1 Main Study (Initial Dose)....39
6.4.2 Repeat Dose Sub-Study....39
6.4.3 Site Activities/Assessments by Masking Requirement....40
6.5 Trial Treatment 41
6.6 Main Study (Initial Dose)....41
6.7 Repeat Dose Sub-Study....41
6.8 Trial Duration....41
6.9 Trial Material Accountability 42
7 SELECTION AND WITHDRAWAL OF SUBJECTS....42
7.1 Main Study (Initial Dose) Eligibility....42
7.1.1 Inclusion Criteria....42
7.1.2 Exclusion Criteria....43
7.2 Repeat Dosing Eligibility 45

7.2.1 Inclusion Criteria....45
7.2.2 Exclusion Criteria....46
7.3 Entry/Randomization Criteria:....46
7.4 Procedural Exclusion Criteria....46
7.5 Subject Recruitment and Screening....46
7.6 Withdrawal Criteria....46
7.7 Withdrawal Methods....47
7.8 Collection of Data from Withdrawn Subjects....47
7.9 Subject Replacement....47
7.10 Trial Termination....47
8 SUBJECT TREATMENT....48
8.1 Treatment Regimen....48
8.1.1 Main Study (Initial Dose)....48
8.1.2 Repeat Dose Sub-Study....48
8.2 Prior and Concomitant Therapy....48
8.3 Rescue Therapy....49
8.3.1 [redacted]....49
8.4 Contact Lens Use....49
8.5 Study Assessments by Visit....49
8.6 Main Study: Initial Dosing and Follow up....50
8.6.1 Visit 1 (-56 days prior to Baseline) Screening....50
8.6.2 Visit 2 (-4 to -1 day) Baseline Visit/Day 0....50
8.6.3 Visit 3/Day 1 (Injection Day)....51
8.6.3.1 Assessments Performed Prior to Procedure:....51
8.6.3.2 Treatment With OTX-TIC / Durysta Intracameral Implant....51
8.6.3.3 Post-Injection Procedure....52
8.6.3.4 Discharge Instructions....52
8.6.4 Visit 4 (Day 3 Post Injection Follow up ±1 day)....52
8.6.5 Visit 5 (Day 7 Follow up ±1 day)....52
8.6.6 Visit 6 (Follow up Week 2, ±1 day)....53
8.6.7 Visit 7 (Follow up Week 6, 2 ± days)....53
8.6.8 Weekly Follow-up Requirements for OTX-TIC 5µg subjects only between Week 10 and Week 15....54
8.6.9 Visit 8 (Follow up Week 12, 2 ± days)....54
8.6.10 Visit 9 (Follow up Month 4.5, 3 ± days)....55
8.6.11 Visit 10 (Follow up Month 6/Early Termination/Repeat Dosing Screening & Baseline, 3 ± days)....55
8.6.12 Post Month 6 Month Follow Up (3 ± days)....57
8.6.13 Post Month 6 Exit Visit (3 ± days)....57
8.7 Repeat Dosing Sub-Study....58
8.7.1 Visit 11R/Day 1-R or Visit 11R2/Day 1-R2 (Repeat Injection Day; 6 months +7 days)....58
8.7.1.1 Assessments Performed Prior to Repeat Injection:....58
8.7.1.2 Treatment With OTX-TIC Intracameral Implant / Sham Injection....58

8.7.1.3 Post-Repeat Injection Procedure 58
8.7.1.4 Discharge Instructions 59
8.7.1.5 Sham/OTX-TIC [redacted] Reinjection 59
8.7.2 Visit 12R or Visit 12R2 (Day 3-R/Day 3-R2 Post Injection Follow up ±1 day) 59
8.7.3 Visit 13R/Visit 13R2 (Day 7-R/Day7-R2 Follow up ±1 day) 60
8.7.4 Visit 14R/Visit 14R2 (Follow up Week 2-R/Week 2-R2, ±1 day) 60
8.7.5 Visit 15R/Visit 15R2 (Follow up Week 6-R/Week6-R2, 2 ± days) 61
8.7.6 Visit 16R/Visit 16R2 (Follow up Week 12-R/Week 12-R2, 3 ± days) 61
8.7.7 Visit 17R/Visit 17R2 (Follow up Month 4-R/Month 4-R2, 3 ± days) 62
8.7.8 Visit 18R/Visit 18R2 (Follow up Month 5-R/Month 5-R2, 3 ± days) 62
8.7.9 Visit 19R/Visit 19R2 (Follow up Month 6-R/Month 6-R2, 3 ± days/Early Termination) 63
8.7.10 Post Month 6-R/Post Month 6-R2 Follow Up (3 ± days) 63
8.7.11 Post Month 6-R/ Post Month 6-R2 Exit Visit (3 ± days) 64
8.8 Unscheduled Visits 64

9 CENTRAL READING CENTER 65

10 ADVERSE EVENTS 65
10.1 Definition of an Adverse Event 65
10.2 Definition of Serious Adverse Event 65
10.3 Disease-Related Events or Outcomes Not Qualifying as AE/SAE's 66
10.4 Monitoring and Recording of AEs and SAEs 66
10.4.1 Adverse Events 66
10.4.2 Serious Adverse Events 66
10.4.3 All Events 66
10.5 Immediate Reporting of Serious Adverse Events and Pregnancies 67
10.6 Death 67
10.7 Evaluating AEs and SAEs 67
10.7.1 Severity 67
10.7.2 Relationship to OTX-TIC or Durysta product or procedure 68
10.7.3 Expectedness of Events 68
10.8 Procedures for Handling Special Situations 68
10.8.1 Intracameral Implant Removal 68
10.8.2 Pregnancy 69
10.8.3 Unmasking for Medical Emergencies 69
10.8.4 Regulatory Reporting 69

11 STATISTICAL METHODS AND DATA ANALYSIS 69
11.1 Statistical Methods 69
11.1.1 Main Study (Initial Dose) 69
11.1.2 Repeat Dosing Sub-Study 70
11.2 Sample Size Determination 70
11.3 Unit of Analysis 70
11.4 Subject Population(s) for Analysis 70
11.4.1 Modified Intent-to-Treat Population (mITT) 70

11.4.2 Per-Protocol Population 70
11.4.3 Safety 70
11.4.4 All Screened Subjects 70
11.4.5 Repeat Dosing Sub-Study Population 70
11.5 Statistical Significance 71
11.6 Efficacy Analyses 71
11.6.1 Primary Efficacy Endpoint Analysis 71
11.6.2 Secondary Efficacy Analyses 71
11.6.3 The details of secondary efficacy analyses will be described in the SAP.Demographics and Baseline Data 72
11.7 Patient Reported Outcomes Analyses 72
11.8 Safety Analyses 72
11.9 Repeat Dosing Sub-Study Analyses 72
11.10 Reporting Deviations 73
12 STUDY MANAGEMENT AND DATA COLLECTION 73
12.1 Confidentiality 73
12.2 Source Documents 74
12.3 Case Report Forms 74
12.4 Records Retention 74
13 STUDY MONITORING, AUDITING, AND INSPECTING 74
13.1 Study Monitoring Plan 74
14 ETHICAL CONSIDERATIONS 75
15 REFERENCES 76

TABLE OF TABLES

Table 1: OTX-TIC (travoprost) Intracameral Implant General Characteristics 25
[redacted] 25
Table 3: Safety Margins for Ocular and Systemic Toxicity a 32
Table 4: Treatment Assignment Paradigm 34
Table 5: Treatment Assignment Paradigm Repeat Dose Sub-Study 36
Table 6: Prohibited/Restricted Medications 49

TABLE OF FIGURES

[redacted] 25
Figure 2: Study Schematic for Main Study (Initial Dose) 35
Figure 3: Study Schematic for Repeat Dose Sub-Study 37
Figure 4: Reporting Information for SAEs and Pregnancies 67

[redacted]

Appendix 1 Time and Events Schedules 78
a. Initial Dose and Follow-up.....78
b. Repeat Dose and Follow-up 80
[redacted]

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Meaning
AE	Adverse Event
API	Active pharmaceutical ingredient
AS-OCT	Anterior segment Optical coherence tomography
BCVA	Best corrected visual acuity
CRC	Central Reading Center
CRF	Case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HED	human equivalent dose
IRB	Institutional Review Board
IEC	Institutional Ethics Committee
IOP	Intraocular Pressure
NOAEL	No Observed Adverse Effect Level
RNFL	Retinal Nerve Fiber Layer
OAG	Open-angle glaucoma
OCT	Optical coherence tomography
OHT	Ocular hypertension
OTX-TIC	OTX-TIC (travoprost) Intracameral Implant
PAS	Peripheral anterior synechia
[redacted]	[redacted]
PGA	Prostaglandin Analogues
PLA	Polylactide
POAG	Primary Open Angle Glaucoma
SE	Study eye
NSE	Non-study eye

2 SYNOPSIS

Protocol Title	A prospective, multi-center, randomized, parallel-group, controlled study to evaluate the efficacy and safety of OTX-TIC (travoprost) intracameral implant in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT)
Protocol Number	OTX-TIC-2020-201
Phase of Clinical Study	2
Investigational Products	 **Name** [redacted] OTX-TIC 5 µg* Travoprost Intracameral Implant [redacted] OTX-TIC 26 µg Travoprost Intracameral Implant [redacted] Active control (Durysta™ Implant) [redacted] *Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022
Study Objective	To assess the intraocular pressure (IOP) lowering efficacy, and safety of a single [redacted] dose of the OTX-TIC drug product (2 dose strengths) compared to a single injection of Durysta™ in subjects with OAG or OHT
Number of Investigational Sites	Approximately 25 sites in the United States (US)
Number of Subjects Planned	Approximately 86 subjects will be enrolled
Study Population	Subjects with stable OAG or OHT

<table>
<tr><td>Study Design and Overview</td><td>This is a multicenter, randomized, parallel-group (2 dose strengths of OTX-TIC versus Durysta™) clinical study. Subjects will be randomized (1:1:1 ratio) into one of 3 groups as described below:
<table>
<tr><th>Treatment</th><th>N</th><th>Study Eye (SE) Treatment</th><th>Non-study eye (NSE) treatment*</th></tr>
<tr><td>OTX-TIC 5 µg+</td><td>~16+</td><td>Dose strength: 5µg</td><td>Eye-drops: PGA QD</td></tr>
<tr><td>OTX-TIC 26 µg</td><td>~35</td><td>Dose strength: 26µg</td><td>Eye-drops: PGA QD</td></tr>
<tr><td>Control</td><td>~35</td><td>Durysta™</td><td>Eye-drops: PGA QD</td></tr>
</table>
QD= once daily
* The NSE, if needed, should 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.
+ Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022. All other arms continue to enroll.

Study groups and treatment:
• OTX-TIC 5 µg (Group 1): will consist of approximately 35 subjects, each to receive a single OTX-TIC implant (5 µg) in the study eye. Will consist of approximately 16 subjects enrolled by 09DEC2022. No additional subject will be enrolled in this arm.
• OTX-TIC 26 µg (Group 2): will consist of approximately 35 subjects, each to receive a single OTX-TIC implant (26µg) in the study eye.
• Active control (Durysta™) (Group 3): will consist of approximately 35 subjects, each to receive a Durysta™ implant in the study eye.
Subject can have only one eye treated with OTX-TIC or Durysta ™ as part of this study; that eye will be designated as the 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.</td></tr>
<tr><td>Study Duration and Study Visits</td><td>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</td></tr>
</table>

	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). 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 implant is present at the Month 6 visit, in which case the 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, 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. * Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022. All other arms continue to enroll. **Repeat Dosing 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: • For subjects that received an initial dose of OTX-TIC 26 µg:

	○ [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] • For subjects that received an initial dose of Durysta: ○ Sham Only The treatment would occur at Visit 11R (Day 1-R) which must occur within 7 days of Visit 10 (Month 6). 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 Visit 11R where complete resorption of the initial implant [redacted] is confirmed [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). [redacted]
Inclusion Criteria	Individuals of either gender will be eligible for study participation if they: 1. Are 18 years of age or older at the time of screening

	2. Provide written informed consent and are able to comply with all study requirements 3. [redacted] 4. Have a negative pregnancy test result for women of childbearing potential at Baseline 5. Have a documented diagnosis of OHT, or OAG (including primary, pigmentary and pseudoexfoliation glaucoma) in the **study eye** 6. Have a mean baseline IOP following an up to 8-week washout period of current therapy (if needed) in the: 6.1 **Study eye** of: ≥22 mmHg and ≤32 mmHg at 8 am (hour T_0) at Baseline Visit 2 (Day 0) after the washout period* ≥ 19 mmHg and ≤ 32 mmHg at 10 am (hour T_0 + 2) at Baseline Visit 2 (Day 0) after washout period* *Note: For subjects whose IOP is < 22 mmHg at 8 am or < 19 mmHg at 10 am at Baseline, a second visit to assess their IOP can be scheduled no longer than 14 days after the 1st Baseline visit per Investigator discretion (no later than 70 days after screening). If < 5 days only IOP should be repeated. If > 5 days, days, all baseline assessments except the fundus exam should be repeated. 6.2. **Non-study eye** of: ≥17 mmHg and ≤32 mmHg at 8 am (hour T_0) at Baseline Visit 2 (Day 0) after the washout period 7. [redacted]

