

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

**Investigational Protocol
OTX-16-002**

Revision E: May 2, 2017

**Sponsor:
Ocular Therapeutix, Inc.
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Bedford, MA 01730 USA**

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

I hereby agree to participate in the clinical investigation of **OTX-TP** sponsored by Ocular Therapeutix, Inc. (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 guidelines 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 intracanalicular depot 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 employed by 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 Clinical Affairs at Ocular Therapeutix (781) 357-4000.

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 Study Sponsor encourages me to pursue independent publications related to my experience with this intracanalicular depot 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 intracanalicular depot 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 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 Study Sponsor or FDA without the prior written consent of the Study Sponsor.

Accepted by:

Principal Investigator Signature	Date	Printed Name
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Sub-Investigator Signature	Date	Printed Name
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Sub-Investigator Signature	Date	Printed Name
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**Note: Please add sub-Investigator signatures on an additional page, if needed.*

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PROTOCOL REVISION HISTORY

Date	Revision	Description of Modifications	Rationale for Modification
	A	Initial Release	N/A
Sep. 30, 2016	B	Slit Lamp exam requirement changed to 8:00 am only for diurnal visits	PM slit lamp not medically necessary
		BCVA at Baseline Visit 2	Omitted mistakenly in prior version
		Clarified Visit Names (15 Day visit to 2 week visit, etc.)	To match industry standard, and to provide greater clarity for Investigational Sites
		Clarified exclusion of systemic beta blockers	To allow for inclusion of subjects on stable dose beta blockers
		Clarified Inclusion Criterion #5, Exclusion Criterion #2, and Exclusion Criterion #31	Clarified language
		Fixed minor typos and protocol inconsistencies (e.g., added Iris color to Screening Visit on page 35)	Correction of minor clerical errors
		Clarified washout window for patients taking prostaglandins, and widened the window between Baseline Visit 1 and Baseline Visit 2.	To provide greater flexibility in visit scheduling for Investigational Sites
		Changed length of time IOP must be controlled from 3 months to 2 months	Based on Investigator and medical advisor feedback, restriction was tighter than medically necessary
		Made mandatory the visual field assessment at Baseline	Aid Investigator decision regarding selection of appropriate subjects
		Removed ability to enroll patients currently being treated with Beta Blockers, clarified Inclusion Criterion #3, and clarified Exclusion Criterion #1.	To ensure enrollment of only subjects who are known to respond to topical prostaglandins
		Clarified Inclusion Criterion #4	To further ensure IOP at enrollment is stable
		Moved Exclusion Criterion #28 up to #3 (which, therefore, effected the numbering of the other criteria)	To emphasize the importance of the criterion
		Clarified/Updated description of naïve subjects: Meaning, requirements, timeline, etc.	To ensure enrollment of only subjects who are known to respond to topical prostaglandin
		Clarified instructions for IOP measurement technique and number of readings required.	To ensure clarity of instructions provided to Investigational Sites
		Updated Baseline Visit 1 to remove diurnal IOP measurement requirement.	Not medically necessary, wash out will be confirmed with diurnal BL2 values.
		Moved Hyperemia Assessment, and Subject Comfort Assessment to Baseline Visit 2, from Baseline Visit 1	To move the majority of exams to Baseline Visit 2, and ease subject burden.
		Added Slit Lamp Exam to Baseline Visit 2	To ensure most current Slit Lamp information available for eligibility verification
		Added AE Assessment text to Screening, Run-in Visits, and Baseline Visit 1 and 2.	Inadvertently omitted in prior revision.
		Added ability to perform IOP on a different screening day.	To allow flexibility in visit scheduling.
		Added Interim Analysis.	To allow for getting efficacy results sooner once all subjects complete efficacy visits without having to wait for the completion of safety follow-ups.

Date	Revision	Description of Modifications	Rationale for Modification
Oct., 28 2016	C	Added sub-strata to randomize subjects within sites based on previous medication regimen at the time of Screening.	To further ensure balanced randomization based upon recent IOP reduction therapy
		Added Instructions for determining eligibility and randomization of subjects exiting from prior ophthalmic investigational research studies (Appendix A)	To provide more guidance for enrolling subjects exiting from prior ophthalmic investigational research studies as additional randomization schema are more detailed
		Added description of PEG tip	Inadvertent exclusion from previous revisions
		Fixed minor typos and protocol inconsistencies	Correction of minor clerical errors
Nov., 18 2016	D	Removed “Baseline Visit 1” from Inclusion Criterion 4 in both the protocol synopsis and in Section 4.4.1	Inadvertently remained after previous revision.
		Fixed minor typos and protocol inconsistencies	Correction of minor clerical errors
		Added additional clarity to Pachymetry performed at Screening in the protocol synopsis.	To ensure the same clear guidance is provided both times Screening Pachymetry is discussed.
		Clarified time requirement for reporting of serious events.	To ensure clarity for Investigational Sites.
May 2, 2017	E	Clarified safety exam performance requirements	To ensure clarity for schedule of exams that must be performed by Investigational Sites.
		Clarify when infections should be cultured	To ensure clarity for Investigational Sites.
		Define “history” in Exclusion Criteria 1	To ensure clarity for Investigational Sites.
		Made consistent which assessments must be performed at each visit	Correction of minor clerical errors
		Update required timing for automated perimetry	To allow sites a larger window for performance of automated perimetry.
		Clarified Inclusion 3, Exclusion 3, and Exclusion 31 in regards to Stratum C subjects	To provide clarity on Inclusion/Exclusion Criteria for Stratum C Subjects.
		Updated Sponsor contact information	Based on staffing changes.
		Updated prohibited medication section.	To remove inconsistent language around medication usage.

1. SYNOPSIS

Study Title:	A Prospective, Multicenter, Randomized, Parallel-Arm, Double Masked, Vehicle Controlled Phase 3a Study Evaluating the Safety and Efficacy of OTX-TP in the Treatment of Subjects with Open-Angle Glaucoma or Ocular Hypertension
Test Article:	<p>Test Article: OTX-TP (sustained release travoprost) Intracanalicular Depot</p> <p>Control: PV (Placebo Vehicle) Intracanalicular Depot</p>
Phase of Clinical Study:	3a
Study Objective:	To evaluate the safety and IOP lowering efficacy of OTX-TP, a sustained release travoprost drug product, placed in the canaliculus of the eyelid in the treatment of subjects with open-angle glaucoma or ocular hypertension.
Product Description:	<p>The OTX-TP drug product is a dried polyethylene glycol (PEG) based, rod-shaped hydrogel intracanalicular depot designed to be placed in the superior or inferior canaliculus. The hydrogel swells on contact with moisture to occlude the lumen, thus holding the intracanalicular depot in place. Once OTX-TP swells to fill the canaliculus, it is contained in the canaliculus until the hydrogel is resorbed. Embedded in the hydrogel intracanalicular depot are bioabsorbable poly (lactic acid) (PLA) microparticles containing encapsulated travoprost. OTX-TP contains conjugated fluorescein to serve as a visualization aid for the Investigator through the use of a blue light source and yellow filter to confirm product presence. The intracanalicular depot also has an inert PEG tip to aid in insertion.</p> <p>The PV used as the study control is the same fluorescein-conjugated PEG hydrogel intracanalicular depot with inert PEG tip as OTX-TP, except that it does not contain travoprost.</p> <p>Travoprost is a synthetic prostaglandin F_{2α} analogue used for reducing elevated intraocular pressure in subjects with open-angle glaucoma or ocular hypertension. Travoprost is the active pharmaceutical ingredient in Travatan[®], Travatan Z[®] and Izba[™] (Alcon Laboratories Inc., Fort Worth, TX) which have been approved by the US FDA under application numbers 021257, 021994, and 204822, respectively.</p> <p>OTX-TP is an extended release drug delivery depot designed to release travoprost over a period of up to 12 weeks.</p>

	<p>As both the hydrogel and PLA microparticles degrade by hydrolysis, both OTX-TP and PV soften, liquefy and are cleared through the nasolacrimal duct.</p>
<p>Intended Use:</p>	<p>OTX-TP (sustained release travoprost) Intracanalicular Depot is intended for the reduction of elevated intraocular pressure in subjects with open-angle glaucoma (OAG) or ocular hypertension (OH).</p>
<p>Study Design:</p>	<p>This is a prospective, multicenter, randomized, parallel-arm, double masked, placebo vehicle controlled trial to evaluate the safety and IOP-lowering efficacy of OTX-TP, a sustained release drug product placed in the canaliculus of the eye in subjects with open-angle glaucoma or ocular hypertension. A total of up to 550 subjects (1100 eyes) with a clinical diagnosis of open-angle glaucoma or ocular hypertension in both eyes will be receive either OTX-TP or PV in this trial to evaluate the safety and efficacy of the OTX-TP drug product.</p> <p>The subjects enrolled in this parallel arm study will be randomized to receive either OTX-TP (sustained release travoprost) Intracanalicular Depot or PV (placebo vehicle) intracanalicular depot, respectively. Subjects randomized to the treatment group will receive OTX-TP in either the superior or inferior canaliculus of each affected eye on Day 1. Subjects randomized to the control group will receive PV in either the superior or inferior canaliculus of each affected eye on Day 1.</p> <p>Subject randomization is 3:2 with a total of approximately 330 subjects in the OTX-TP arm and 220 in the PV arm.</p>