Exclusion Criteria	**Non-ocular exclusion criteria:** Individuals are not eligible for study participation if they: 1. Have an uncontrolled systemic disease or a debilitating disease (e.g., cardiovascular, hypertension, uncontrolled diabetes) 2. Are currently pregnant or breast-feeding or of childbearing potential without the use of adequate contraceptive methods during the length of the study 3. Have a known or suspected allergy to travoprost, and bimatoprost or to any component of the study products 4. Use or anticipated use of oral, intramuscular, or intravenous corticosteroids from 2 months prior to Baseline Visit through the Exit Visit 5. Have participated in any study involving an investigational drug either in the U.S. or outside the U.S. within the past 30 days 6. Are an employee of the site that is directly involved in the management, administration, or support of the study, or are an immediate family member of the same 7. Have any history of bleeding disorder or use of medications which in the Investigator's opinion places the subject at high risk during placement of the implant 8. Have any condition or use of any recreational drug that in the opinion of the site Investigator, would compromise study outcomes, patient's compliance with study requirements, including study completion **Ocular exclusion criteria:** Individuals are not eligible for study participation if they: 1. [redacted] 2. [redacted] 3. Patient is non-responsive to topical prostaglandins, prostamides or prostaglandin analogs (eg., Xalatan, Lumigan, Travatan) based upon the assessment by the Investigator 4. [redacted] 5. [redacted] 6. Are unwilling to discontinue use of contact lenses 3 days prior to pachymetry and throughout the entire study 7. [redacted]

	8. [redacted] 9. [redacted] 10. [redacted] 11. [redacted] 12. [redacted] 13. Have a history of significant ocular trauma within the past six months in the **study eye** 14. [redacted] 15. [redacted] 16. [redacted] 17. [redacted] 18. [redacted] 19. [redacted]

	• [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]
Eligibility for Repeat Dose Sub-Study	**Inclusion Criteria** Individuals of either gender previously dosed with OTX-TIC 26 µg or Durysta who have reached Month 6 (Visit 10) will be eligible for study participation if they: 1. Provide written signed informed consent and are able to comply with all sub-study requirements 2. [redacted] **Exclusion Criteria** Subjects are not eligible for study participation if they: 1. Have received Rescue Therapy prior to the Month 6 follow up visit (Visit 10). 2. Have an ongoing adverse event that would contraindicate an intracameral injection. 3. Are not a good candidate for repeat injection based upon the assessment by the Investigator 4. >15% increase in central corneal thickness from Screening (Visit 1). 5. OTX-TIC [redacted] is confirmed as present in the study eye [redacted] AND IOP lowering medications are required at Month 6 (Visit 10).
Primary Efficacy Evaluations	• IOP changes from baseline at 8AM, 10AM, and 4PM at Week 2, Week 6, and Week 12 in the study eye

Secondary Efficacy Evaluations	• 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 • Proportion of subjects who are well-controlled (mean diurnal IOP <=21 mmHg) on the fewer, same, and more number of topical IOP-lowering medications at all study visits compared to screening. • IOP changes from baseline at all study visits in the 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
Ocular Safety Evaluations	• Incidence of adverse event reporting • Summaries of OTX-TIC implant assessments [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
Patient Reported Outcome Evaluations	• Implant Acceptability Questionnaire at 12 weeks and 6 months.
Repeat Dosing Sub-Study Evaluations	• 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 the 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.
Procedural Exclusion Criteria	Unsuccessful intracameral injection (record reason for injection failure on the electronic Case Report Form, i.e., eCRF) is considered a procedural exclusion. The study will be supplemented with additional subjects to account for these subjects in order to ensure that the necessary number of subjects receive the implant to inform on safety, and efficacy.
Sample Size Considerations	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.
Statistical Methods	Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum and maximum. Summaries for discrete variables will include frequencies and percentages. Baseline will be defined as the last non-missing measure prior to initiation of IP. 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. **For Main Study:** Due to the limited sample size, descriptive summary statistics will be used for the study reporting. No formal statistical hypothesis testing will be performed. 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. The final analyses for the main study will be conducted when all patients have reached their Month 6 visit or have exited the study prior to that. Subjects will continue to be followed per the protocol if they meet criteria to continue beyond Month 6. The study will be unmasked and will continue until all subjects have exited the study. An analysis

	update of data beyond Month 6 will be done after all subjects have exited the study. **For Repeat Dose Sub-Study:** Subjects in the repeat dose sub-study will be summarized in a similar fashion to main study. Analysis details will be provided in the SAP.

3 PRINCIPAL CONTACTS

Please reference the OTX-TIC-2020-201 Contact List.

4 BACKGROUND INFORMATION

4.1 Overview of Disease (Glaucoma)

Glaucoma is a progressive, chronic disease affecting more than 2 million people over 40 years of age in the United States alone (Simmons 2010). This number is expected to increase significantly to 4.73 million by the year 2025 (Market Scope 2020). In fact, glaucoma has been reported to be one of the leading causes of irreversible blindness, and worldwide it is the second leading cause of blindness (Quigley and Broman, 2010). Some have projected that by the year 2040 more than 110 million people will be diagnosed with glaucoma (Tham et. al. 2014).

Glaucoma is defined as optic neuropathy leading to the loss of retinal ganglion cells and their axons and progressing in later stages to loss of visual field and, in very advanced cases, central visual acuity. Open-angle glaucoma is the most common form of the disease (Simmons 2010) and primary open angle glaucoma (POAG) refers to eyes with open anterior drainage angles and elevated IOP.

Elevated fluid pressure within the eye (i.e., elevated IOP), defined as pressures above the normal range of 10 to 21 mmHg, is the main risk factor for glaucoma. People with elevated IOP levels without any optic-nerve damage are diagnosed with ocular hypertension, as opposed to glaucoma. However, people with ocular hypertension may be at risk of progressive damage to the optic nerve (glaucoma).

For both glaucoma and ocular hypertension (OHT), the critical factor for effective therapy is to lower the IOP, and in doing so, the disease progression is slowed along with the rate of visual field loss (EMEA 2004). Drugs that are classified as prostaglandins have been shown to effectively lower IOP (AAO 2015). The Preferred Practice Patterns of the AAO recommend prostaglandins as the first line of therapy for primary open-angle glaucoma (POAG) and OHT. Thus, it is understandable that the most commonly prescribed topical medications for the treatment of glaucoma in the United States are the prostaglandin analogues.

Travoprost is a synthetic prostaglandin F 2a analogue. Its chemical name is (isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(a,a,a-trifluoro-m–isopropyl-tolyl)oxy]-1-butenyl]-cyclopentyl]-5-heptenoate. This prodrug is a synthetic prostaglandin analogue that is enzymatically converted to a free acid form in the human cornea (Al-Jazzaf 2003). Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing trabecular meshwork and uveoscleral outflow (Lim et. al. 2008, Torris et. al. 2008). Travoprost is the active ingredient in Travatan®, Travatan Z®, and Izba™ (all Alcon Laboratories, Inc., Ft Worth, TX), which are all topical ophthalmic solutions intended to reduce elevated IOP. The dosage is typically one drop daily of a 0.004% or 0.003% solution applied daily to the affected eye(s).

Successful treatment for glaucoma requires daily self-administered treatment with topical eye drops. While topical antihypertensive medication is effective in treating primary open angle glaucoma, any one of the available therapies will only be as effective as the adherence to administration by individual patients. Known limitations associated with the application of topical eye drops include: (1) difficulty in administering drops, (2) limited accuracy of drops getting into the eye, (3) potential washout of drops by lacrimation or subsequent

administration of other drops, (4) the need for a caregiver to administer drops and (5) poor subject compliance (Olthoff et. al. 2005). Kholdebarin, et. al. (2008) reported that 34% of patients used improper administration technique. For some patients there is the need to administer multiple drops and this may compound the situation due to washout effects. In one study (Kholdebarin, et. al. 2008), nearly 9% of the patients who required more than one medication in the same eye failed to wait at least three minutes between administrations. Importantly, regardless of the number of medications, patients are expected to remain on treatment indefinitely and motivation to do so plays an important role (Singh et. al. 2005). There is clearly a need to provide an alternative to the daily administration of single or multiple eye drops for the treatment of glaucoma, especially in an aging population with the disease.

The risk of potential blindness as a long-term effect increases in cases of poorly managed glaucoma, and patient compliance becomes a highly critical issue. Studies have shown that less than 50% of glaucoma patients continue therapy and refill prescriptions as required (Friedman et. al. 2007) and most patients are likely to discontinue use of a topical therapy within 1.2 years after filling their first prescription according to health insurance claims (Nordstrom et. al. 2005). Thus, a delivery system that would provide long-term 24 hour control of IOP could address a multitude of issues and delay, if not prevent, loss of vision resulting from glaucoma for the life of the patient. One such product (Durysta™ [bimatoprost implant, Allergan plc, Dublin, Ireland]) was approved for single intracameral administration by the FDA in March 2020. Durysta, a sustained-release implant, demonstrated non-inferiority when compared to Timolol in lowering IOP over a 12-week period during the Phase III trials (Shirley 2020).

Drug delivery to the anterior segment continues to be a challenge with the ultimate goal of improving patient compliance, achieving an excellent safety profile and providing for sustained delivery over an extended period of time (Yelleppedi and Palakurthi, 2015).

4.2 Investigational Product Rationale

Ocular Therapeutix, Inc. is a biopharmaceutical company specifically focused on developing products to address unmet and underserved medical needs in ophthalmology. [redacted]

Table 2, and Figure 1 below).

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted] This clinical study will evaluate the efficacy and safety of a single [redacted] OTX-TIC implant (2 dose strengths) in comparison to a single injection of Durysta™ to lower IOP in subjects with OAG or OHT.

4.3 Nonclinical Findings

The nonclinical toxicology, pharmacology and pharmacokinetics of travoprost following systemic and topical ocular administrations are well understood (Travatan® NDA 021257 and Travatan Z® NDA 021994, and Izba NDA 204822). Evaluations have been performed in numerous species (mice, rats, rabbits, monkeys) with travoprost at systemic and ocular dosages significantly higher than released from OTX-TIC.

Ocular Therapeutix has performed nonclinical safety, pharmacodynamic and pharmacokinetic evaluations of OTX-TIC (travoprost) implant in beagle dogs in eight studies. Single species nonclinical safety studies were conducted in the most appropriate species, beagle dogs, since they provide an appropriately sized angle in the inferior aspect of the anterior chamber for the implant to reside in the iridocorneal angle for long-term nonclinical safety, pharmacodynamic and pharmacokinetic studies. Rabbits were additionally utilized to assess pharmacokinetics of drug release from OTX-TIC because the AH volume and turnover rate of a rabbit approximates that of a human (Vezina 2012). The test articles, and where applicable the vehicle controls absent travoprost, were formulated and manufactured similarly to the proposed clinical doses. Studies included both single-dose and repeat dose studies. The single-dose studies administered a single implant and evaluated travoprost doses of 18, 14, 15, and 41 µg delivered over 120 days, a travoprost dose of 12 µg delivered over 90 days, and a travoprost dose of 4 µg delivered over 60 days. The repeat-dose toxicity study evaluated travoprost doses of 13 µg (one implant) administered four times every 8-weeks, and 26 µg (one implant) and 52 µg (two implants) administered every 18-weeks that delivered travoprost over 9-months.

Additional details about non-clinical findings can be found in the Investigator's Brochure (IB).

4.4 Risk-Benefit Analysis

The benefits of OTX-TIC (travoprost) intracameral implant are thought to be the reduction of elevated intraocular pressure and improved treatment outcomes through eliminating subject non-compliance associated with the use of daily drops.

This will be the second study to evaluate OTX-TIC in subjects with open glaucoma or ocular hypertension and will provide a better understanding of the potential risks associated with OTX-TIC in humans, as the risks are not fully known. The initial, Phase 1 study, CLN-Protocol-0045 (NCT 04360174) a prospective, multi-center, open-label study to evaluate the safety, tolerability and efficacy of OTX-TIC (travoprost implant) for intracameral injection in subjects with primary open-angle

glaucoma (OAG) or ocular hypertension (OHT) compared with topical travoprost eye drops in the non-study eye, is still on-going. All planned subjects (total of 19) have been treated with 15 µg (formulation 1, Cohort 1, n= 5), 26 µg (formulation 1, Cohort 2, n=4), 15µg (formulation 2, Cohort 3, n= 5), or 5 µg (formulation 3, Cohort 4, n= 5). To date, OTX-TIC has shown to be generally well tolerated with a good safety profile. There were no serious ocular adverse events to date. The most common adverse event is low grade inflammation that was treated with topical steroids or topical nonsteroidal anti-inflammatory drugs (NSAIDs). Three subjects in Cohort 1 were noted to have the formation of peripheral anterior synechiae. All three of these events were assessed as mild. Three subjects in Cohort 3, developed IOP elevations at around the time of implant resorption. Two of those subjects were treated with topical steroids before the increase in IOP was noted. All three events were reported recovered/resolved by the time participants exited the study. The endothelial cell images were also obtained during this study. These images showed no changes in the quality or quantity of the endothelial cells over time. To date pachymetry showed no changes from baseline during the same time periods. Additional preliminary details about the clinical findings can be found in the IB.