	<p>Randomization will be stratified by investigational site and previous ocular anti-hypertensive therapy with 3 levels:</p> <p>Stratum A: Subjects who were on prostaglandin treatment at the time of the Screening Visit and have shown an adequate IOP rise after a 6-week washout (interval from Screening to Baseline Visit 1 is 6 weeks). This may include subjects exiting from a prior ophthalmic investigational research study based on criteria specified in Appendix A.</p> <p>Stratum B: Subjects who were treatment-naïve at Screening and have shown an adequate prostaglandin response after a 2-week run-in period on prostaglandin treatment followed by a 6-week washout (interval from Screening to Baseline Visit 1 is 8 weeks). This may include subjects exiting from a prior ophthalmic investigational research study based on criteria specified in Appendix A.</p> <p>Stratum C: Subjects who have recently exited from a prior ophthalmic investigational research study and have written approval from the Medical Monitor to be allowed to participate in the current study without additional exposure to prostaglandin (Refer to Appendix A).</p> <p>Once it is determined that the subject continues to meet eligibility for the study at Baseline Visit 2, the subject will be randomized into the study corresponding to the subject's previous ocular anti-hypertensive therapy category and both eyes will be provided with the same assigned treatment, OTX-TP or PV.</p> <p>Both eyes will receive either OTX-TP or PV, but only the eye with the higher IOP at 8:00AM at Baseline Visit 2 that meets all enrollment criteria will be considered as the study eye and included in the primary efficacy analysis. If both eyes are eligible and have the same IOP at 8AM on Baseline Visit 2 (Day 1), the right eye will be the study eye and the left eye will be considered the secondary study eye. All eyes will be included in the safety analysis.</p> <p>Subjects currently being treated with a prostaglandin analogue at the time of the Screening Visit will undergo a 6 week (- 2 days/+ 3 days) washout period starting at the Screening Visit and prior to Baseline Visit 1. The Baseline Visit 2/Insertion Visit, Day 1 will be conducted two to four days after the Baseline Visit 1. IOP measurements at the baseline visits will confirm that the washout period was sufficient.</p>
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	<p>Subjects not currently treated with a prostaglandin analogue will undergo a 2 week run-in starting at the Screening Visit, to confirm they are a prostaglandin responder. At least two IOP measurements will be taken over a two week period (Run-in Visit 1 at 2 days [+ 3 days] post-initiation of prostaglandin therapy; and Run-in Visit 2 at 11 days [+ 3 days] post-initiation of prostaglandin therapy). The Run-in IOP measurements will be conducted at 8 AM +/- 1 hour, to confirm the response to prostaglandin therapy. Once the response is confirmed, the subjects will undergo a 6 week (- 2 days/+ 3 days) washout period prior to Baseline Visit 1. The Baseline Visit 2/Insertion Visit, Day 1, will be conducted two to four days after the Baseline Visit 1. The IOP measurement at Baseline Visit 2 must demonstrate a ≥ 5 mmHg increase from Run-in Visit 2. IOP measurements at the baseline visits will confirm that the washout period was sufficient.</p> <p>Subjects who have exited from another ophthalmic investigational research study within the last 8 weeks will be started on a 6 week prior trial recovery period <i>and</i> stop all glaucoma/OHT meds, after completing Informed Consent and the Screening Visit. They will then be discussed with the Medical Monitor, in order to obtain written approval to be allowed to participate in the current study. The approval will be captured on the appropriate eCRF. Timing and requirements for the period between Screening and Baseline Visit 1 will vary, please refer to Appendix A for additional specifications.</p> <p>At Baseline Visit 2/Insertion Visit (Day 1), if insertion is unsuccessful in one eye, the intracanalicular depot from the contralateral eye (if already inserted) will not be removed. The subject will be prescribed IOP-lowering drops at the Investigator's discretion for the eye that did not receive a depot. These subjects will be followed for safety only, and the eye that received a depot will be included in the safety analysis. The study will be supplemented with additional subjects to account for these subjects in order to ensure that the necessary number of subjects who receive a depot bilaterally are followed through the 12 Week Visit for efficacy and safety.</p> <p>All subjects will undergo follow-up visits at 2, 4, 6, 8, 10, and 12 Weeks. If at any visit, the investigator deems it necessary to initiate IOP-lowering drops as rescue therapy due to an increase in IOP, the subject will begin the IOP-lowering drops at the Investigator's discretion and followed through the remainder of the study for safety. Sensitivity analyses, to determine robustness of results, will be performed using Monte Carlo Markov Chain approach to impute non-monotone missing</p>
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information and pattern mixture models control-based pattern imputation for monotone missing information (including subjects who drop out and data for time points after a subject's primary study eye is prescribed IOP-lowering drops), LOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops, and baseline time-consistent observation carried forward to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops and observed data only.

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

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

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

If removal is unsuccessful in one or both eyes at the 12 Week Visit, the subject will return at the 20 Week Visit. The Investigator will attempt removal of the intracanalicular depot(s) from the respective eye(s) at this visit. The subject may be prescribed IOP-lowering drops if necessary at the 12 Week Visit at the Investigator's discretion.

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

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

	<p>Week Visit. The number of replacements will be tracked and documented on the appropriate CRF.</p> <p>At the 20 Week Visit, the Investigator will attempt removal of the intracanalicular depot, if still present. If removal at the 20 Week Visit is successful bilaterally, the subject will be exited from the study upon confirmation of the bilateral absence of the intracanalicular depot.</p> <p>If removal at the 20 Week Visit is not successful in one or both eyes, the subject will be required to return to the clinic every 30 (\pm 10) days until the intracanalicular depot is confirmed to be no longer present or removal of the intracanalicular depot is successful for the respective eye(s). Removal will be attempted at every visit until the intracanalicular depot is no longer present.</p> <p>If the intracanalicular depot is not present bilaterally at the 20 Week Visit, the subject will be exited from the study at the end of that visit. The subject may be prescribed IOP-lowering drops if necessary at the 20 Week Visit at the Investigator's discretion. The study will be conducted at approximately 50 qualified investigative sites in the United States following Institutional Review Board (IRB) approval. A site may randomize up to a maximum of 55 subjects. All subjects will be required to provide informed consent prior to study participation.</p>
Primary Endpoint:	<ul style="list-style-type: none"> • Mean IOP at the following time points 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.
Secondary Endpoints:	<ul style="list-style-type: none"> • Mean change from baseline IOP at the following time points 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits. • Mean percent change from baseline IOP at the following time points 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits.
Other Data to be Collected	<ul style="list-style-type: none"> • Ocular complaints • Visualization of intracanalicular depot by the Investigator at each time point • Ease of insertion of intracanalicular depot • Number of intracanalicular depots required in each eye for the 12 week period per subject
Safety Evaluations	<ul style="list-style-type: none"> • Best corrected visual acuity (BCVA) • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) • Subject ocular comfort assessment • Dilated fundus exam • Adverse events

<p>Inclusion Criteria:</p>	<p>Subjects must meet all of the following criteria to be eligible:</p> <ol style="list-style-type: none"> 1. Greater than or equal to 18 years of age at Screening. 2. Documented diagnosis of ocular hypertension with an open angle of Schaffer Grade 3 or greater or open-angle glaucoma without pseudoexfoliation or pigment dispersion or evidence of traumatic angle recession. 3. IOP is currently controlled as assessed by the Investigator: <ul style="list-style-type: none"> • With a topical prostaglandin, and there has been no change in IOP lowering therapy over 8 weeks prior to Screening, or, • without IOP-lowering medication over 8 weeks prior to Screening and after a 2-week run-in period on prostaglandin therapy demonstrates an adequate response. <p>Note: For Subjects entering through Stratum C, a required Medical Monitor review will ensure subjects have:</p> <ul style="list-style-type: none"> • demonstrated 8 weeks of stable treatment (or no treatment) for glaucoma and/or ocular hypertension prior to enrollment in the previous recent ophthalmic clinical trial(s). • documented history of an adequate prostaglandin response as described in the protocol, or will undergo a prostaglandin run-in trial as described in the protocol for patients who do not have such a history. 4. Baseline IOP (following washout or run-in) in at least 1 eye (the same eye) of: <ul style="list-style-type: none"> • ≥ 24mmHg at Hour 0 (T₀) at Baseline Visit 2 (Day 1) • ≥ 22mmHg at (T₀+ 2h) and (T₀ + 8h) at Baseline Visit 2 (Day 1) • At 8AM Baseline Visit 2 (Day 1), ≥ 5 mmHg increase from Screening for subjects previously on prostaglandins • At 8AM Baseline Visit 2 (Day 1), ≥ 5 mmHg increase from Run-in Visit 2 for subjects not previously on prostaglandins prior to the Screening Visit <p>Note: the same eye must meet all of the above listed IOP eligibility criteria</p> 5. IOP must be ≤ 34mmHg in each eye at all time points at the Baseline Visit 1 (Day -2 to -4) and Baseline Visit 2 (Day 1).
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	<ol style="list-style-type: none"> 6. Informed of the nature of the study and subject is able to comply with study requirements and visit schedule. 7. Provided written informed consent, approved by the appropriate Institutional Review Board.
<p>Pre-Procedure Exclusion Criteria:</p>	<p>Subjects who meet any of the following criteria are not eligible:</p> <ol style="list-style-type: none"> 1. A history, prior to Screening, of an inadequate response (< 5mmHg decrease from prior to any treatment) or no response to topical prostaglandin for OAG/OH. 2. For subjects on IOP-lowering medication(s): History of concurrent treatment with 3 or more IOP-lowering medications for longer than 2 weeks. Any combination medication will be considered as 2 medications. 3. Currently (or within 8 weeks prior to Screening) on any ocular or systemic medication [i.e., carbonic anhydrase inhibitors, corticosteroids (including topical dermal steroids for the face), etc.] that may: <ul style="list-style-type: none"> • Have an effect on the subject's IOP or will require use of such ocular or systemic medications during the study period. • No topical ophthalmic medications other than prostaglandins allowed at the time of the screening visit. Systemic beta blockers will be allowed, but any initiation of or alterations in systemic regimen of beta-blocker containing medications from 8 weeks prior to screening through the final study visit is excluded. <p>Subjects currently treated with topical prostaglandin analogues are required to undergo a washout period of 6 weeks (- 2 days/+ 3 days).</p> <p>Note: For Subjects entering through Stratum C, changes in ocular or systemic prior ophthalmic study medications, that may have an effect on the Subject's IOP, will be allowed, but inclusion in the study will be based on a required Medical Monitor review. Stratum C subjects will also be allowed to screen for the study while on ophthalmic medications other than prostaglandins, however, these medications should be stopped at Screening, and a Prior Trial Recovery Period shall be started.</p> 4. A BCVA worse than 0.6 LogMAR (20/80 Snellen) in either eye as measured using an ETDRS chart. 5. Punctum size smaller than 0.4 mm or greater than 0.9 mm in either eye as measured using a standard punctum gauge.

	<ol style="list-style-type: none"> 6. Known or suspected allergy and/or hypersensitivity to Travoprost or any prostaglandin, fluorescein, or to any component of the study products. 7. History of ocular trauma within the past 6 months in either eye. 8. Evidence of angle recession by gonioscopy. 9. Presence of any abnormality based upon the assessment by the Investigator preventing reliable applanation tonometry of either eye. 10. Narrow or potentially occludable anterior chamber angle defined as an anterior chamber angle of less than or equal to Grade 2 (Schaffer classification) as measured by gonioscopy. 11. Central corneal thickness < 480 μm or > 620 μm in either eye. 12. Cup to disc ratio > 0.80 (horizontal or vertical measurement) in either eye. 13. Functionally significant central visual field loss or documented significant progressive field loss within the last year in either eye based upon the assessment by the Investigator. 14. History of complications, AEs, trauma or disease in the nasolacrimal area, whether or not it was due to punctal plug use, including but not limited to dacryocystitis, inflammation or canaliculitis in either eye. 15. Structural lid abnormalities (i.e., ectropion, entropion) in either eye based upon the assessment by the Investigator. 16. Active epiphora in either eye based upon the assessment by the Investigator. 17. Presence of nasolacrimal duct obstruction in either eye based upon an assessment by the Investigator. 18. Active lid disease in either eye (i.e., moderate or severe blepharitis, meibomitis) that requires medical treatment. 19. History of ocular infection (bacterial, viral, or fungal) in either eye within the previous 3 months. 20. History of any severe ocular pathology (including severe dry eye) in either eye. 21. History of chronic/recurrent inflammatory eye disease (i.e., scleritis, uveitis, herpes keratitis) in either eye. 22. Required use of any ocular topical medication(s), any over-the-counter drop(s), ointment(s), gel(s) or lid scrubs, other than the study ocular hypotensive medication(s) in either eye during the study period. <p style="margin-left: 40px;">Note: Use of artificial tears or ocular lubricants should be avoided but if necessary, intermittent use may be allowed up to twice a day.</p> 23. Any ophthalmic surgical procedures (e.g. glaucoma laser, minimally invasive glaucoma surgery, cataract, refractive) in
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	<p>either eye within the last six months or will likely require ophthalmic surgery before completing the study.</p> <p>24. History of penetrating or lamellar keratoplasty in either eye (including endothelial keratoplasty).</p> <p>25. History of keratorefractive surgery in either eye (i.e., LASIK, PRK, RK, AK, LRI, Corneal inlay, intracorneal ring segment).</p> <p>26. Advanced diabetic retinopathy, branch retinal vein occlusion, or central retinal vein occlusion in either eye.</p> <p>27. History of macular edema in either eye.</p> <p>28. Any uncontrolled systemic or debilitating disease (e.g. cardiovascular disease, hypertension, diabetes, or cystic fibrosis) or a medical condition that may increase the risk associated with study participation or administration of study treatment or that may interfere with the interpretation of study results based upon the assessment of the Investigator (e.g., autoimmune disease if the subject is on chronic medications and has ocular involvement; host-versus-graft disease).</p> <p>29. Requiring contact lens use at any point during the study after the Screening Visit including on the day of the Baseline Visits. In addition, contact lens wear must be discontinued a minimum of 3 days prior to pachymetry for soft contact lenses and a minimum of 14 days prior to pachymetry for rigid gas permeable contact lenses.</p> <p>30. Currently pregnant or breast-feeding or who wishes to become pregnant during the length of study participation.</p> <p>31. Currently participating or has participated within the last 30 days in any non-ophthalmic drug, device or other investigational research study prior to the start of this study.</p> <p style="text-align: center;">Note: Previous participation in any ophthalmic investigational research study within 8 weeks will require written approval for enrollment from the Medical Monitor based on instructions provided in Appendix A.</p> <p>32. Investigator determines subject should not be included for reasons not already specified (e.g., systemic or other ocular disease/abnormality, not a candidate for topical prostaglandin, therapy, specifically travoprost) if the health of the subject or the validity of the study outcomes may be compromised by the subject's enrollment.</p>
<p>Procedural Exclusion Criterion</p>	<p>1. Unsuccessful punctal dilation of either eye (if needed) or punctum of either eye is too small to allow transient dilation to 0.7 mm prior for insertion of OTX-TP or PV.</p>

<p>Screening Assessment</p> <p>(Visit timing will vary based on randomization stratum: A, B, or C)</p> <p>This visit may be conducted over two days, separating the IOP Measurement, Automated perimetry, and/or pachymetry only.</p> <p>All IOP Measurements must be conducted within ± 60 minutes of the required time, and must be conducted at approximately the same time at each of the follow-up visits.</p>	<ul style="list-style-type: none"> • Informed consent • Demographic data • Iris color • Medical and ophthalmic history • Medication history • Urine pregnancy test (if applicable): if female of childbearing potential, subject must utilize reliable contraceptive methods for the duration of the study as judged by the Investigator, and have a negative urine pregnancy test <p>The following will be performed on both eyes:</p> <ul style="list-style-type: none"> • Assessment of Best Corrected Visual Acuity (BCVA) • Automated perimetry • Pachymetry <p>The average of the 3 measurements will be calculated to determine subject eligibility. Contact lens wear must be discontinued 3 days prior to pachymetry for soft contact lenses and 14 days prior to pachymetry for rigid gas permeable contact lenses. For contact lens wearers, the pachymetry assessment may be scheduled for a separate day from the Screening Visit based on the type of contact lens (i.e., 3 days after the Screening Visit for soft contact lenses and 14 days after the Screening Visit for rigid gas permeable contact lenses)</p> <ul style="list-style-type: none"> • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) • Punctum exam (for normality of punctal appearance, lid apposition, and tear meniscus) • Punctum size assessment using a punctum gauging system provided by the Sponsor • IOP measurement (Goldmann applanation tonometry) at 8AM ± 60 minutes • Gonioscopy • Dilated fundus exam • Adverse event assessment <p>At the end of the Screening Visit:</p> <ul style="list-style-type: none"> • Subjects will be instructed to start washout, run-in, or prior trial recovery period based on prior prostaglandin therapy and/or prior participation in an ophthalmic investigational research study. Please refer to Appendix A for subjects who need to start the prior trial recovery period.
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<p>Run-in Visit 1 and Run-in Visit 2</p> <p>(Run-in Visit 1 at 2 days [+ 3 days] post-initiation of prostaglandin therapy; and Run-in Visit 2 at 11 days [+ 3 days] post-initiation of prostaglandin therapy)</p>	<p><i>At 8AM (T₀)</i></p> <ul style="list-style-type: none"> • IOP measurement (Goldmann applanation tonometry) • Adverse event assessment <p>Visits only applicable to Stratum B subjects. After prostaglandin response is confirmed, subjects will washout for 6 Weeks (-2/+3 days).</p>
<p>IOP Confirmation Visit</p> <p>(End of the 6 week prior trial recovery period [-2 days/+ 5 days])</p>	<p><i>At 8AM (T₀)</i></p> <ul style="list-style-type: none"> • IOP measurement (Goldmann applanation tonometry) • Adverse event assessment <p>Visit only applicable to subjects exiting from a prior ophthalmic investigational research study.</p>
<p>Baseline Visit 1</p> <p>(Visit timing will vary based on randomization stratum: A, B, or C)</p> <p>All IOP Measurements must be conducted within ± 60 minutes of the required time, and must be conducted at approximately the same time at each of the follow-up visits.</p>	<p>The following will be performed for both eyes on the day of the baseline visit:</p> <p><i>At 8AM (T₀)</i></p> <ul style="list-style-type: none"> • Medication and medical history update • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) • IOP measurement • Adverse event assessment
<p>Baseline Visit 2/ Insertion Visit</p> <p>(Day 1)</p> <p>All IOP Measurements must be conducted within ± 60 minutes of the required time, and must be conducted at approximately the same time at each of the follow-up visits.</p>	<p>The following will be performed for both eyes on the day of the baseline visit:</p> <p><i>At 8AM (T₀)</i></p> <ul style="list-style-type: none"> • IOP measurement • Assessment of BCVA • Subject ocular comfort assessment • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) <p><i>10AM (T₀+2h)</i></p> <ul style="list-style-type: none"> • IOP measurement <p><i>4PM (T₀+8h)</i></p> <ul style="list-style-type: none"> • IOP measurement • Randomization • Punctum exam prior to insertion of OTX-TP or PV • Punctum size pre/post dilation • Insertion of intracanalicular depot into superior or inferior canaliculus of each eye for each subject <p><i>At 8AM (T₀), 10AM (T₀+2h) and 4PM (T₀+8h)</i></p> <ul style="list-style-type: none"> • Adverse event assessment