The most common adverse events associated with topical travoprost include ocular or conjunctival hyperemia, eyelash growth, iris and eyelid color change, and loss of orbital fat. Other adverse reactions also associated with travoprost that should be considered as expected are:

1. Abnormal vision
2. Blurred vision
3. Blepharitis
4. Cataract
5. Conjunctivitis
6. Corneal staining
7. Decreased visual acuity
8. Dry eye
9. Epiphora
10. Foreign body sensation
11. Keratitis
12. Lid margin crusting
13. Macular edema
14. Ocular infection (that, if severe, could lead to temporary or permanent impairment of sight)
15. Ocular inflammation
16. Ocular pain and discomfort
17. Ocular pruritis
18. Periorbitopathy
19. Photophobia

20. Tearing
21. Subconjunctival hemorrhage

Other adverse events reported by patients during post-approval use of travoprost include:

1. Arrhythmia
2. Vomiting
3. Epistaxis
4. Tachycardia
5. Insomnia

With any new product, there is always a chance of developing problems from the treatment. Not all risks or problems of using OTX-TIC are yet known. Some possible problems that could occur from the use of the study product or from the intraocular injection procedure include but are not limited to:

1. Foreign body sensation
2. Allergic reaction
3. Decreased vision or blindness
4. Corectopia
5. Corneal edema
6. Changes in foveal thickness
7. Chemosis
8. Corneal endothelial changes
9. Endophthalmitis
10. Hyphema
11. Infection
12. Inflammatory reaction including iritis
13. IOP increase
14. Need for additional surgery
15. Retinal detachment
16. Synechia (anterior, posterior)
17. Traumatic cataract

However, the risks associated with OTX-TIC have been minimized by formulating the intracameral implant with constituents that have a long history of safe use in ophthalmic drugs and medical devices. Furthermore, results of biocompatibility and preclinical testing at comparable and elevated doses have confirmed that OTX-TIC had minimal to no inflammatory or toxic response of ocular tissues in the canine model.

Subjects will be selected and enrolled using clearly defined inclusion and exclusion criteria to ensure that subjects with conditions/comorbidities that put them at higher risk for procedural complications are excluded. Appropriate therapeutic intervention following standard medical practices will be used in the event of medical complications including the availability of rescue medication. If IOP is high despite treatment with OTX-TIC, rescue medication will be made available to the subjects throughout the study. The specific medication type will be based on the Principal Investigators' discretion.

This study will be monitored to ensure the identification, documentation and analysis of all adverse events, compliance with the protocol, the terms of the participating Institutional Review Board (IRB) and/or Institutional Ethics Committee (IEC) protect the safety and rights of all subjects, and applicable federal regulations. In addition, risks will be minimized through selection of investigators who have the required background and experience. Only those investigators trained to treat subjects with glaucoma or ocular hypertension will be considered for participation as investigators in this study. All investigators who will inject the OTX-TIC will undergo training prior to initial use.

4.4.1 Halt of Enrollment of OTX-TIC 5µg arm

Ocular Therapeutix conducted a safety review due to an IOP elevation in a subject 12-weeks post-injection that was reported on 06Dec2022. As part of this review, the Ocular Therapeutix Medical Monitor for protocol OTX-TIC-2020-201, unmasked the treatment assignments of 6 subjects with IOP elevations noted between weeks 10 and 14 post-injection, which confirmed that these subjects were all within one treatment group: the OTX-TIC 5µg arm. There have not been other IOP elevations reported at other timepoints including timepoints beyond 14 weeks. Subjects with observed elevated IOP were successfully treated with topical and oral ocular hypotensive medications per the data reported in the EDC system (15Dec2022). To date, approximately 16 subjects have been treated in the OTX TIC 5µg group (based on 48 subjects enrolled in a 1:1:1 randomization).

As of 06Dec2022, the OTX-TIC-2020-201 clinical trial has enrolled 48 subjects across the 3 arms of the study which consist of OTX-TIC 26µg, OTX-TIC 5µg and Durysta. Thirty-seven (37) have completed at least 12 weeks of follow-up post injection, 22 have completed at least 4.5 months of follow-up post injection, and 7 have completed 6 months or more of follow-up post injection. Ocular Therapeutix is evaluating the reasons for the observed IOP elevation; however, as each subject with IOP elevation was from the OTX-TIC 5µg arm, the OTX-TIC 5µg arm is closed for further enrollment out of abundance of caution. One possible cause may be that these IOP elevations were due to the fast resorption properties of the OTX-TIC 5µg implant. The OTX-TIC 26µg implant is designed to resorb more slowly than the OTX-TIC 5µg implant.

To address this risk moving forward, Ocular Therapeutix is proceeding with the following plan:

1. The OTX-TIC-2020-201 protocol will be amended to halt enrollment of any additional subjects in the OTX-TIC 5µg arm.
2. Subjects that were dosed with the OTX-TIC 5µg implant and have yet to reach the 15 weeks post-injection timepoint will be unmasked (4 additional subjects). All investigators will be informed which of their subjects received this treatment and are yet to reach the 15 weeks post-injection timepoint, and the investigators will then be able to inform these subjects. All subjects in this arm that have not yet reached the 15 weeks post-injection timepoint will have additional study requirements moving forward (see item #3).

3. Additional weekly IOP checks and slit-lamp exams will be required between Week 10 and Week 15 (unscheduled visits) for these subjects. Subjects will be informed of symptoms of elevated IOP and will be advised to contact their clinical trial site if any of these symptoms develop. Any elevation in IOP identified will be treated with an IOP-lowering regimen per investigator discretion.
4. Treatment assignments (OTX-TIC 5µg) of 6 subjects that were unmasked during the safety review will be shared with the Investigators who will then be able to inform these subjects. These subjects will have additional visits as described in item #3 above if they are yet to reach the 15 weeks post-injection timepoint. If they have reached the 15 weeks post-injection timepoint, they will continue with their trial follow up with no change in their visit schedule.
5. Subjects that were dosed with the OTX-TIC 5µg implant and are beyond the 14 weeks post-injection timepoint will stay masked and continue with their trial follow up with no change in their visit schedule.
6. Subjects in the OTX-TIC 26µg and Durysta arms will stay masked and continue with their trial follow up with no change in their visit schedule.
7. The OTX-TIC-2020-201 clinical trial will continue with enrollment in the Durysta and OTX-TIC 26µg arms upon IRB approval of the protocol amendment as currently no other safety signals related to IOP elevation have been observed.

4.5 Dose and Administration Justification

Ocular Therapeutix demonstrated safety of OTX-TIC in five animal studies, Table 3. First, in a 120-day GLP toxicity study in beagle dogs that administered an 18 µg travoprost dose delivered over the study duration. Second, in a dose response, PK/pharmacodynamics, persistence and tolerability study in beagle dogs that administered either a 14 or 41 µg travoprost dose delivered over 4-months. Third, in a dose response study, pharmacodynamics, persistence and tolerability study in beagle dogs that administered either a 15 or 30 µg travoprost dose delivered over 4-months [redacted] Fourth, in a dose response study, pharmacodynamics, persistence and tolerability study in beagle dogs that administered either a 12 or 4 µg travoprost dose [redacted]. Fifth, in a 9-month GLP repeat-dose toxicity study in beagle dogs that evaluated travoprost doses of 13 µg (one implant) administered four times over the study at 8-weeks intervals, and 26 µg (one implant) and 52 µg (two implants) administered twice over the study at 18-weeks intervals that provided sustained delivery of travoprost over 9-months.

OTX-TIC travoprost doses 14 and 41 µg were assessed for efficacy via IOP reduction in normotensive beagles. IOP results for the 14 and 41 µg doses demonstrated a mean IOP reduction of -27% and -37%, respectively, from baseline over the intended dosing period post OTX-TIC administration through the sustained drug release period and then a trending return towards baseline values consistent with absent travoprost acid (TA) concentrations in the beagle AH (discussed below).

[redacted]

OTX-TIC [redacted] containing either a 12 µg dose delivered over 90 days or a 4 µg dose delivered over 60 days demonstrated a similar mean decrease in IOP (primary pharmacodynamics marker) and pupil constriction (secondary pharmacodynamic marker) through 12-weeks, 22%, and 26%, respectively.

Systemic human exposure from steady state drug release of travoprost from the OTX-TIC (5 µg) should be approximately 0.083 µg/day, and from the OTX-TIC (26 µg dose) should be approximately 0.217 µg/day, as OTX-TIC would be administered in a unilateral injection for the initial Phase 1 study. A dose of 18 µg OU (36 µg total) at steady state delivered 0.3 µg/day and was tested in the beagle single dose toxicity study without significant toxicological systemic or ocular findings. A dose of 52 µg (two implants per eye) at steady state delivered 0.4 µg/day and was tested in the beagle toxicity study without significant toxicological systemic or ocular findings. A systemic subcutaneous dose was assessed in rats with travoprost with a reported no observed adverse effect level (NOAEL) level of 10 µg/kg/day (from Travatan NDA #021257). The proposed maximal dose for OTX-TIC of 0.217 µg/day in a 60 kg human would be approximately 2765-fold less than the systemic NOAEL in rats.

Calculations of human equivalent dose (HED) of NOAELs and applications of safety factors used to calculate the ocular and systemic safety factors for the planned clinical starting dose of 5 µg/eye and the dose of 26 µg/eye are presented in Table 3. Ocular HED is based on normalization of differences in ocular volumes between humans (4.25 mL) and beagles (3.77 mL), and systemic HED is based on dose per unit weight.

Table 3: Safety Margins for Ocular and Systemic Toxicity [a]

NOAEL Study	Beagle Dose per Eye	Intraocular HED [b]	Ocular Safety Factor for 5 µg and 26 µg Human Dose per Eye	Total Systemic Dose	Systemic HED [c]	Systemic Safety Factor for 5 µg and 26 µg Human Dose [d]
120 Day OTX-TIC Implant Intracameral Ocular Toxicity in Beagles (n=8) (TR-1316)	18 µg/eye	20.3 µg (18 × 1.13)	4.1 (5 µg) 0.8 (26 µg)	36 µg	133 µg	26.6 (15 µg) 5.1 (26 µg)
OTX-TIC Dose Response PK, Pharmacodynamics, Persistence and Tolerability Study in Beagle Dogs (n=6/dose group) (TD-1410)	14 µg/eye	15.8 µg (14 x 1.13)	3.21 (5 µg) 0.6 (26 µg)	28 µg	104 µg	20.8 (5 µg) 4.0 (26 µg)
	41 µg/eye	46.3 µg (41 × 1.13)	9.3 (5 µg) 1.8 (26 µg)	82 µg	311 µg	62.2 (5 µg) 11.7 (26 µg)
OTX-TIC Implant: 9-Month Repeat Dose Intracameral Ocular Toxicity Study in Dogs (n=8) (TIC-NC-TOX-2021-001)	13 µg/eye	14.7 µg (13 x 1.13)	2.9 (5 µg) 0.5 (26 µg)	13 µg	48 µg	9.6 (5 µg) 1.9 (26 µg)
	26 µg/eye	29.4 µg (26 × 1.13)	5.9 (5 µg) 1.1 (26 µg)	26 µg	96 µg	19.3 (5 µg) 3.7 (26 µg)
	52 µg/eye	58.8 µg (52 × 1.13)	11.8 (5 µg) 2.3 (26 µg)	52 µg	193 µg	38.5 (5 µg) 7.4 (26 µg)

[a] The ocular and systemic safety factors may vary by up to 20% to allow for the drug content specification range of 5 µg ± 1 µg or 26 µg ± 5 µg.
[b] Intraocular HED is derived by dividing human eye volume (4.25 mL) by beagle eye volume (3.77 mL)(Vezina 2012) multiplied by the dose per eye consistent with normalization between species based on the intraocular compartmental volume description in section V.C. of the FDA Guidance .
[c] Systemic HED is derived by converting total systemic dose to µg/kg in beagles (9 kg) then dividing by a factor of 1.8 and multiplying by human weight (60 kg) consistent with Table 1 in FDA Guidance ((Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers).
[d] The systemic safety factor is the systemic HED divided by the proposed clinical dose of either 5 or 26 µg.

Local travoprost acid (TA) concentrations from a single eye drop of 1.2 µg/day travoprost administered to rabbits was shown to have a C_{max} in the aqueous humor (AH) of approximately 12.5 ng/mL. Higher dose studies at a 20-fold higher (24 µg/day) travoprost daily topical dose for 3 months and an 8.3-fold higher dose (10 µg/day) for 6-months in rabbits had probable TA concentrations much higher in the rabbit AH than the single eye drop study at 1.2 µg/day. These repeat dose topical toxicity studies in rabbits had no toxicologically significant ocular or systemic findings (from Travatan Z NDA #021994). The sustained TA concentrations in the beagle AH for the OTX-TIC studies were an average of 1.4 ng/mL (range 0.3 to 4.2 ng/mL) for the 18 µg dosage strength from Days 1 to 112, an average of 1.1 ± 0.2 ng/mL (range 1.0 to 1.4 ng/mL) for the 14 µg dosage strength through 120 days, and an average of 3.3 ± 0.4 ng/mL (range of 2.8 to 3.8 ng/mL) for the 41 µg dosage strength through 120 days. Following 120 days the values drop to 0.1 ng/mL for both dosage strengths and then are below the LOQ for the remainder of the study. Local TA concentrations in the AH in beagles with elevated doses of OTX-TIC are below levels demonstrated to have no toxicologically significant ocular or systemic findings in 3-

and 6-months repeat dose toxicity studies in rabbits. Travoprost released from OTX-TIC demonstrated TA concentrations in the rabbit AH comparable to Travatan eye drops.