<p>4 Week (Day 29 ±3 days), 8 Week (Day 57 ±3 days), and 10 Week (Day 71 ±3 days) Visit</p> <p>All IOP Measurements must be conducted within ± 60 minutes of the required time, and must be conducted at approximately the same time at each of the follow-up visits.</p>	<p>The following will be performed on both eyes: <i>At 8AM only</i></p> <ul style="list-style-type: none"> • Medication and medical history update • Subject ocular comfort assessment • Assessment of Ocular complaints • Assessment of BCVA • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) • Confirmation of intracanalicular depot presence by the Investigator • Punctum exam • IOP measurement • Adverse event assessment
<p>2 Week (Day 15 ±3 days), and 6 Week (Day 43 ±3 days) Visit</p> <p>All IOP Measurements must be conducted within ± 60 minutes of the required time, and must be conducted at approximately the same time at each of the follow-up visits.</p>	<p>The following will be performed for both eyes: <i>At 8AM (T₀)</i></p> <ul style="list-style-type: none"> • Medication and medical history update • Subject ocular comfort assessment • Assessment of Ocular complaints • Assessment of BCVA • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) • Confirmation of intracanalicular depot presence by visual assessment • Punctum exam <p><i>At 8AM (T₀), 10AM (T₀+2h) and 4PM (T₀+8h)</i></p> <ul style="list-style-type: none"> • IOP measurement • Adverse event assessment <p>At any visit prior to the 6 Week Visit, if the intracanalicular depot is not visualized in one or both eyes by the Investigator, the Investigator will insert a new intracanalicular depot in the respective eye(s) after confirming patency. For any depot replacements, IOP assessments should be completed prior to replacement. The subject will continue to return for follow-up visits per the study schedule through the 12 Week Visit. The number of replacements will be tracked and documented on the appropriate Case Report Form (CRF).</p> <p>If the intracanalicular depot is still present in one or both eyes at the 12 Week Visit, the Investigator will attempt to remove the intracanalicular depot from the respective eye(s). If removal is successful bilaterally, the subject will be exited from the study. The subject may be prescribed IOP-lowering drops at the Investigator's discretion.</p>

	<p>If removal is unsuccessful in one or both eyes, the subject will return at the 20 Week Visit. The subject may be prescribed IOP-lowering drops at the Investigator's discretion.</p> <p>If the intracanalicular depot is not present bilaterally at the 12 Week Visit, the subject will be exited at the end of that visit. The subject may be prescribed IOP-lowering drops at the Investigator's discretion.</p> <p>At any visit from the 6 Week Visit prior to the 12 Week Visit, if the intracanalicular depot is not visualized in one or both eyes by the Investigator, the Investigator will insert a new intracanalicular depot in the respective eye (s) after confirming patency. For any depot replacements, IOP assessments should be completed prior to replacement. The subject will return for follow-up visits through the 12 Week Visit and then at the 20 Week Visit. The number of replacements will be tracked and documented on the appropriate CRF. The removal of the replaced intracanalicular depot(s) will be conducted at the 20 Week Visit.</p>
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<p>12 Week (Day 85 ±3 days) Visit</p> <p>All IOP Measurements must be conducted within ± 60 minutes of the required time, and must be conducted at approximately the same time at each of the follow-up visits.</p>	<p>The following will be performed for both eyes:</p> <p><i>At 8AM(T₀)</i></p> <ul style="list-style-type: none"> • Medication and medical history update • Iris color • Subject ocular comfort assessment • Assessment of Ocular complaints • Assessment of BCVA • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) • Confirmation of intracanalicular depot presence by visual assessment • Punctum exam <p><i>At 8AM (T₀), 10AM (T₀+2h) and 4PM (T₀+8h)</i></p> <ul style="list-style-type: none"> • IOP measurement • Adverse event assessment <p><i>At 4PM (T₀+8hr)</i></p> <ul style="list-style-type: none"> • Dilated fundus exam <p>For subjects who received a replacement intracanalicular depot prior to the 6 Week Visit:</p> <p>If the intracanalicular depot is still present in one or both eyes at the 12 Week Visit, the Investigator will attempt to remove the intracanalicular depot from the respective eye(s). If removal is successful bilaterally, the subject will be exited from the study. If removal is unsuccessful in one or both eyes, the subject will return at the 20 Week Visit.</p> <p>If the intracanalicular depot is not present bilaterally at the 12 Week Visit, the subject will be exited at the end of the visit.</p> <p>The subject may be prescribed IOP-lowering drops at the Investigator's discretion.</p>
<p>20 Week (141 ±7 Days)</p> <p>All IOP Measurements must be conducted within ± 60 minutes of the required time, and must be conducted at approximately the same time at each of the follow-up visits.</p>	<p>The following will be performed on both eyes (if necessary):</p> <p><i>At 8AM only</i></p> <ul style="list-style-type: none"> • Medication and medical history update • Subject ocular comfort assessment • Assessment of Ocular complaints • Assessment of BCVA • Slit lamp biomicroscopy • Assessment and grade of ocular hyperemia (at slit lamp) • Confirmation of intracanalicular depot presence by visual assessment • Punctum exam • IOP measurement • Adverse event assessment

	<p>For subjects who received a replacement intracanalicular depot starting at the 6 Week Visit and prior to the 12 Week Visit:</p> <p>If the intracanalicular depot is still present in one or both eyes at the 20 Week Visit, the Investigator will attempt to remove the intracanalicular depot from the respective eye(s). If removal is successful bilaterally, the subject will be exited from the study. If removal at the 20 Week Visit is not successful in one or both eyes, the subject will be required to return to the clinic every 30 (\pm 10) days until the intracanalicular depot is confirmed to be no longer present.</p> <p>If the intracanalicular depot is not present bilaterally at the 20 Week Visit, the subject will be exited at the end of the visit. The subject may be prescribed IOP-lowering drops at the Investigator's discretion.</p>
Statistical Methods	<p>Hypotheses:</p> <p>H₀: The difference between study eyes that received OTX-TP and study eyes that received PV (OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is ≥ 0 mmHg for at least one time point over all visits.</p> <p>H₁: The difference between study eyes that received OTX-TP and study eyes that received PV (OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is < 0 mmHg for all time points over all visits.</p> <p>Sample Size:</p> <p>Assuming a common standard deviation of 3.75 mmHg within a treatment group, a mean difference of 1.5 mmHg or greater between treatment groups at each of the 3 time points of each of the 3 visits, and a 3:2 randomization ratio, 294 subjects in the OTX-TP arm and 196 subjects in the PV arm yield $>90\%$ power to conclude superiority of OTX-TP to PV in mean IOP at all of the 9 time points using a 2-sided alpha = 0.05 and assuming independence among time points. The power increases with increasing positive correlation among time points.</p> <p>To account for 10% of subjects discontinuing before the 12 Week Visit, approximately 330 subjects will be randomized into the OTX-TP arm and 220 subjects will be randomized into the PV arm.</p> <p>Primary Analysis:</p>

	<p>The primary analysis of the primary efficacy outcome will employ a linear model with IOP at the given visit (2 Week, 6 Week, and 12 Week) and time point (8AM, 10AM, and 4PM) as the response, time point specific baseline IOP as a covariate, and treatment as a main effect factor, using the intent to treat population with multiple imputation methods using Monte Carlo Markov Chain approach to impute missing data and using last time-consistent observation carried forward to impute data for time points after a subject’s study eye is prescribed IOP-lowering drops. Each time point within each visit will be modeled separately. The least squares mean differences (test – control) between OTX-TP and PV will be presented along with 2-sided 95% confidence intervals (CIs) around the difference and 2-sided p-values testing the difference equal to 0. Inference will be made on the 2-sided p-value at a 2-sided alpha = 0.05 at each time point and visit.</p> <p>The study will be considered a success if the 2-sided p-value < 0.05 and the point estimate of the difference is < 0 at all time points over the three visits.</p> <p>Sensitivity analyses, to determine robustness of results, will be performed using multiple imputation methods with pattern mixture models, last time-consistent observation carried forward (LOCF), and baseline time-consistent observation carried forward to impute missing values and observed data only. Additionally, sensitivity analyses will be performed on the per protocol population using observed data only.</p>
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2. PRINCIPAL CONTACTS

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3. INTRODUCTION

Ocular Therapeutix, Inc. (OTX) is a biopharmaceutical company focused on developing medical device and drug products to address unmet and underserved medical needs in ophthalmology. OTX was founded to further develop its proprietary polyethylene glycol (PEG) hydrogel technology in various ophthalmic applications. Ocular Therapeutix has designed a bioabsorbable intracanalicular depot as the platform for drug delivery products, which can be used to deliver various active pharmaceutical ingredients that have been included in other FDA-approved drug products. The intracanalicular depot is designed to be inserted into the inferior or superior punctum and then be retained in the canaliculus for the entire duration in which the drug is being delivered. Over this time and through hydrolysis, the intracanalicular depot softens, liquefies and is cleared through the nasolacrimal duct. Another similar hydrogel product, ReSure Sealant, manufactured by Ocular Therapeutix was FDA approved for ophthalmic use (reference PMA P130004) on January 8, 2014.