OTX-TIC proposed in the Phase 2 clinical study contains either a 5 µg dose (n=~35) or a 26 µg dose (n=~35) of travoprost designed to provide a sustained release of therapeutic levels of drug over a period of up to 6 months for the lower dose and approximately up to 9 months for the higher dose. OTX-TIC tested in 19 participants in the Phase 1 clinical study contained either a 15 µg dose (starting – Cohort 1, n=5), 26 µg dose (Cohort 2, n=4) of travoprost designed to provide a sustained release of therapeutic levels of drug over approximately 3 to 6 months. Preliminary efficacy clinical data in subjects dosed with 15 µg (Cohort 1) and 26 µg (Cohort 2) demonstrated a decrease in IOP of 7 to 11 mm for up to 9 months [redacted]. Safety findings included low grade inflammation, peripheral anterior synechia (PAS) (only observed in the Cohort 1). A third cohort (n=5) was added to the Phase 1 study at a dose of 15 µg [redacted] having a release duration of approximately 75% of Cohorts 1 and 2. A fourth cohort was added at a dose of 5 µg (n=5) [redacted] having a release duration approximately 50% of Cohorts 1 and 2. Cohorts 3 (15 µg dose, fast degrading) and 4 also demonstrated a decrease in IOP of 7-11mmHg in the early time-points, with the effect lasting between 3-6 months; [redacted] Preliminary findings indicate OTX-TIC has generally been well tolerated with a favorable safety profile. No serious ocular adverse events have been observed in any of the four cohorts to date.

4.6 Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Council on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of investigational products (IPs) will be adhered to in the countries involved.

4.7 Trial Population

Approximately 86 subjects diagnosed with (OAG) or (OHT) will be screened and randomly assigned to one of three treatment groups.

5 TRIAL OBJECTIVES

5.1 Main Study (Initial Dose)

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

* Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022. All other arms continue to enroll.

5.2 Repeat Dose Sub-Study

The objectives of the sub-study are to explore the preliminary safety of a repeat [redacted] 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.

6 TRIAL DESIGN

6.1 Description of Trial

This is a prospective, multi-center, randomized, parallel-group, controlled study to evaluate the efficacy, and safety of OTX-TIC (travoprost) intracameral implant in subjects with open angle glaucoma or ocular hypertension (OHT). Approximately 105 subjects will be enrolled in this study at approximately 20 sites in the US. Subjects will be a randomized to one of three treatment groups as noted in Table 4. Non study eyes will be treated with the PGA, if not contraindicated.

Table 4: Treatment Assignment Paradigm

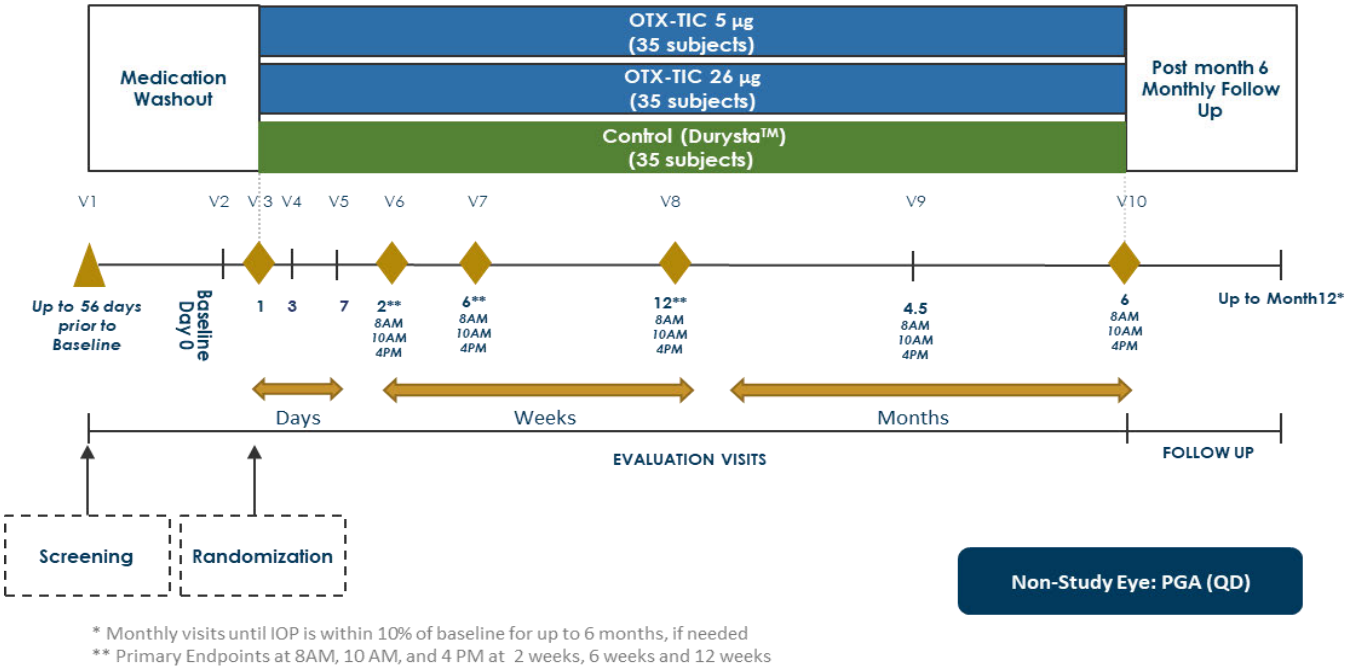
Treatment Group	Number of Subjects	Study Eye (SE) Treatment	Non-Study Eye (NSE) treatment *
Group 1: OTX-TIC 5 µg (travoprost) Intracameral Implant[+]	~16[+]	Dose strength: 5µg	Eye-drops: PGA QD
Group 2: OTX-TIC 26 µg (travoprost) Intracameral Implant	35	Dose strength: 26µg	Eye-drops: PGA QD
Group 3: Active Control	35	Durysta™	Eye-drops: PGA QD

* 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.
[+] Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022. All other arms continue to enroll. The number of subjects is an approximation based on masked enrollment at the time of the OTX-TIC 5µg arm closure.

This main 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 42 days prior to **Baseline Visit (Visit 2**), which includes a washout period of glaucoma medications, if needed. At **Visit 3 (Injection/Day 1)** eligibility will be confirmed and subjects who are eligible will be randomly assigned to one of three treatment groups (OTX-TIC 5 µg, OTX-TIC 26 µg, or Control) in a 1:1:1 ratio. OTX-TIC 5 µg will consist of approximately 16 subjects enrolled by 09DEC2022. No additional subjects will be enrolled in this arm. Enrollment in the other 2 arms will continue in a 1:1 ratio. Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022. The treatment follow-up visits will occur at **2 days (Visit 4) and 6 days (Visit 5) post-injection** for safety evaluation 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 also be performed. Following that, subjects will return at **Month 6 (Visit 10)** for final evaluations, and eligibility for the repeat dosing sub-study.

This main study will be conducted per the schedule shown in Figure 2.

Figure 2: Study Schematic for Main Study (Initial Dose)



* Monthly visits until IOP is within 10% of baseline for up to 6 months, if needed
** Primary Endpoints at 8AM, 10 AM, and 4 PM at 2 weeks, 6 weeks and 12 weeks

For subjects that do not qualify or are not willing to participate in the repeat dose sub-study, they can be discharged from the 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 lower by at least 10% compared to the baseline measurement) or the implant is present at the Month 6 visit, in which case the 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, 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.

6.2 Description of the Repeat Dosing 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 26 µg or Durysta subjects that have not required Rescue Therapy prior to Visit 10 will be asked to participate. Subjects may choose to 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 will return for **Visit 11R (Injection/Day 1-R) where e**ligibility will be confirmed, and subjects will be assigned to one of three treatment groups (Table 5):

- For subjects that received an initial dose of OTX-TIC 26 µg in the main study:
  - [redacted] Sham followed by OTX- TIC 26 µg [redacted]

- [redacted] OTX-TIC 26 µg

- For subjects that received an initial dose of Durysta in the main study:
  - Sham Only

Subjects in these 3 groups would be treated as assigned, at Visit 11R (Day 1-R), which must occur within 7 days of Visit 10 (Month 6). [redacted]

Table 5: 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 Implant [redacted]	< 35	Dose strength: 26µg	Eye-drops: PGA QD
Group 2: OTX-TIC 26 µg (travoprost) Intracameral Implant [redacted]	< 35	Dose strength: 26µg	Eye-drops: PGA QD
Group 3: Sham injection	< 35	Sham injection	Eye-drops: PGA QD

* [redacted]

** 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.

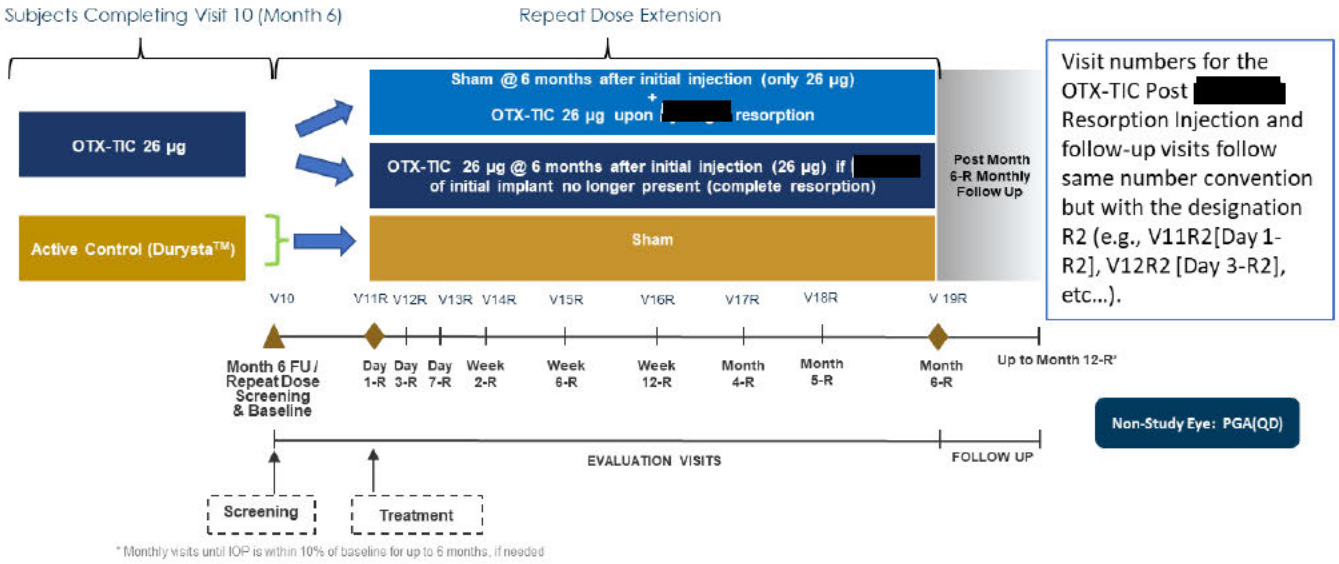
The NSE should continue to be treated with PGA (if not contraindicated) QD in the evening; every effort should be made to ensure the dose and frequency remain unchanged for the duration of the study The treatment follow-up visits will occur on **Day 2-R (Visit 12R), Day 7-R (Visit 13R), Week 2-R (Visit 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 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, 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 Visit 11R where complete resorption of the initial implant [redacted] is confirmed [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 follow the same follow-up schedule but will have the designation R2 (including post 6-month follow-up should either biological activity continue, or the implant continue to be visualized).

[redacted] This study will be conducted per the schedule shown in Figure 3.

Figure 3: Study Schematic for Repeat Dose Sub-Study



6.3 Study Endpoints

6.3.1 Efficacy Endpoints

6.3.1.1 Primary Efficacy Endpoints

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

6.3.1.2 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 the fewer, 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.

6.3.2 Ocular Safety Evaluations

- Incidence of adverse event reporting
- Summaries of OTX-TIC implant assessments [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 in 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 parameters

6.3.3 Repeat Dosing Sub-Study Evaluations

- 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 the 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 the fewer, 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.

6.3.4 Patient Reported Outcome Evaluations

- Implant Acceptability Questionnaire at 12 weeks and 6 months.

6.4 Randomization, Non-Randomized Treatment Assignment and Masking

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.

6.4.1 Main Study (Initial Dose)

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, but as of as of 09Dec2022, enrollment of the OTX-TIC 5 µg treatment group was closed. 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.

6.4.2 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 qualifications in Section 7.2 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 in the main study:
  - [redacted] Sham followed by OTX- TIC 26 µg [redacted]
  - [redacted] OTX-TIC 26 µg
- For subjects that received an initial dose of Durysta in the main study:

- 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).

6.4.3 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

6.5 Trial Treatment

6.6 Main Study (Initial Dose)

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

*Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022. All other arms continue to enroll.

Active Control:

- Durysta™ (Bimatoprost Implant)

6.7 Repeat Dose Sub-Study

- For subjects that received an initial dose of OTX-TIC 26 µg in the main study:
  - [redacted] Sham followed by OTX- TIC 26 µg [redacted]
  - [redacted] OTX-TIC 26 µg
- For subjects that received an initial dose of Durysta in the main study:
  - Sham Only

6.8 Trial 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 + OTX-TIC 26 µg [redacted] group. 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. [redacted] 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.

6.9 Trial Material Accountability

All IP required for this study will be provided by Ocular Therapeutix, Inc., or its designee. The recipient will acknowledge receipt of study drug, indicating shipment content and condition. Damaged supplies may be replaced upon notification to Ocular Therapeutix, Inc., or its designee. Accurate records of all IP administered by study site should be maintained and recorded. A study monitor will periodically check the supplies of IP held at the site to verify accountability of all IP. All used and unused IP (non-dispensed) will either be returned to Ocular Therapeutix, Inc., or its designee, or destroyed at the site upon written confirmation from Ocular Therapeutix, according to site procedures. The investigator must keep an accurate accounting of IP received from the supplier by maintaining a detailed inventory. This includes the amount of IP received by the site, amount administered to subjects, the amount destroyed by the site and the amount returned to the sponsor or designee (as applicable), upon completion of the study. All IP that is used during the course of the study must be accounted for on a drug accountability form.

Accurate records of receipt and disposition of the IP (e.g. dates, subject number, kits used, kits unused, etc.) must be maintained by designated site personnel.

OTX-TIC (travoprost) and Durysta implants are sterile, preservative-free ophthalmic implants. OTX-TIC (travaprost) implant, OTX-TIC Injector, OTX-TIC Sham Injector and Durysta implant pre-loaded in an applicator are provided in sterile, single use packages. The product is packaged in a hermetically sealed foil pouch to maintain stability and sterility over time. The product is terminally sterilized and stored refrigerated.

At the investigational site, IP must be kept in a safe storage area with limited access (e.g., in a refrigerator in a locked/limited access area). The refrigerator should be temperature monitored. IP should be stored at controlled refrigerated temperatures from 2°C to 8°C.

The IP must not be used outside of this clinical study. The investigator or site personnel may not supply IP to other clinical sites, investigators, or subjects, or allow the IP to be used other than as directed by this protocol without prior authorization from Ocular Therapeutix, Inc.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

The trial will include approximately 105 subjects from approximately 20 sites.

7.1 Main Study (Initial Dose) Eligibility

7.1.1 Inclusion Criteria

Subjects will be eligible for study participation if they:

Individuals of either gender will be eligible for study participation if they:

1. Are 18 years of age or older at the time of screening
2. Provide written signed informed consent and are able to comply with all study requirements
3. [redacted]

- [redacted]

4. Have a negative pregnancy test result for women of childbearing potential at Baseline
5. Have a documented diagnosis of OHT, or OAG (including primary, pigmentary and pseudoexfoliation glaucoma) in the **study eye**
6. Have a mean baseline IOP following an up to 8-week washout period of current therapy (if needed) in the:

   6.1 **Study eye** of:

   ≥22 mmHg and ≤32 mmHg at 8 am (hour T_0) at Baseline Visit 2 (Day 0) after the washout period*

   ≥ 19 mmHg and ≤ 32 mmHg at 10 am (hour T_0 + 2) at Baseline Visit 2 (Day 0) after washout period*

   *Note: For subjects whose IOP is < 22 mmHg at 8 am at Baseline or < 19 mmHG at 10 am at Baseline, a second visit to assess their IOP can be scheduled no longer than 14days after the 1st Baseline visit (no later than 70 days after screening). If < 5 days only IOP should be repeated. If > 5 days, days, all baseline assessments except the fundus exam should be repeated.

   6.2. **Non-study eye** of:

   ≥17 mmHg and ≤32 mmHg at 8 am (hour T_0) at Baseline Visit 2 (Day 0) after the washout period

7. [redacted]
8. [redacted]

7.1.2 Exclusion Criteria

Subjects are not eligible for study participation if they:

Non-ocular exclusion criteria:

1. Have an uncontrolled systemic disease or a debilitating disease (e.g., cardiovascular, hypertension, uncontrolled diabetes)
2. Are currently pregnant or breast-feeding or of childbearing potential without the use of adequate contraceptive methods during the length of the study
3. Have a known or suspected allergy to travoprost and bimatoprost, or to any component of the study products

4. Anticipated use of oral, intramuscular, or intravenous corticosteroids from 2 months prior to Baseline visit through Exit Visit
5. Have participated in any study involving an investigational drug either in the U.S. or outside the U.S. within the past 30 days
6. Are an employee of the site that is directly involved in the management, administration, or support of the study, or are an immediate family member of the same
7. Have any history of bleeding disorder of use of medications which in the Investigator's opinion places the subject at high risk during insertion of the implant
8. Have any condition or use of any recreational drug that in the opinion of the site Investigator, would compromise study outcomes, patient's compliance with study requirements, including study completion

Ocular exclusion criteria:

Individuals are not eligible for study participation if they:

1. [redacted]
2. [redacted]
3. Patient is non-responsive to topical prostaglandins, prostamides or prostaglandin analogs (eg., Xalatan, Lumigan, Travatan) based upon the assessment by the Investigator
4. [redacted]
5. [redacted]
6. Are unwilling to discontinue use of contact lenses 3 days prior to pachymetry and throughout the entire study
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]

12. [redacted]
13. Have a history of significant ocular trauma within the past six months in the **study eye**
14. [redacted]
15. [redacted]
16. [redacted]
17. [redacted]
18. [redacted]
19. [redacted]

7.2 Repeat Dosing Eligibility

7.2.1 Inclusion Criteria

Individuals of either gender previously dosed with OTX-TIC 26 µg or Durysta and have completed the Month 6 (Visit 10) will be eligible for study participation if they:

1. Provide written signed informed consent and are able to comply with all sub-study requirements
2. Central Corneal Endothelial Cell Density by specular microscopy ≥ 1800 cells/mm^2 in the study eye by automated analysis prior to repeat dosing assignment and confirmed as being qualified by the Central Reading Center at the Month 6 Visit (Visit 10). Additionally, the subject should not have a > 15% change in cell count from Screening (Visit 1).

7.2.2 Exclusion Criteria

Subjects are not eligible for study participation if they:

1. Have received Rescue Therapy prior to the Month 6 follow up visit (Visit 10).
2. Have an ongoing adverse event that would contraindicate an intracameral injection.
3. Are not a good candidate for repeat injection based upon the assessment by the Investigator
4. [redacted]
5. OTX-TIC [redacted] is confirmed as present in the study eye [redacted] AND IOP lowering medications are required at Month 6 (Visit 10).

7.3 Entry/Randomization Criteria:

To qualify for intracameral injection at Day 1 (Visit 3) for initial dose and Day 1-R (Visit 11R) for repeat dose, a subject must continue to meet all screening inclusion/exclusion criteria.

7.4 Procedural Exclusion Criteria

Unsuccessful intracameral injection (record reason for injection failure on the electronic Case Report Form, i.e., eCRF) is considered a procedural exclusion. The study will be supplemented with additional subjects to account for these subjects in order to ensure that the necessary number of subjects receive the implant to inform on safety, and efficacy.

7.5 Subject Recruitment and Screening

Each subject that is screened will be assigned a Subject Identification (ID) consisting of a 2-digit Site number plus a 3-digit Subject number. The Subject ID will be used as the primary subject identifier for the duration of the study. Once all inclusion and exclusion criteria are met at Visits 1 and 2, each qualifying subject will be randomized via the IRT system and will be assigned a randomization number.

The subject must sign the Informed Consent Form (ICF) before his or her participation in the study. A copy of the ICF must be provided to the subject or the subject's legal guardian. If applicable, it will be provided in a certified translation of the subject's first or native language. The original signed ICF for each participating subject shall be filed with records kept by the investigator and must be available for verification by study monitors at any time, and a copy will be given to each subject.

7.6 Withdrawal Criteria

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.

7.7 Withdrawal Methods

The Sponsor may terminate this study at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of adverse events (AE) in this or other studies point to a potential health hazard for trial subjects.
- Insufficient subject enrollment.
- Any information becoming available during the study that substantially changes the expected benefit risk profile of the study treatments.

7.8 Collection of Data from Withdrawn Subjects

In the event that study discontinuation of a randomized subject is necessary in the main study, the Investigator should make every attempt to have the subject complete Visit 10 assessments, if discontinued prior to Month 6 visit; and the Post Month 6 Exit visit assessments if discontinued after the Month 6 visit. The assessments should be completed as soon as possible. The reason for premature discontinuation should be recorded in the subject chart and entered in the eCRF.

If study discontinuation of a randomized subject is necessary in the repeat dose sub-study, the Investigator should make every attempt to have the subject complete Visit 19-R/R2 assessments, if discontinued prior to Month 6-R/R2 visit; and the Post Month 6-R/R2 Exit visit assessments if discontinued after the Month 6-R/R2 visit. The assessments should be completed as soon as possible. The reason for premature discontinuation should be recorded in the subject chart and entered in the eCRF.

7.9 Subject Replacement

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.

7.10 Trial Termination

Should it become apparent during the trial that there is a significant safety concern or there is an issue with enrollment, the trial may be terminated. In addition, should information become known during the course of the trial that would negatively impact the trial, the trial may be terminated. In addition, the FDA or another regulatory authority may terminate the trial.

8 SUBJECT TREATMENT

8.1 Treatment Regimen

8.1.1 Main Study (Initial Dose)

Treatment	N	Study Eye (SE) Treatment	Non-Study Eye (NSE) treatment*
OTX-TIC 5 µg+	~16	Dose strength: 5µg	Eye-drops: PGA QD
OTX-TIC 26 µg	~35	Dose strength: 26µg	Eye-drops: PGA QD
Control	~35	Durysta™	Eye-drops: PGA QD

* The non-study eye, if needed, should be treated with a 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.
+ Enrollment of the OTX-TIC 5µg arm is closed as of 09Dec2022. All other arms continue to enroll. The number of subjects is an approximation based on masked enrollment at the time of the OTX-TIC 5µg arm closure.

8.1.2 Repeat Dose Sub-Study

Treatment	N	Study Eye (SE) Treatment	Non-Study Eye (NSE) treatment*
Sham + OTX-TIC 26 µg [redacted]	<18	Sham injection followed by OTX-TIC [redacted] Dose strength: 26µg	Eye-drops: PGA QD
OTX-TIC 26 µg [redacted]	<18	OTX-TIC Dose strength: 26µg	Eye-drops: PGA QD
Sham	<35	Sham injection	Eye-drops: PGA QD

* The non-study eye, if needed, should be treated with a 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.

8.2 Prior and Concomitant Therapy

The use of any concurrent ophthalmic medications and systemic medications, prescription or over-the-counter, from up to 1 year prior to the Screening Visit, in addition to all prior medications for OAG or OHT for the last 3 years is to be recorded on the subject's medical records and corresponding eCRF along with the reason the medication was taken, starting at the Screening Visit through the end of the study. The use of any dilation and other standard of care drops used for the ophthalmic assessments including IOP measurement and the injection procedure (i.e., betadine or topical anesthetic) will not be recorded, except for the antibiotics, NSAIDs or steroids. Recreational drug use will also be recorded. Standard post-ocular injection treatment should include topical broad-spectrum antibiotic drops and topical steroids up to four times a day for a week, at the Investigator's discretion. If use of topical steroids is needed beyond Day 7 after treatment, please contact the Sponsor.

The following restrictions related to medications and treatments are summarized in Table 6.

Table 6: Prohibited/Restricted Medications

Minimum Washout Period Prior to Baseline are:
5 days:
Pilocarpine or carbonic anhydrase inhibitors
Minimum Washout Period Prior to Baseline are:
2 weeks:
α adrenergic agonists
Minimum Washout Period Prior to Baseline are:
4 weeks:
β adrenergic blockers
prostaglandin analogues
Tetracycline compounds (tetracycline, doxycycline or minocycline)
Inhaled, intramuscular or intra-articular corticosteroids (mouth or nasal spray form)
Rho kinase inhibitors

8.3 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. The IOP lowering medication should be recorded on the appropriate eCRF.

8.3.1 Treatment of IOP elevations in Subjects that received OTX-TIC 5µg implants

Any elevation in IOP identified in subjects that received OTX-TIC 5µg implants between week 10 and 15 will be treated with an IOP-lowering regimen per investigator discretion.

8.4 Contact Lens Use

All subjects that wear soft contact lenses should remove them at least 3 days prior and abstain from wearing them until after each study visit beginning with the Screening Visit (Visit 1). This practice should be continued by the subjects at every visit until the completion of the final Exit Visit. Subject compliance with contact lens removal 3 days prior to and resumption of use after study visits should be recorded in the subject's source documentation.

Additionally, after removal of contact lenses prior to the Injection Visit (Visit 3) subjects should not resume their contact lens use until at least 7 days post-injection, after completion of the Day 7 follow-up visit (Visit 5).

This same procedure should continue for any subjects that participate in the repeat dose sub-study.

8.5 Study Assessments by Visit

Perform study procedures as referenced in Appendix 1 (Time and Events Schedules).

Note: All subjects will have both eyes evaluated at all visits. IOP measurements should not be completed before BCVA, Visual Field, and Endothelial Cell Count at any visit. Any dilated fundus exams should be completed last.

8.6 Main Study: Initial Dosing and Follow up

8.6.1 Visit 1 (-56 days prior to Baseline) Screening

Note: For naïve treatment subjects a minimum of 2 days (provided eligibility confirmation received from the Reading Center) between the Screening Visit 1 and the Baseline Visit 2 (Day 0).