3.1. Background and Rationale

Glaucoma is a highly frequent chronic disease affecting more than 2 million people over 40 years of age in the United States alone¹. It is defined as optic neuropathy leading to the loss of optic-nerve tissue and progressing into loss of vision. In fact, it has been reported to be one of the leading causes of irreversible blindness. Open-angle glaucoma is the most common form of the disease².

Elevated fluid pressure within the eye (intraocular pressure, IOP), defined as pressures above the normal range of 10 to 21 mmHg⁴ is the main risk factor for glaucoma. People with elevated IOP levels without any optic nerve damage or visual field loss are diagnosed with ocular hypertension, as opposed to glaucoma. However, people with ocular hypertension are still at risk for progressive damage to the optic nerve.

For both glaucoma and ocular hypertension, the critical factor for effective therapy is to lower the IOP. Laser treatments, surgery and various topical drugs have been shown to be effective treatments. Among the topical drugs are different classes such as beta-blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors and prostaglandin analogues⁴.

Travoprost is a synthetic prostaglandin F 2 α analogue. Its chemical name is (Z)-7- [(1 R ,2 R ,3 R ,5 S)-3,5-dihydroxy-2-[(1 E ,3 R)-3-hydroxy-4-[(α,α,α -trifluoro-m-isopropyl-tolyl)oxy]-1-butenyl]-cyclopentyl]-5-heptenoate. It is a prostaglandin analogue that is enzymatically converted to a free acid form in human cornea. Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce IOP by increasing trabecular meshwork and uveoscleral outflow. Travoprost is the active pharmaceutical ingredient in Travatan[®], Travatan Z[®], and Izba[™](Alcon Laboratories, Inc., Ft Worth, TX), which are all topical ophthalmic solutions for use to reduce elevated IOP. Dosage is typically one drop daily of a 0.004% or 0.003% solution.

1 Simmons, S. T, *Glaucoma Today and Where We Are Going*, Advanced Ocular Care, July/August 2010.

2 Scientific Discussion for the approval of Travatan, European Medicines Agency 2004.

There are limitations associated with the application of commercially available topical travoprost drops:

- Poor subject compliance³
- Difficulty in administering drops
- Limited accuracy of drops getting into the eye
- Potential washout of drops
- Conjunctival hyperemia
- Prostaglandin associated periorbitopathy⁴

With potential blindness being the long term effect of poorly managed glaucoma, subject compliance and proper instillation of eye drop medications become highly critical issues. Studies have shown less than 50% of glaucoma subjects continue therapy and refill prescriptions as required^{5 6}. Furthermore, a recent study of an elderly cataract population (similar in demographics to the glaucoma population) disclosed that over 90% of patients administered eye drops incorrectly.⁷

To meet the clinical need for a safe and effective intracanalicular depot, the product should meet the following requirements:

Easy to Insert	Insertion times no longer than currently available commercial punctal plugs.	
Retention	Remain in the lacrimal canaliculus for the desired duration of therapy.	
Extended Delivery	An ideal product must deliver travoprost continuously for the intended course of therapy such that the subject continually receives treatment until the product is removed or replaced.	
Biocompatible	Must be biocompatible, chemically inert, non-immunogenic, and synthetic (i.e. devoid of animal tissues).	A

bioabsorbable hydrogel intracanalicular depot has been developed by OTX as a platform for ophthalmic drug delivery. OTX-TP (sustained release travoprost) Intracanalicular Depotis expected to have significant advantages over the commercially available eye drops treatments in that it:

- Remains in the lacrimal canaliculus for desired duration of therapy, eliminating subject non-compliance.
- Delivers therapeutic levels of travoprost continuously for the intended duration of therapy.

3 Francis, B. A, *How Do You Ensure Patient Compliance with Glaucoma Therapy*, Ophthalmology Web, July 8, 2010.

4 Peplinski LS, Albani Smith K. *Deepening of lid sulcus from topical bimatoprost therapy*. Optom Vis Sci 2004;81:574-7.

5 Schwartz GF, Quigley HA. Adherence and Persistence with Glaucoma Therapy. *Surv Ophthalmol.* 53.1 (2008): 57-68.

6 Friedman, D. S. et al., *Using Pharmacy Claims Data to Study Adherence to Glaucoma Medications: Methodology and Findings of the Glaucoma and Adherence and Persistency Study (GAPS)*, Investigative Ophthalmology & Visual Science, November 2007, Vol. 48, No. 11.

7 An JA, Kasner O, Samek DA, Levesque V. *Evaluation of eyedrop administration by inexperienced patients after cataract surgery*. J Cataract Refract Surg 2014; 40:1857-1861

The purpose of the Phase 3a clinical study described herein is to evaluate the safety and IOP-lowering efficacy of OTX-TP when placed in the lacrimal canaliculus in subjects with open angle glaucoma or ocular hypertension. OTX-TP will be compared to a placebo vehicle intracanalicular depot placed in the canaliculus of the eyelid. In addition, the Investigator will confirm the presence of the intracanalicular depot during study follow up visits, and if the Investigator confirms the intracanalicular depot is no longer present at any time prior to the 12 Week Visit, a new depot will be inserted. It is expected that this route of administration will maximize the consistency of dosing.

3.2. Report of Prior Investigations

Ocular Therapeutix has developed several types of PEG hydrogel intracanalicular depots that are similar to OTX-TP. These intracanalicular depots utilize the same bioabsorbable PEG hydrogel technology used in OTX-TP, but are loaded with different active pharmaceutical ingredients with various intended uses.

OTX-TP has been evaluated for initial safety and feasibility in the treatment of elevated IOP associated with glaucoma in clinical trials conducted in Singapore and South Africa. A total of 78 subjects were enrolled in these studies. There were no serious adverse events reported and no safety concerns were raised. Initial efficacy was confirmed by what Ocular Therapeutix interpreted as clinically meaningful IOP reduction from baseline, thus warranting a larger study. OTX-TP Phase 2b, was a prospective, multicenter, randomized, double-masked, parallel arm study evaluating the safety and efficacy of OTX-TP for the reduction of elevated intraocular pressure in subjects with open-angle glaucoma or ocular hypertension. The trial employed a “double dummy” design: Treatment A (OTX-TP and placebo eye drops) and Treatment B (timolol maleate ophthalmic solution plus placebo depot). A total of 72 subjects were treated bilaterally; 33 in the OTX-TP group and 39 in the timolol group. The primary endpoint measures in the study were the difference between treatment groups in (1) mean change from baseline average diurnal IOP at the Day 60 Visit; (2) mean change from baseline average diurnal IOP at the Day 90 Visit; (3) mean change from baseline at each individual time point at the Day 60 and 90 Visits; (4) mean IOP for the average diurnal IOP and each individual time point at the Day 60 and 90 Visits; and (5) mean percent change from baseline for the average diurnal IOP and each individual time point at the Day 60 and 90 Visits. This results of this trial showed a slightly elevated IOP-lowering effect in the timolol group than in the OTX-TP group.

Another Ocular Therapeutix drug product, DEXTENZA (sustained release dexamethasone) Intracanalicular Depot, has been clinically evaluated for the safety and efficacy compared to a Placebo Vehicle for the treatment of ocular inflammation and pain in subjects undergoing ophthalmic surgery in two prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled Phase 3 studies.

The first Phase 3 study enrolled 247 subjects and met both primary efficacy measures, achieving a statistically significant improvement in the reduction of inflammatory cells and pain. 33.1% of DEXTENZA treated subjects showed an absence of inflammatory cells in the anterior chamber of the eye on Day 14 following drug product insertion, compared to 14.5% of those receiving PV treatment ($p=0.0018$). In addition, 80.4% of subjects receiving DEXTENZA reported absence of pain in the study eye on Day 8 following insertion of the drug product, compared to 43.4% of those receiving PV treatment ($p<0.00001$). DEXTENZA was shown to be safe and efficacious in treating ocular pain in adult subjects having undergone cataract extraction with intraocular lens implantation.

The second Phase 3 study enrolled 241 subjects, met one of the primary efficacy measures achieving a statistically significant improvement in the reduction of pain, but failed to meet its primary efficacy endpoint of demonstrating superiority of DEXTENZA over PV in the reduction of anterior chamber cells of the eye on Day 14. 77.5% of DEXTENZA treated subjects showed an absence of pain in the study eye on Day 8 following drug product insertion, compared to 58.8% of those receiving PV treatment ($p=0.0025$). However, 39.4% of subjects receiving DEXTENZA showed an absence of anterior chamber cells in the study eye on Day 14 following drug product insertion, compared to 31.3% of those receiving PV treatment ($p=0.2182$). The most frequent ocular AEs in the study eye were anterior chamber inflammation (characterized as anterior chamber inflammation, iritis or anterior chamber cell).