- Informed consent
- Demographics
- Medical/Ophthalmic History
- Record Medications
- BCVA (ETDRS) [redacted]
- Visual Field [redacted]
- Endothelial Cell Count (specular microscopy)
- Anterior Segment (AS)-OCT
- Slit Lamp Biomicroscopy including External Eye Exam [redacted]
- IOP Measurement Applanation (Goldmann) [redacted]
- Pachymetry
- Gonioscopy [redacted]
- Dilated Fundus Exam [redacted]
- Posterior Segment (PS)-OCT
- OCT Optic Nerve and RNFL
- Determine Eligibility

If necessary, screening activities can be completed over more than one day. At the end of the screening Visit 1 potentially eligible subjects will be instructed to start washout from current IOP lowering medications in Table 6. Investigators, at their discretion, may have subjects return for unscheduled visits to have their IOPs checked prior to baseline to ensure washout is proceeding as expected.

For screen failures due to reasons that are expected to be temporary one re-screening visit can be conducted. Subjects who are re-screened will be given a new subject number and need to have all screening procedures repeated (including signing of a new informed consent). It should be noted on the CRF that the subject is a re-screen.

For eligible subjects, all information must be recorded in the subject's CRF. For subjects who do not meet the eligibility criteria, the minimum information to be recorded in the CRF will be the following: date of screening, subject number, demography, date ICF was signed, and reason for screen failure.

8.6.2 Visit 2 (-4 to -1 day) Baseline Visit/Day 0

The following assessments will be performed on both eyes. IOP measurements taken on Day 0 will be the baseline IOP measurements.

At 8 a.m. (T_0)

- Record Medications
- Urine Pregnancy Test (when applicable)
- BCVA (ETDRS)

- Slit Lamp Biomicroscopy including External Eye Exam
- IOP Measurement by applanation tonometry (Goldmann)*
- Undilated Fundus Exam
- Determine Eligibility

At 10 a.m. (T_0+ 2 hrs) and 4 p.m. (T_0+ 8 hrs)

- IOP measurement by applanation tonometry (Goldmann)*

* For subjects whose IOP is < 22 mmHg at 8 am (hour T_0) or < 19 mmHG at 10 am at Baseline, a second visit to assess their IOP can be scheduled no longer than 14 days after the 1st baseline visit (no later than 70 days after screening). If < 5 days only IOP should be repeated. If > 5 days, days, all baseline assessments except the fundus exam should be repeated.

NOTE: All IOP measurements at 8 a.m. (T_0) and 4 p.m. (T_0 + 8) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.6.3 Visit 3/Day 1 (Injection Day)

8.6.3.1 Assessments Performed Prior to Procedure:

The following procedures and assessments will be performed prior to treatment:

- Record Medications
- Subject Ocular Comfort Score [redacted]
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- IOP Measurement by applanation tonometry (Goldmann)
- Randomization

8.6.3.2 Treatment With OTX-TIC / Durysta Intracameral Implant

After all evaluations are completed, and the subject is confirmed to be remain eligible, the study drug treatment (OTX-TIC / Durysta implant) assigned to the subject will be administered by the unmasked Investigator and study staff. The study drug treatment will be administered (i.e. OTX-TIC) by the Investigator according to the injection instructions provided under separate cover. The investigator will record the ease of injection [redacted]

If both eyes are eligible (i.e., all inclusion and none of the exclusion criteria are met) the study eye should be selected as the eye with the highest baseline IOP following the washout period, as determined by the Investigator. If both eyes qualify AND both eyes have the same baseline IOP following the washout period, the right eye will be selected as the study eye.

Subjects can have only one eye treated with the investigational product. The contralateral eye, designated as the non-study eye (NSE), if needed, may be treated with PGA (if not contraindicated). All efforts should be made to maintain the treatment of the **NSE** consistent for the duration of the study.

8.6.3.3 Post-Injection Procedure

At least *30 min* post-injection and prior to discharge from the visit the Investigator and study staff are responsible for the following:

- Adverse events (post-injection)
- Subject Ocular Comfort Assessment
- Product Visualization: The investigator will confirm the proper placement of the investigational product via slit lamp.

8.6.3.4 Discharge Instructions

Subjects should be instructed to refrain from rubbing their eyes and to contact the Investigator in the event that they experience excessive pain, excessive discomfort, eye redness, change in vision, or loss of vision.

Standard post-ocular injection treatment should include topical broad-spectrum antibiotic drops and topical steroids up to four times a day for a week, at the Investigator's discretion.

8.6.4 Visit 4 (Day 3 Post Injection Follow up ±1 day)

The following assessments will be performed by the investigator and study staff at *8 a.m. only* (ocular evaluations to be performed on both eyes of each subject):

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit lamp biomicroscopy, including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

NOTE: IOP measurements must be conducted within ± 60 min of the required time and must be conducted at approximately the same time at each of the follow-up visits.

8.6.5 Visit 5 (Day 7 Follow up ±1 day)

The following assessments will be performed by the investigator and study staff at *8 a.m. only* (ocular evaluations to be performed on both eyes of each subject):

- Record Medications
- Record Adverse Event
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit lamp biomicroscopy, including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)

- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

NOTE: IOP measurements must be conducted within ± 60 min of the required time and must be conducted at approximately the same time at each of the follow-up visits.

8.6.6 Visit 6 (Follow up Week 2, ±1 day)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

At 10 a.m. (T_0+ 2 hrs) and 4 p.m. (T_0+ 8 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) and 4 p.m. (T_0 + 8) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.6.7 Visit 7 (Follow up Week 6, 2 ± days)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

At 10 a.m. (T_0+ 2 hrs) and 4 p.m. (T_0+ 8 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) and 4 p.m. ($T_0 + 8$) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.6.8 Weekly Follow-up Requirements for OTX-TIC 5µg subjects only between Week 10 and Week 15

Due to the IOP elevations noted in 6 subjects receiving the OTX-TIC 5µg implant between week 10 and 14 post injection (identified December 6, 2022), all subjects that received the 5µg implant and had not reached 15 weeks post injection timepoint were unmasked. These subjects are to follow the additional visit requirements of this section to identify and treat any IOP elevations during Week 10, Week 11, Week 13, Week 14, and Week 15 post injection. Week 12 follow-up requirements will be followed per section 8.3.1 below. These subjects will return for the following assessments (to be documented as unscheduled visits in the source/EDC):

- Record Medications
- Record Adverse Events
- Slit lamp biomicroscopy, including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)

Any elevation in IOP identified will be treated with an IOP-lowering regimen per investigator discretion. Also, subjects can be seen at additional unscheduled visits after Week 15 post-injection per investigator discretion.

8.6.9 Visit 8 (Follow up Week 12, 2 ± days)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit lamp biomicroscopy, including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Pachymetry
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Undilated Fundus exam
- Implant Acceptability Questionnaire. [redacted]

At 10 a.m. (T_0+ 2 hrs) and 4 p.m. (T_0+ 8 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) and 4 p.m. ($T_0 + 8$) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.6.10 Visit 9 (Follow up Month 4.5, 3 ± days)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Undilated Fundus exam

At 10 a.m. (T_0+ 2 hrs) and 4 p.m. (T_0+ 8 hrs)

- IOP measurement by applanation tonometry (Goldmann) Tonometry

NOTE: All IOP measurements at 8 a.m. (T_0) and 4 p.m. ($T_0 + 8$) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.6.11 Visit 10 (Follow up Month 6/Early Termination/Repeat Dosing Screening & Baseline, 3 ± days)

Any OTX-TIC 26 µg or Durysta™ subject that has not required Rescue Therapy prior to this visit should be presented the option to participate in the Repeat Dosing portion of the study at this visit through the Repeat Dosing Informed Consent. Repeat dosing is optional and subjects may choose to decline. Upon the completion of the Visit 10 requirements in this section, and confirmation of eligibility for repeat dosing, the subject procedures for Repeat Dosing in section 8.7 (Repeat Dosing Sub-Study

) should be followed.

For all other subjects not participating in repeat dosing, the procedures for continuing under the single dose Post 6 Month Follow-up and Exit should be followed as needed (Sections 8.7.1 and 8.7.2) upon completion of Visit 10.

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Visual Field
- Endothelial cell count (specular microscopy) **Must be submitted immediately to Reading Center for confirmation of Eligibility for Repeat Dosing prior to the Repeat Injection Visit**
- Anterior segment (AS)-OCT
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Pachymetry
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Dilated Fundus exam
- OCT Optic nerve and RNFL
- Posterior Segment (PS)-OCT
- Implant Acceptability Questionnaire. [redacted]

At 10 a.m. (T_0+ 2 hrs) and 4 p.m. (T_0+ 8 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) and 4 p.m. (T_0 + 8) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

OTX-TIC 26 µg or Durysta™ subjects without any Rescue Therapy prior to Visit 10 will be presented the opportunity to continue in the repeat dosing Sub-Study. Should they desire to participate the following will be performed:

- Repeat Dosing Informed Consent
- Repeat Dosing Eligibility Confirmation including:
  - [redacted]
  - Confirmation that the subject has not received rescue therapy in the study eye during the study.
  - Confirmation of whether the subject currently requires recue therapy at Visit 10 (Month 6).
  - Confirmation of the subject's [redacted] status [redacted]
    - **If the subject requires rescue therapy with IOP lowering medication and OTX-TIC [redacted] is still present [redacted] at Visit 10 (Month 6), the subject is NOT Eligible for the repeat dose sub-study and should be treated with IOP lowering drops and followed per the main study requirements.**

- ECC Submitted to Reaching Center for eligibility confirmation prior to re-injection.

Any subject **NOT** moving forward with Repeat Dosing that has 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 visit, 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, 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.

8.6.12 Post Month 6 Month Follow Up (3 ± days)

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Undilated Fundus exam

8.6.13 Post Month 6 Exit Visit (3 ± days)

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Visual Field
- Endothelial cell count (specular microscopy)
- Anterior segment (AS)-OCT
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Pachymetry
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Dilated Fundus exam
- OCT Optic nerve and RNFL

- Posterior Segment (PS)-OCT

8.7 Repeat Dosing Sub-Study

The Repeat Dosing Sub-Study is only for OTX-TIC 26 µg or Durysta™ subjects that have consented and qualified at the Visit 10 follow up visit (see Section 8.6.11). [redacted].

8.7.1 Visit 11R/Day 1-R or Visit 11R2/Day 1-R2 (Repeat Injection Day; 6 months +7 days)

The repeat injection visit must be completed within 7 days of Month 6 (Visit 10) upon confirmation of qualifying endothelial cell count by the Reading Center.

8.7.1.1 Assessments Performed Prior to Repeat Injection:

The following procedures and assessments or confirmation will be performed prior to treatment:

- Record Medications
- Subject Ocular Comfort Score [redacted]
- BCVA (ETDRS)
- Visit 10 (Month 6) Endothelial cell count (specular microscopy) eligibility confirmation from Reading Center
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment of previous implant to confirm [redacted] resorption status before repeat dose treatment assignment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Randomization (only at Visit 11R)

8.7.1.2 Treatment With OTX-TIC Intracameral Implant / Sham Injection

After all evaluations are completed, and the subject is confirmed to remain eligible, the study drug treatment (OTX-TIC 26 µg/ Sham) assigned to the subject will be administered by the unmasked Investigator and study staff. The study drug treatment will be administered (i.e., OTX-TIC) by the Investigator according to the injection instructions provided under separate cover. The investigator will record the ease of injection [redacted] The Study Eye will remain the same as the initial study treatment.

The contralateral eye/non-study eye (NSE), if needed, will continue to be treated with PGA (if not contraindicated). All efforts should be made to maintain the treatment of the **NSE** consistent for the duration of the study.

8.7.1.3 Post-Repeat Injection Procedure

At least *30 min* post-repeat injection and prior to discharge from the visit the Investigator and study staff are responsible for the following:

- Adverse events (post-injection)
- Subject Ocular Comfort Assessment
- Product Visualization (via slit lamp only)

8.7.1.4 Discharge Instructions

Subjects should be instructed to refrain from rubbing their eyes and to contact the Investigator in the event that they experience excessive pain, excessive discomfort, eye redness, change in vision, or loss of vision.

Standard post-ocular injection treatment should include topical broad-spectrum antibiotic drops and topical steroids up to four times a day for a week, at the Investigator's discretion.

8.7.1.5 Sham/OTX-TIC Post [redacted] Resorption Reinjection

Subjects that are randomized to the Sham injection followed by OTX-TIC 26µg post [redacted] resorption group will follow the visit schedule as outlined in the sections below. At each visit an Implant Assessment of the initial implant [redacted] will be conducted. At the visit when there is full clearance of the [redacted] implant [redacted] the subject should be administered the OTX-TIC 26 µg injection. In this case the Visit procedures will be the new Injection Visit 11R-2 and the subject should restart the Repeat Dosing Schedule again and then continue with the schedule as outlined in Section 8.7.2 through Section 8.7.11.

In order to differentiate between the Sham and OTX-TIC 26 µg follow up visits for these subjects, the numbering of the visits for the post [redacted] resorption OTX-TIC Injection and follow up follow the same number convention but with the designation R2:

- Visit 11R2 (Day 1-R2 Injection Day)
- Visit 12R2 (Day 3-R2 Post Injection Follow up ±1 day)
- Visit 13R2 (Day 7-R2 Follow up ±1 day)
- Visit 14R2 (Follow up Week 2-R2, ±1 day)
- Visit 15R2 (Follow up Week 6-R2, 2 ± days)
- Visit 16R2 (Follow up Week 12-R2, 2 ± days)
- Visit 17R2 (Follow up Month 4-R2, 3 ± days)
- Visit 18R2 (Follow up Month 5-R2, 3 ± days)
- Visit 19R2 (Follow up Month 6-R, 3 ± days)
- Post Month 6-R2 Follow Up (3 ± days)
- Post Month 6-R2 Exit Visit (3 ± days)

[redacted]

8.7.2 Visit 12R or Visit 12R2 (Day 3-R/Day 3-R2 Post Injection Follow up ±1 day)

The following assessments will be performed by the investigator and study staff at *8 a.m. only* (ocular evaluations to be performed on both eyes of each subject):

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit lamp biomicroscopy, including External Eye Exam
- Implant Assessment [redacted]

- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

NOTE: IOP measurements must be conducted within ± 60 min of the required time and must be conducted at approximately the same time at each of the follow-up visits.