OTX-MP, an intracanalicular depot delivering moxifloxacin, has been clinically evaluated by Ocular Therapeutix for initial safety and feasibility at one clinical site in Singapore. This prospective, single-arm feasibility clinical evaluation enrolled a total of 20 subjects (20 eyes). All subjects were adults undergoing clear corneal cataract surgery. There were no adverse events or serious adverse events reported. Additionally, the safety assessments performed throughout the follow-up period did not raise any safety concerns.

Ocular Therapeutix is conducting non-significant risk IDE medical device clinical trials in the United States to evaluate the PEG hydrogel intracanalicular depot for acute placement, retention, visualization and comfort as well as the safety of the intracanalicular depot replacement as would be required for ongoing delivery of treatment in a chronic disorder. This is a bioabsorbable hydrogel intracanalicular depot (i.e., the PV) that does not contain any active pharmaceutical ingredient. To date, no serious adverse events related to the PV have been reported, and no safety concerns have been raised.

3.2.1. Prior Experience with Travoprost

Travoprost, the active drug component of the OTX-TP, is a synthetic prostaglandin F_{2α} analogue used for reducing elevated intraocular pressure in subjects with open angle glaucoma or ocular hypertension. Travoprost is the active pharmaceutical ingredient in Travatan®, Travatan Z® and IZBA™ (Alcon Laboratories Inc., Fort Worth, TX) which have been approved by the US FDA under application numbers 021257, 021994 and 204822, respectively.

3.3. Description of Intracanalicular depot

3.3.1. OTX-TP (sustained release travoprost) Intracanalicular Depot

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

Embedded in OTX-TP are poly (-lactic- acid) (PLA) microparticles which contain encapsulated travoprost, the active pharmaceutical ingredient. The microparticles are bioabsorbable particles designed to release travoprost in a controlled fashion over the intended duration of therapy. OTX-TP contains approximately 0.32 mg travoprost and is designed to provide a sustained release of therapeutic levels of travoprost for the reduction of elevated intraocular pressure. As OTX-TP hydrates in tear fluid and swells in volume, the microparticles will degrade by hydrolysis and the travoprost is slowly released over a period of up to approximately 90 days.

The OTX-TP also has an inert PEG tip to aid in insertion. This tip dissolves during insertion and placement to provide intracanalicular lubrication.

OTX-TP is provided to the Investigator as a terminally-sterilized dried intracanalicular depot.

The product is packaged in a hermetically sealed foil pouch to maintain stability and sterility over time. It is placed into the punctum by the Investigator using forceps.

3.3.2. Placebo Vehicle Intracanalicular depot (PV)

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

3.4. Intended Use

The intended use that will be utilized in this study is stated below.

OTX-TP (sustained release travoprost) Intracanalicular Depot is intended for the reduction of elevated intraocular pressure in subjects with open-angle glaucoma (OAG) or ocular hypertension (OH).

3.5. Study Design and Duration

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

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

Subject randomization is 3:2 with a total of approximately 330 subjects in the OTX-TP arm and 220 in the PV arm. Randomization will be stratified by investigational site and previous ocular anti-hypertensive therapy.

Both eyes will receive either OTX-TP or PV, but only the eye with the higher IOP at 8:00AM at Baseline Visit 2 that meets all enrollment criteria will be considered as the study eye and included in the primary efficacy analysis. If both eyes are eligible and have the same IOP at 8AM on Baseline Visit 2 (Day 1), the right eye will be the study eye and the left eye will be considered the secondary study eye. All eyes will be included in the safety analysis. All eyes will be included in the safety analysis.

Subjects currently being treated with a prostaglandin analogue at the time of the Screening Visit will undergo a 6 week (- 2 days/+ 3 days) washout period starting at the Screening Visit and prior to Baseline Visit 1. The Baseline Visit 2/Insertion Visit, Day 1 will be conducted two to four days after the Baseline Visit 1. IOP measurements at the baseline visits will confirm that the washout period was sufficient.

Subjects not currently treated with a prostaglandin analogue will undergo a 2 week run-in starting at the Screening Visit to confirm that they are a prostaglandin responder. At least two IOP measurements will be taken over a two week period (Run-in Visit 1 at 2 days [+ 3 days])

post-initiation of prostaglandin therapy; and Run-in Visit 2 at 11 days [+ 3 days] post-initiation of prostaglandin therapy). The Run-in IOP measurements will be conducted at 8 AM +/- 1 hour, to confirm the response to prostaglandin therapy. Once the response is confirmed, the subjects will undergo a 6 week (- 2 days/+ 3 days) washout period prior to Baseline Visit 1. The Baseline Visit 2/Insertion Visit, Day 1 will be conducted two to four days after the Baseline Visit 1. The IOP measurement at Baseline Visit 2 must demonstrate a ≥ 5 mmHg increase from Run-in Visit 2. IOP measurements at the baseline visits will confirm that the washout period was sufficient. Subjects who have exited from another ophthalmic investigational research study within the last 8 weeks will be started on a 6 week prior trial recovery period *and* stop all glaucoma/OHT meds, after completing Informed Consent and the Screening Visit. They will then be discussed with the Medical Monitor, in order to obtain written approval to be allowed to participate in the current study. The approval will be captured on the appropriate eCRF. Timing and requirements for the period between Screening and Baseline Visit 1 will vary, please refer to [Appendix A](#) for additional specifications.

At Baseline Visit 2/Insertion Visit, if insertion is unsuccessful in one eye, the intracanalicular depot from the contralateral eye (if already inserted) will not be removed. The subject will be prescribed IOP-lowering drops at the Investigator's discretion for the eye that did not receive a depot. The subjects will be followed for safety only, and the eye that received a depot will be included in the safety analysis. The study will be supplemented with additional subjects to account for these subjects in order to ensure that the necessary number of subjects who received a depot bilaterally are followed through the 12 Week Visit for efficacy and safety.

All subjects will undergo follow-up visits at 2, 4, 6, 8, 10, and 12 Weeks. If at any visit, the Investigator deems it necessary to initiate IOP-lowering drops as rescue therapy due to an increase in IOP, the subject will begin IOP-lowering drops at the Investigator's discretion and followed through the remainder of the study for safety.

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

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

If the intracanalicular depot is still present in one or both eyes at the 12 Week Visit, the Investigator will attempt to remove it (For removal methods, refer to [Appendix C](#)). If removal is successful bilaterally, the subject will be exited from the study upon confirmation of the bilateral absence of the intracanalicular depot. If the intracanalicular depot is not present bilaterally at the 12 Week Visit, the subject will be exited at the end of that visit.

If removal is unsuccessful in one or both eyes at the 12 Week Visit, the subject will return at the 20 Week Visit. The Investigator will attempt removal of intracanalicular depot from the respective eye (s) at this visit. The subject may be prescribed IOP-lowering drops if necessary at the 12 Week Visit at the Investigator's discretion.

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

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

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

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

If the intracanalicular depot is not present bilaterally at the 20 Week Visit, the subject will be exited from the study at the end of that visit. The subject may be prescribed IOP-lowering drops if necessary at the 20 Week Visit at the Investigator's discretion.

Rescue Therapy for Subjects with unacceptable IOP increase after treatment:

If at any visit prior to and including the 2 Week visit, the Investigator determines that the subject's IOP is increasing to unacceptable levels, the Investigator will prescribe IOP lowering drops at his or her discretion and will confirm adequate IOP lowering response at the next visit. The IOP lowering medication should be recorded on the appropriate CRF. The intracanalicular depot will not be removed, and the subject will be followed through the 12 Week Visit for the remaining scheduled study visits.

Additionally, 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 to ensure the subject's safety.

The study will be conducted at up to 50 qualified investigative sites in the United States following Institutional Review Board (IRB) approval. A site may randomize up to a maximum of 55 subjects. All subjects will be required to provide informed consent prior to study participation.

The anticipated duration of the clinical investigation is approximately 18 months. The expected duration of participation for each subject will vary depending on whether they have received previous treatment, and how long the intracanalicular depot is retained

3.5.1. Control of Bias

The following study design parameters will minimize bias:

- The study design is a parallel-arm, prospective, placebo controlled study.
- The study is double-masked.
- The study will be conducted across multiple centers.
- The study is randomized (3:2, treatment group to control group).

4. STUDY DESIGN

4.1. Study Objective

To evaluate the safety and IOP lowering efficacy of OTX-TP, a sustained release travoprost drug product, placed in the canaliculus of the eye in the treatment of subjects with open-angle glaucoma or ocular hypertension.

4.2. Study Endpoints

4.2.1. Endpoints

The primary study endpoint measure to be evaluated is:

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

The secondary endpoint measures to be evaluated are:

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

4.2.2. Other Data to be Collected

Additionally, data will be collected for the following:

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

4.2.3. Safety Evaluations

The following safety evaluations will be completed:

- Best corrected visual acuity (BCVA)
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Subject ocular comfort assessment (to be completed at all visits after/including Baseline visit 2)
- Dilated fundus exam (to be completed on at Screening and 12 week)
- Adverse events

4.3. Selection and Training of Investigators

Only ophthalmologists who are experienced with treating glaucoma or ocular hypertension will be considered for participation as Principal Investigators in this study. Optometrists who are experienced with treating glaucoma or ocular hypertension will be considered for participation as Sub-Investigators. All investigators that will use the intracanalicular depot must be experienced in intracanalicular depot insertion and will undergo training per the OTX-TP instructions for use prior to initial use.