8.7.3 Visit 13R/Visit 13R2 (Day 7-R/Day7-R2 Follow up ±1 day)

The following assessments will be performed by the investigator and study staff at *8 a.m. only* (ocular evaluations to be performed on both eyes of each subject):

- Record Medications
- Record Adverse Event
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit lamp biomicroscopy, including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

NOTE: IOP measurements must be conducted within ± 60 min of the required time and must be conducted at approximately the same time at each of the follow-up visits.

8.7.4 Visit 14R/Visit 14R2 (Follow up Week 2-R/Week 2-R2, ±1 day)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

At 10 a.m. (T_0+ 2 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.7.5 Visit 15R/Visit 15R2 (Follow up Week 6-R/Week6-R2, 2 ± days)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired

At 10 a.m. (T_0+ 2 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.7.6 Visit 16R/Visit 16R2 (Follow up Week 12-R/Week 12-R2, 3 ± days)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit lamp biomicroscopy, including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Pachymetry
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Undilated Fundus exam
- Implant Acceptability Questionnaire. [redacted]

At 10 a.m. (T_0+ 2 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.7.7 Visit 17R/Visit 17R2 (Follow up Month 4-R/Month 4-R2, 3 ± days)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only, gonioscopy images will be acquired

At 10 a.m. (T_0+ 2 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.7.8 Visit 18R/Visit 18R2 (Follow up Month 5-R/Month 5-R2, 3 ± days)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only, gonioscopy images will be acquired

At 10 a.m. (T_0+ 2 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP

assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

8.7.9 Visit 19R/Visit 19R2 (Follow up Month 6-R/Month 6-R2, 3 ± days/Early Termination)

The following will be performed by the investigator and study staff. Ocular evaluations will be performed on both eyes.

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Visual Field
- Endothelial cell count (specular microscopy)
- Anterior segment (AS)-OCT
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Pachymetry
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Dilated Fundus exam
- OCT Optic nerve and RNFL
- Posterior Segment (PS)-OCT
- Implant Acceptability Questionnaire. [redacted]

At 10 a.m. (T_0+ 2 hrs) and 4 p.m. (T_0+ 8 hrs)

- IOP measurement by applanation tonometry (Goldmann)

NOTE: All IOP measurements at 8 a.m. (T_0) and 4 p.m. (T_0 + 8) must be conducted within ± 60 min of the required time, and measurements at 10 a.m. should be conducted 2 hours after the T_0 exam (± 30 min). All IOP assessments must be conducted at approximately the same time at each of the follow-up visits. IOP will be measured using a 2-person Masked reading method.

Any subject that has 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 visit, 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 Post Month 6-R Exit Visit.

8.7.10 Post Month 6-R/Post Month 6-R2 Follow Up (3 ± days)

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Undilated Fundus exam

8.7.11 Post Month 6-R/ Post Month 6-R2 Exit Visit (3 ± days)

At 8 a.m. (T_0)

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Visual Field
- Endothelial cell count (specular microscopy)
- Anterior segment (AS)-OCT
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]
- IOP Measurement by applanation tonometry (Goldmann)
- Pachymetry
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Dilated Fundus exam
- OCT Optic nerve and RNFL
- Posterior Segment (PS)-OCT

8.8 Unscheduled Visits

An unscheduled visit may be performed during the course of the trial in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. All ocular examinations need to be performed on both eyes.

Evaluations that may be conducted at an Unscheduled Visit may include:

- Record Medications
- Record Adverse Events
- Subject Ocular Comfort Score
- BCVA (ETDRS)
- Slit Lamp Biomicroscopy including External Eye Exam
- Implant Assessment [redacted]

- IOP Measurement by applanation tonometry (Goldmann)
- Gonioscopy with Product Visualization and description. At selected sites only gonioscopy images will be acquired
- Any other assessments needed in the judgment of the investigator

9 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.

10 ADVERSE EVENTS

The investigator and study staff are responsible for detecting and recording AEs and SAEs, during scheduled safety evaluations and whenever such information is brought to their attention.

This section of the protocol provides definitions and detailed procedures to be followed.

During each visit, the Investigator will question the subject about adverse events using an open question taking care not to influence the subject's answers. Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided. At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

10.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after IP administration even though it may have been present prior to the start of the study.
- Signs, symptoms of a drug interaction
- Signs, symptoms of a suspected overdose of either IP or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- A laboratory abnormality occurring after the start of the study (i.e., after screening) that results in subject withdrawal from the study or medical treatment or further follow-up.

10.2 Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" 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 in-patient hospitalization or prolongation of existing hospitalization. Hospitalizations for elective surgeries do not constitute an SAE.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered SAEs, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above.

10.3 Disease-Related Events or Outcomes Not Qualifying as AE/SAE's

IOP increases due to lack of efficacy of the investigational product does not constitute an adverse event, however IOP increases due to other reasons besides lack of efficacy should be reported as adverse event per the investigator's discretion.

10.4 Monitoring and Recording of AEs and SAEs

10.4.1 Adverse Events

Any AE experienced by the subject from Visit 3 (Injection/Day 1) through Visit 16 (Month 12 visit) is to be recorded in the eCRF, regardless of the severity of the event or its relationship to study treatment.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented.

10.4.2 Serious Adverse Events

Any SAE experienced by the subject from Visit 3 (Injection/Day 1) through the Exit Visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment.

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

10.4.3 All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 10.2.
- The severity of the event as defined in Section 10.7.1.
- The relationship of the event to study treatment as defined in Section 10.7.2.

10.5 Immediate Reporting of Serious Adverse Events and Pregnancies

In order to adhere to all applicable laws and regulations for reporting an SAE or pregnancy, the study site must formally notify the pharmacovigilance team within 24 hours of the study site staff becoming aware of the SAE or pregnancy. It is the Investigator's responsibility to ensure that the SAE or pregnancy reporting information is emailed or faxed as described in Figure 4. It may be necessary for the pharmacovigilance team to directly communicate with the Investigator if additional information is required.

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to the pharmacovigilance team on the subject's condition within 24 hours. New or updated information will be recorded on the SAE reporting form. The updated SAE reporting form should be sent to the pharmacovigilance team within 24 hours as described in Figure 4.

All additional follow-up evaluations must be reported to the pharmacovigilance team. Such data should be sent by fax or email (Figure 4) within 10 calendar days. All SAEs will be followed until the Investigator and Ocular Therapeutix agree that the event is satisfactorily resolved.

Figure 4: Reporting Information for SAEs and Pregnancies

To report initial or follow up SAE or Pregnancy information email or fax a copy of the SAE or Pregnancy report form to the following:

ProPharma Group

[redacted]

10.6 Death

The death must be recorded on the appropriate eCRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the pharmacovigilance team.

10.7 Evaluating AEs and SAEs

10.7.1 Severity

The following definitions should be considered when evaluating the severity of AEs and SAEs.

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.

An AE with changing severity over the course of the event should be reported as one event with the highest severity reported. An AE that is assessed as severe should not be confused with a SAE. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.2 definition of an SAE.

10.7.2 Relationship to OTX-TIC or Durysta product or procedure

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Unrelated	This category applies to those (S)AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.); there is no reasonable probability that the (S)AE may have been caused by the procedure or the ophthalmic product. If the investigator determines that the AE is unlikely to be related to the study drug, then this would be the appropriate category.
Related	The following criteria should be applied in considering inclusion of an (S)AE in this category: It bears a reasonable temporal relationship to the procedure or the presence of the product It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other factors (e.g., disease under study, concurrent disease(s) and concomitant medications) and modes of therapy administered to the subject It disappears or decreases on removal of the IP It follows a known pattern of response to the procedure or product

10.7.3 Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure as determined by Ocular Therapeutix, Inc.

10.8 Procedures for Handling Special Situations

10.8.1 Intracameral Implant Removal

If an event occurs that necessitates the removal of study drug (OTX-TIC or Durysta), the decision shall be made in consultation with the Medical Monitor. When possible, the explanted drug should be preserved and sent for physical examination and histopathological analysis [redacted]

10.8.2 Pregnancy

Females should not become pregnant during the study period. If this occurs the subject should notify the Investigator immediately. The Investigator must report the pregnancy as outlined in Section 10.5. In addition, the Investigator or study site staff must report the outcome of the pregnancy to the pharmacovigilance team.

10.8.3 Unmasking for Medical Emergencies

In the case of a medical emergency or occurrence of an SAE, the randomization code may be unmasked and made available to the Investigator, Sponsor, and/or other study personnel involved in the conduct of the study. In the absence of medical need, the randomization code will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the Investigator will treat each subject, as medically required. If the Investigator feels it is necessary to unmask a subject's treatment assignment after an emergency situation, the Investigator may call the Medical Monitor and notify the Sponsor. The treatment assignment will be revealed on a subject-by-subject basis with the approval of the Medical Monitor and Sponsor, leaving the masking of the remaining subjects intact. Ocular Therapeutix will make the final determination if the unmasking request will be granted. Once the unmasking request is granted the investigator or designee should use the IRT system to unmask the subject's randomization code. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

10.8.4 Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Ocular Therapeutix to be associated to the study product. Ocular Therapeutix will report SUSARs to the appropriate authorities within the required regulatory timeframes. Reports of SUSARs will be made to IRBs, and Investigators, as needed.

11 STATISTICAL METHODS AND DATA ANALYSIS

11.1 Statistical Methods

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum and maximum. Summaries for discrete variables will include frequencies and percentages. 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 value. The baseline in the main study will be used for the baseline of repeat dose sub-study.

11.1.1 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.

11.1.2 Repeat Dosing 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 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 will be done with the additional beyond Month 6-R/R2 data after all subjects have exited the study.

11.2 Sample Size Determination

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.

11.3 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.

11.4 Subject Population(s) for Analysis

11.4.1 Modified Intent-to-Treat Population (mITT)

The mITT Population will include all subjects who received an implant in the study eye, investigational product (OTX-TIC or Durysta). 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.

11.4.2 Per-Protocol Population

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

11.4.3 Safety

The Safety population includes all randomized subjects who received an implant. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

11.4.4 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.

11.4.5 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.

11.5 Statistical Significance

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

11.6 Efficacy Analyses

11.6.1 Primary Efficacy Endpoint Analysis

Due to the limited sample size, descriptive summary statistics will be used for the study reporting. No formal statistical hypothesis testing will be performed.

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 analysis will be repeated with all observed data.

The details of primary efficacy analyses will be described in the SAP.

11.6.2 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 presented 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 presented 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 the fewer, 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 presented 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).

The Summary of rescue medications will be presented by treatment group and overall separately for study eye and non-study eye using mITT population.

Kaplan-Meier estimates of time to rescue therapy will be presented by treatment group and by eye (study vs non-study eye) for each treatment group.

11.6.3 The details of secondary efficacy analyses will be described in the SAP.Demographics and Baseline Data

The demographic and baseline medical history data will be summarized descriptively. For quantitative variables, the summaries will include the number of observations, mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

11.7 Patient Reported Outcomes Analyses

Implant Acceptability Questionnaire results at 12 weeks and 6 months will be summarized using counts and percentages. Summaries will include subject preference for implant over self-administered drop therapy, subject likeliness to have the implant procedure again, and subject likeliness to recommend the implant to someone else.

11.8 Safety Analyses

Incidence of adverse events will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. OTX-TIC implant assessment [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) and changes from baseline in Posterior Segment (PS)-OCT will be summarized descriptively using quantitative and qualitative summary statistics as appropriate.

11.9 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 presented for automated and manual methods at all repeat dosing sub-study assessment visits by treatment group for the study eye and non-study eye with the observed data only.

The observed and change from baseline in central corneal thickness with Pachymetry will be presented at all repeat dosing sub-study assessment visits by treatment group for the study eye and non-study eye with the observed data only.

The observed and change from baseline in IOP will be presented 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.

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 presented 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 the fewer, 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 presented 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 dosing sub-study population.

[redacted]The details of repeat dosing sub-study analyses will be described in the SAP.

11.10 Reporting Deviations

Should there be changes in any analyses described in the protocol, the statistical analysis plan will document them. Should there be changes in any analyses described in the statistical analysis plan, the final clinical study report will describe them.

12 STUDY MANAGEMENT AND DATA COLLECTION

12.1 Confidentiality

All trial subject data collected and processed for the purposes of this trial should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of CRO, drug safety, the sponsor, the IRB/IEC approving this trial, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the trial subject's original medical and trial records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

12.2 Source Documents

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's trial subject files, as well as the results of diagnostic tests. The investigator's electronic copy of the eCRFs serves as the investigator's record of a subject's trial-related data.