4.4. Subject Selection

4.4.1. Pre-Procedure Inclusion Criteria

Subjects must meet all of the following criteria to be eligible:

1. Greater than or equal to 18 years of age at Screening.
2. Documented diagnosis of ocular hypertension with an open angle of Schaffer Grade 3 or greater or open-angle glaucoma without pseudoexfoliation or pigment dispersion or evidence of traumatic angle recession.
3. IOP is currently controlled as assessed by the Investigator:
 - With a topical prostaglandin, and there has been no change in IOP lowering therapy over 8 weeks prior to Screening, or,
 - without IOP-lowering medication over 8 weeks prior to Screening and after a 2-week run-in period on prostaglandin therapy demonstrates an adequate response

Note: For Subjects entering through Stratum C, a required Medical Monitor review will ensure subjects have:

- demonstrated 8 weeks of stable treatment (or no treatment) for glaucoma and/or ocular hypertension prior to enrollment in the previous recent ophthalmic clinical trial(s).
 - documented history of an adequate prostaglandin response as described in the protocol, or will undergo a prostaglandin run-in trial as described in the protocol for patients who do not have such a history.
4. Baseline IOP (following washout or run-in) in at least 1 eye (the same eye) of:
 - ≥ 24 mmHg at Hour 0 (T_0) at Baseline Visit 2 (Day 1)
 - ≥ 22 mmHg at ($T_0 + 2$ h) and ($T_0 + 8$ h) at Baseline Visit 2 (Day 1)
 - At 8AM Baseline Visit 2 (Day 1), ≥ 5 mmHg increase from Screening for subjects previously on prostaglandins
 - At 8AM Baseline Visit 2 (Day 1), ≥ 5 mmHg increase from Run-in Visit 2 for subjects not previously on prostaglandins prior to the Screening Visit

Note: the same eye must meet all of the above listed IOP eligibility criteria
 5. IOP must be ≤ 34 mmHg in each eye at all time points at the Baseline Visit 1 (Day -2 to -4) and Baseline Visit 2 (Day 1).
 6. Informed of the nature of the study and subject is able to comply with study requirements and visit schedule.
 7. Provided written informed consent, approved by the appropriate Institutional Review Board.

4.4.2. Pre-Procedural Exclusion Criteria

Subjects who meet any of the following criteria are not eligible:

1. A history, prior to Screening, of an inadequate response (< 5mmHg decrease from prior to any treatment) or no response to topical prostaglandin for OAG/OH.
2. For subjects on IOP-lowering medication(s): History of concurrent treatment with 3 or more IOP-lowering medications for longer than 2 weeks. Any combination medication will be considered as 2 medications.
3. Currently (or within 8 weeks prior to Screening) on any ocular or systemic medication [i.e., carbonic anhydrase inhibitors, corticosteroids (including topical dermal steroids for the face), etc.] that may:
 - Have an effect on the subject's IOP or will require use of such ocular or systemic medications during the study period.
 - No topical ophthalmic medications other than prostaglandins allowed at the time of the screening visit. Systemic beta blockers will be allowed, but any initiation of or alterations in systemic regimen of beta-blocker containing medications from 8 weeks prior to screening through the final study visit is excluded.

Subjects currently treated with topical prostaglandin analogues are required to undergo a washout period of 6 weeks (- 2 days/+ 3 days).

Note: For Subjects entering through Stratum C, changes in ocular or systemic prior ophthalmic study medications, that may have an effect on the Subject's IOP, will be allowed, but inclusion in the study will be based on a required Medical Monitor review. Stratum C subjects will also be allowed to screen for the study while on ophthalmic medications other than prostaglandins, however, these medications should be stopped at Screening, and a Prior Trial Recovery Period shall be started.

4. A BCVA worse than 0.6 LogMAR (20/80 Snellen) in either eye as measured using an ETDRS chart.
5. Punctum size smaller than 0.4 mm or greater than 0.9 mm in either eye as measured using a standard punctum gauge.
6. Known or suspected allergy and/or hypersensitivity to Travoprost or any prostaglandin, fluorescein, or to any component of the study products.
7. History of ocular trauma within the past 6 months in either eye.
8. Evidence of angle recession by gonioscopy.
9. Presence of any abnormality based upon the assessment by the Investigator preventing reliable applanation tonometry of either eye.
10. Narrow or potentially occludable anterior chamber angle defined as an anterior chamber angle of less than or equal to Grade 2 (Schaffer classification) as measured by gonioscopy
11. Central corneal thickness < 480 µm or > 620 µm in either eye.
12. Cup to disc ratio > 0.80 (horizontal or vertical measurement) in either eye.
13. Functionally significant central visual field loss or documented significant progressive field loss within the last year in either eye based upon the assessment by the Investigator.
14. History of complications, AEs, trauma or disease in the nasolacrimal area, whether or not it was due to punctal plug use, including but not limited to dacryocystitis, inflammation or canaliculitis in either eye.
15. Structural lid abnormalities (i.e., ectropion, entropion) in either eye based upon the assessment by the Investigator.

16. Active epiphora based upon the assessment by the Investigator.
17. Presence of nasolacrimal duct obstruction based upon an assessment by the Investigator.
18. Active lid disease in either eye (i.e., moderate or severe blepharitis, meibomitis) that requires medical treatment.
19. History of ocular infection (bacterial, viral, or fungal) in either eye within the previous 3 months.
20. History of any severe ocular pathology (including severe dry eye) in either eye.
21. History of chronic/recurrent inflammatory eye disease (i.e., scleritis, uveitis, herpes keratitis) in either eye.
22. Required use of any ocular topical medication(s), any over-the counter drop(s), ointment(s), gel(s) or lid scrubs, other than the study ocular hypotensive medication(s) in either eye during the study period.
Note: Use of artificial tears or ocular lubricants should be avoided but if necessary, intermittent use may be allowed up to twice a day.
23. Any ophthalmic surgical procedures (e.g. glaucoma laser, minimally invasive glaucoma surgery, cataract, refractive) in study eye within the last six months or will likely require ophthalmic surgery before completing the study.
24. History of penetrating or lamellar keratoplasty in either eye (including endothelial keratoplasty).
25. History of keratorefractive surgery in either eye (i.e., LASIK, PRK, RK, AK, LRI, Corneal inlay, intracorneal ring segment).
26. Advanced diabetic retinopathy, branch retinal vein occlusion, or central retinal vein occlusion in either eye.
27. History of macular edema in either eye.
28. Any uncontrolled systemic or debilitating disease (e.g. cardiovascular disease, hypertension, diabetes, or cystic fibrosis) or a medical condition that may increase the risk associated with study participation or administration of study treatment or that may interfere with the interpretation of study results based upon the assessment of the Investigator (e.g., autoimmune disease if the subject is on chronic medications and has ocular involvement; host-versus-graft disease).
29. Requiring contact lens use at any point during the study after the Screening Visit including on the day of the Baseline Visits. In addition, contact lens wear must be discontinued a minimum of 3 days prior to pachymetry for soft contact lenses and a minimum of 14 days prior to pachymetry for rigid gas permeable contact lenses.
30. Currently pregnant or breast-feeding or who wishes to become pregnant during the length of study participation.
31. Currently participating or has participated within the last 30 days in any non-ophthalmic drug, device or other investigational research study prior to the start of this study.
Note: Previous participation in any ophthalmic investigational research study within 8 weeks will require written approval for enrollment from the Medical Monitor based on instructions provided in [Appendix A](#).
32. Investigator determines subject should not be included for reasons not already specified (e.g., systemic or other ocular disease/abnormality, not a candidate for topical prostaglandin, therapy, specifically travoprost) if the health of the subject or the validity of the study outcomes may be compromised by the subject's enrollment.

4.4.3. Procedural Exclusion Criteria

All subjects who meet the following procedural exclusion criteria are considered screen failures and are *not* eligible for enrollment into the study:

1. Unsuccessful punctal dilation of either eyelid (if needed) or punctum of either eye is too small to allow transient dilation to 0.7 mm prior to insertion of OTX-TP or PV.

4.5. Study Procedures and Data Collection**4.5.1. Study Schedule**

The schematic of the study schedule is presented in [Table 1](#), [Table 2](#), and [Table 3](#), respectively for: Stratum A, Stratum B, and Stratum C. For subjects exiting prior ophthalmic investigational research studies, please refer to [Appendix A](#) to determine the appropriate randomization stratum and the respective study schedule. Procedures for study assessments can be found in [Appendix B](#).

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

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

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

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

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

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

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

4.5.2. Data Collection

Data collected from all study procedures and assessments will be collected and documented on the appropriate Case Report Form (CRF) for the study. All data should be entered in compliance with the latest version of the eCRF Completion Guidelines.