12.3 Case Report Forms

All subject data will be captured in the subject source documents which will be transcribed to the eCRFs. The investigator is responsible for ensuring that trial data is completely and accurately recorded on each subject's eCRF, source documents, and all trial-related materials. All trial data should also be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available. Recorded data should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff that have been trained on the system and have access to the system. Minimal data will be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the trial and database lock, electronic media containing copies of all applicable subjects' eCRFs will be provided to each investigator site to be maintained on file by the investigator.

12.4 Records Retention

All trial related correspondence, subject records, consent forms, record of the distribution and use of all IP and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator must notify the sponsor prior to destroying trial documentation even after the above-mentioned time has passed.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

13 STUDY MONITORING, AUDITING, AND INSPECTING

13.1 Study Monitoring Plan

Each investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by Ocular Therapeutix, Inc., prior to seeking approval from the IRB/Ethics Committee. Investigators' proficiency in observing and scoring ophthalmic observations will be established and documented via review of academic training and experience, prior to examining subjects. Each investigator will be responsible for enrolling only those subjects who have met protocol

eligibility criteria. During study conduct, Ocular Therapeutix, Inc and/or its representative will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will review source documents to confirm that the data recorded on the electronic case report forms (eCRFs) are accurate. Further details of the trial monitoring will be outlined in a monitoring plan.

The investigator and institution will allow Ocular Therapeutix, Inc., monitors or its representatives and appropriate regulatory authorities direct access to source documents to perform this verification. Data Managers will also review data and may interact with site personnel for clarifications.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits, or inspections and that sufficient time is devoted to the process.

14 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of International Council on Harmonization, Good Clinical Practice Guideline, IRB regulations, any applicable government regulations.

This protocol, the ICF, relevant supporting information, and all types of subject recruitment or advertisement information must be submitted to the IRB for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB prior to implementing changes in the study. The investigator is responsible for keeping the IRB apprised of the progress of the study, any SAEs, and any changes made to the protocol according to the requirements of the site's IRB.

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Appendix 1 Time and Events Schedules

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 2 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 (as defined in Section 8.6.10) 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 Durysta™ 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 (as defined in Section 8.7.9) 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

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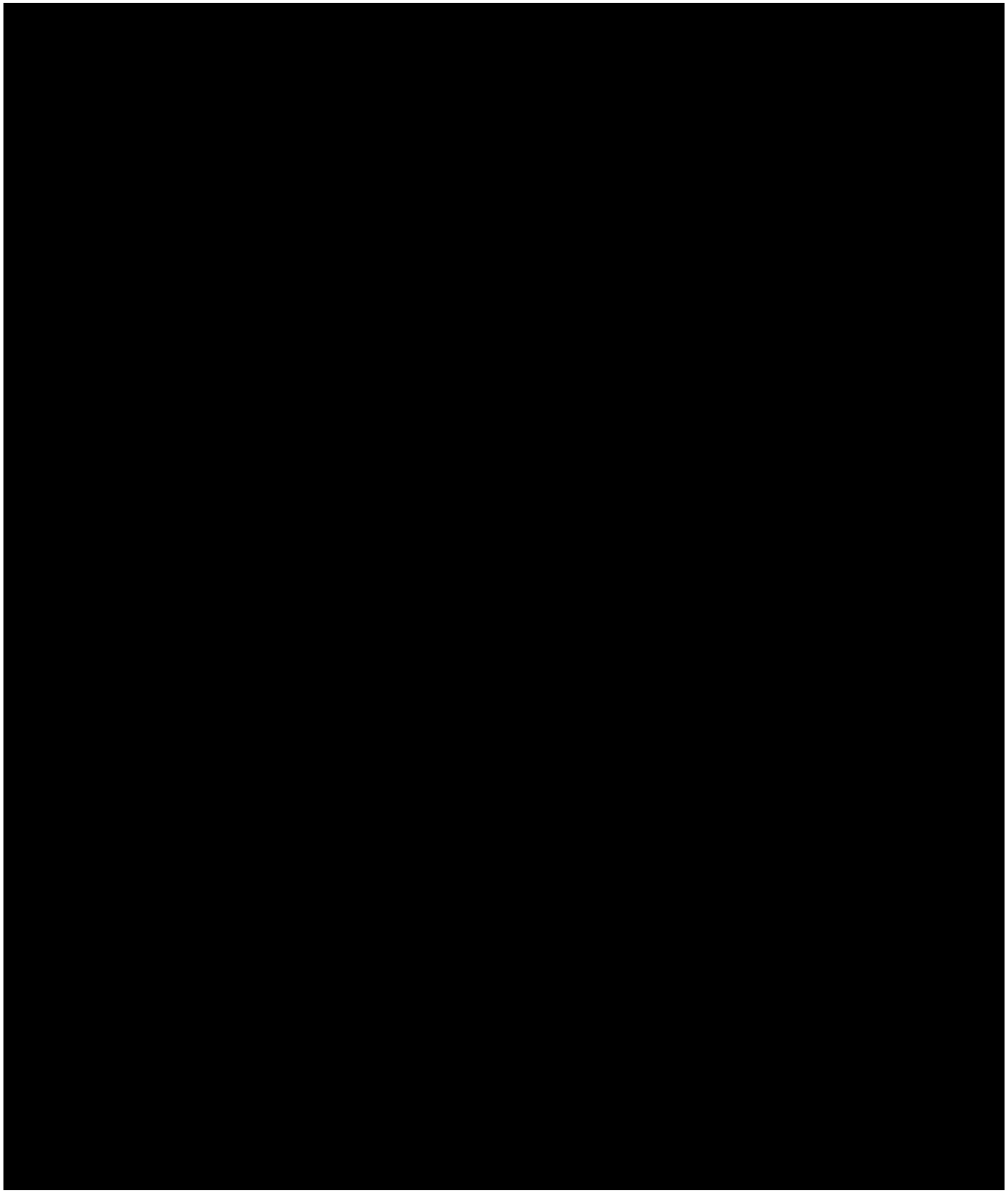

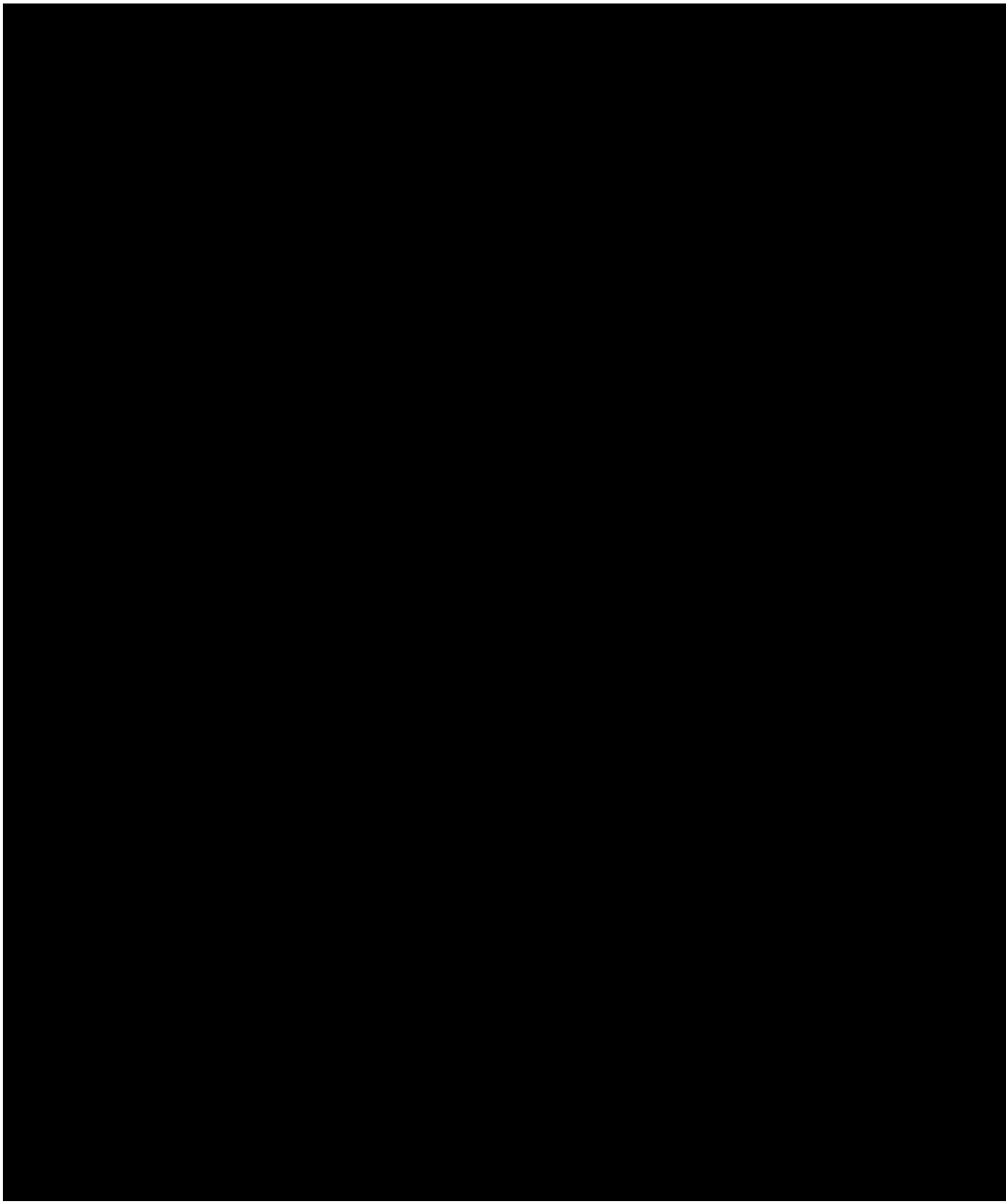

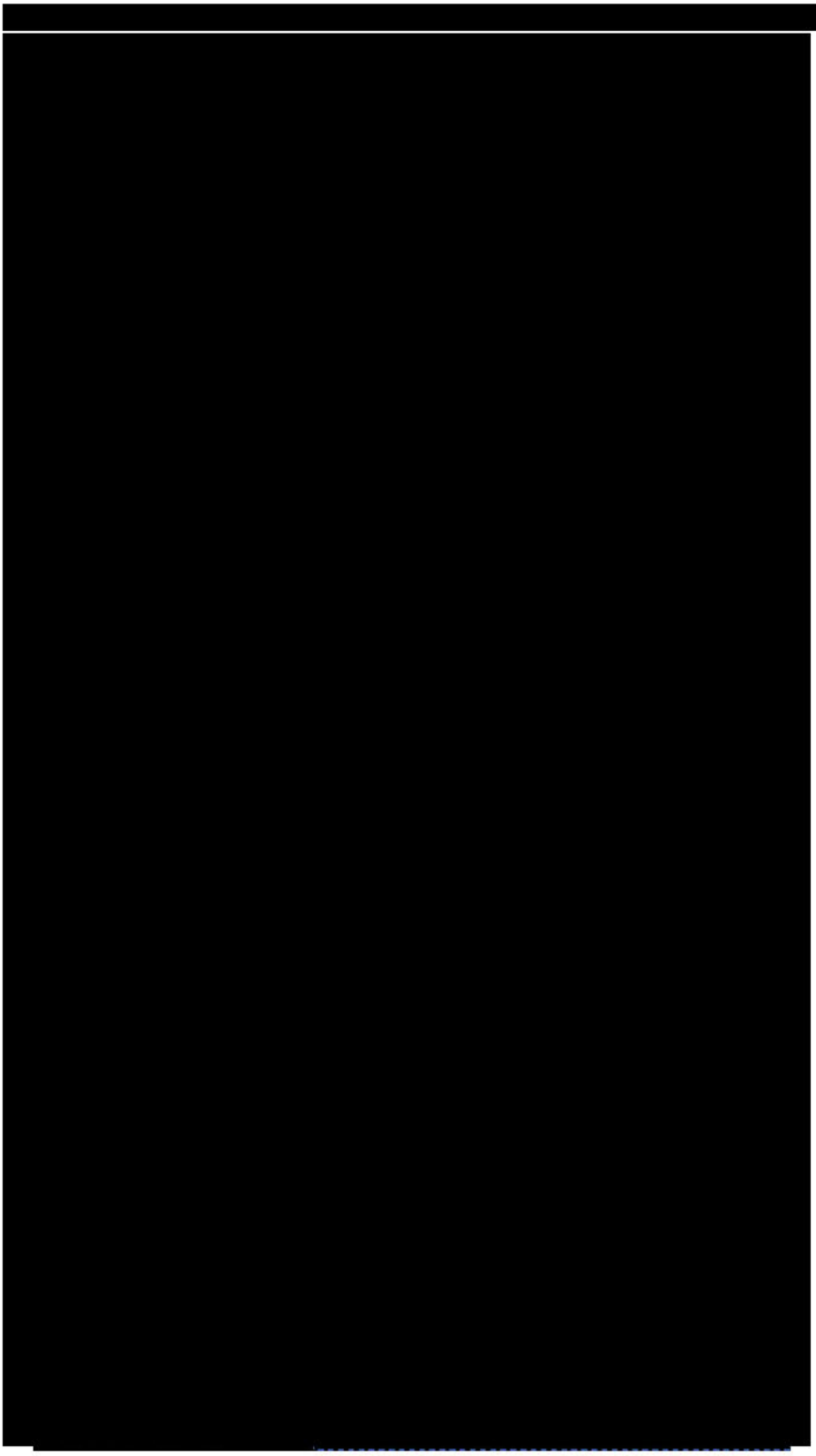

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