4.5.3. Subject Enrollment

Prior to enrollment in the study, subjects will be evaluated to determine potential eligibility. The subject's willingness and ability to meet the follow-up requirements will be determined. If the subject desires to participate in the study, written informed consent will be obtained prior to performance of any study-specific examinations. Following all the baseline assessments, the subject will be assessed to determine if the eligibility criteria are met. If the subject meets the procedural eligibility requirement and agrees to participate, the subject will be randomized. A subject is considered enrolled in the study at the time the subject signs the Informed Consent Form. Once a subject qualifies for the study and is randomized, they must be followed whether or not the subject received the study assigned treatment. In the event that after randomization the insertion of the intracanalicular depot is successful in the first eye, but unsuccessful in the second eye, the intracanalicular depot will not be removed from the first eye and the subject will be prescribed IOP-lowering drops at the Investigator's discretion for the eye that did not receive the depot. The subjects will be followed for safety only, and the eye that received the depot will be included in the safety analysis. The study will be supplemented with additional subjects in order to ensure that up to 495 subjects who receive a depot bilaterally are followed through the 12 Week Visit for safety and efficacy.

In the event that after randomization the insertion of the intracanalicular depot is unsuccessful in the first eye, the subject will be exited from the study. The study will be supplemented with additional subjects in order to ensure that up to 495 subjects who receive a depot bilaterally are followed through the 12 Week Visit for safety and efficacy.

Subjects who are enrolled but determined to be ineligible during the screening assessment, run-in visits, IOP confirmation visit, or baseline visits prior to randomization will be considered screen failures, will be withdrawn from the study, and will not require additional study follow-up visits. These subjects should be entered in the EDC system per the latest version of the eCRF Completion Guidelines.

For subjects who fail eligibility criteria at the Baseline Visit, the reason for the screen failure will be clearly delineated on the applicable eCRF.

All subjects who receive a depot in the study will be required to adhere to the follow-up schedule outlined in this protocol. Subjects withdrawing consent after insertion initiation will not be required to undergo follow-up after withdrawal; however, these subjects will still be considered part of the study cohort to which they were originally assigned.

4.5.4. Informed Consent

Once a study candidate's eligibility has been determined and the Investigator agrees, a member of the research team will present the study to the subject. The background of the proposed study, the study procedures, follow up schedule, and the risks and potential benefits of the procedures and study will be explained to the subject. Prior to enrollment in the study, all subjects must review and complete an IRB approved Informed Consent Form (ICF). Failure to obtain a signed ICF renders the subject ineligible for the study. Subjects must be willing to return to the clinic

for study visits at 2, 4, 6, 8, 10, and 12 weeks after the insertion as required. Additional visits may be required based on depot replacement.

4.5.5. Randomization

Prior to the initiation of the study, a treatment randomization scheme will be generated using a 3:2 ratio (Active Treatment to Placebo Control). Randomization will be stratified by investigational site (i.e., one randomization schema per study site) and previous ocular anti-hypertensive therapy with 3 levels:

Stratum A: Subjects who were on prostaglandin treatment at the time of the Screening Visit and have shown an adequate IOP rise after a 6-week washout (interval from Screening to Baseline Visit 1 is 6 weeks). This may include subjects exiting from a prior ophthalmic investigational research study based on based on criteria specified in [Appendix A](#).

Stratum B: Subjects who were treatment-naïve at Screening and have shown an adequate prostaglandin response after a 2-week run-in period on prostaglandin treatment followed by a 6-week washout (interval from Screening to Baseline Visit 1 is 8 weeks). This may include subjects exiting from a prior ophthalmic investigational research study based on based on criteria specified in [Appendix A](#).

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

Once it is determined that the subject continues to meet eligibility for the study at Baseline Visit 2, the subject will be randomized into the study through assigning the next sequential kit within the kits corresponding to the subjects previous ocular anti-hypertensive therapy category and both eyes will be provided with the same assigned treatment, OTX-TP or PV.

4.5.6. Masking

The Investigator and the subject will be masked to the treatment assignment throughout the duration of therapy. At the conclusion of the study, the Principal Investigator will be unmasked to the treatment assignment of the subjects who received OTX-TP or PV. Subjects in both groups will be prescribed IOP-lowering drops based on the Investigator's discretion.

OTX-TP and the PV are identical in appearance, and will be supplied in identical packages so as they cannot be distinguished by the user. If it is medically necessary to identify the product used, the Investigator will follow procedures outlined in [Section 5.6](#).

4.5.7. Study Assessments

Please refer to [Appendix B](#) for procedures for conducting the study assessments (e.g. BCVA, slit lamp biomicroscopy, ocular hyperemia grading, pachymetry, IOP measurement, dilated fundus exam, gonioscopy, automated perimetry and punctum exam).

4.5.7.1. Screening Visit

The following procedures and assessments will be completed at least 6 weeks (-2/+3 days) prior to the Baseline Visit 1 for Stratum A, at least 8 weeks (-2/+3 days) prior to Baseline Visit 1 for Stratum B, and as instructed by Medical Monitor for Stratum C, to allow for adequate washout of potential subject's current OAG/OHT medication(s):

- Obtain informed consent

- Demographic information: age, gender, ethnicity, height, weight (height and weight may be self-reported by subject)
- Iris color
- Medical and ophthalmic history
- Medication history
- Urine pregnancy test (if applicable): If female of childbearing potential, subject must utilize reliable contraceptive methods for the duration of the study as judged by the Investigator, and have a negative urine pregnancy test.

The following procedures and assessments will be performed for both eyes:

- Best Corrected Visual Acuity
- Automated perimetry
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Punctum exam (for normality of punctal appearance, lid apposition, and tear meniscus)
- Punctum size assessment using a punctum gauging system provided by the Sponsor
- IOP measurement (Goldmann applanation tonometry) at 8AM \pm 60 minutes
- Pachymetry: The average of the 3 measurements will be calculated to determine subject eligibility. Contact lens wear must be discontinued 3 days prior to pachymetry for soft contact lenses and 14 days prior to pachymetry for rigid gas permeable contact lenses. For contact lens wearers, the pachymetry assessment may be scheduled for a separate day from the Screening Visit based on the type of contact lens (i.e., 3 days after the Screening Visit for soft contact lenses and 14 days for rigid gas permeable lenses).
- Gonioscopy
- Dilated fundus exam
- Adverse event assessment
- At the end of the Screening Visit:
 - Subjects will be instructed to start washout, run-in, or prior trial recovery period based on randomization stratum. Please refer to [Appendix A](#) for subjects who need to start the prior trial recovery period.

4.5.7.2. Run-in Visits 1 and 2

For subjects in Stratum B, Run-in Visit 1 will be 2 days (+ 3 days) post-initiation of prostaglandin therapy for subjects; and Run-in Visit 2 will be 11 days (+ 3 days) post-initiation of prostaglandin therapy.

The following will be performed for both eyes:

At 8AM (T₀)

- IOP measurement (Goldmann applanation tonometry)
- Adverse event assessment

Run-in Visits are only applicable to Stratum B subjects. After prostaglandin response is confirmed, subjects will washout for 6 Weeks (-2/+3 days).

4.5.7.3. IOP Confirmation Visit (*only applicable for subjects exiting from a prior ophthalmic investigational research study*)

At the end of the 6 week prior trial recovery period (-2 days/+ 5 days), subjects will return for a visit to confirm adequacy of IOP, in that the subject continues to meet the IOP criteria.

The following will be performed for both eyes:

At 8AM (T₀)

- IOP measurement (Goldmann applanation tonometry)
- Adverse event assessment

4.5.7.4. Baseline Visit 1

For all subjects the following procedures and assessments will be performed for both eyes after completing appropriate washout, run-in and washout, or prior trial recovery period and IOP confirmation. Please refer to [Appendix A](#) for subjects who have exited from a prior ophthalmic investigational research study.

Note: All 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.

The following will be performed for both eyes:

At 8AM (T₀)

- Medication and medical history update
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- IOP measurement
- Adverse event assessment

4.5.7.5. Baseline Visit 2/Insertion Visit: Day 1

The following procedures and assessments will be performed for both eyes on the day of treatment:

Note: All 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.

The following will be performed for both eyes on the day of treatment:

At 8AM (T₀)

- IOP measurement
- Assessment of BCVA
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Subject ocular comfort assessment

Subjects will be asked to grade their comfort level by asking them the following question:

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

10AM (T₀+2h)

- IOP measurement

4PM (T₀+8h)

- IOP measurement
- Randomization
- Punctum exam prior to insertion of OTX-TP or PV
- Punctum size pre/post dilation

- Insertion of intracanalicular depot into superior or inferior canaliculus of each eye for each subject

At 8AM (T₀), 10AM (T₀+2h) and 4PM (T₀+8h)

- Adverse event assessment

4.5.7.6. Point of Randomization

At the conclusion of all assessments at the Baseline Visit 2, the Investigator will confirm that subject does not meet the protocol specified procedural exclusion criteria. If subject is still eligible, the Investigator will conduct the punctum size assessment.

The Investigator will use a standard punctum gauge to assess the size of the punctum. If the punctum measures < 0.4 mm or > 0.9 mm, the subject will be screen failed and will not be randomized.

The Investigator will utilize a commercially available dilator probe from standard practice or as provided by Sponsor to dilate the punctum to 0.7 mm, as required for proper insertion of the intracanalicular depot. If the Investigator determines that the punctum cannot be dilated to approximately 0.7 mm, the subject will be screen failed and will not be randomized.

If the subject remains eligible for the study, the Investigator will randomize the subject and insert OTX-TP or PV into the superior or inferior canaliculus of the subject's eyes.

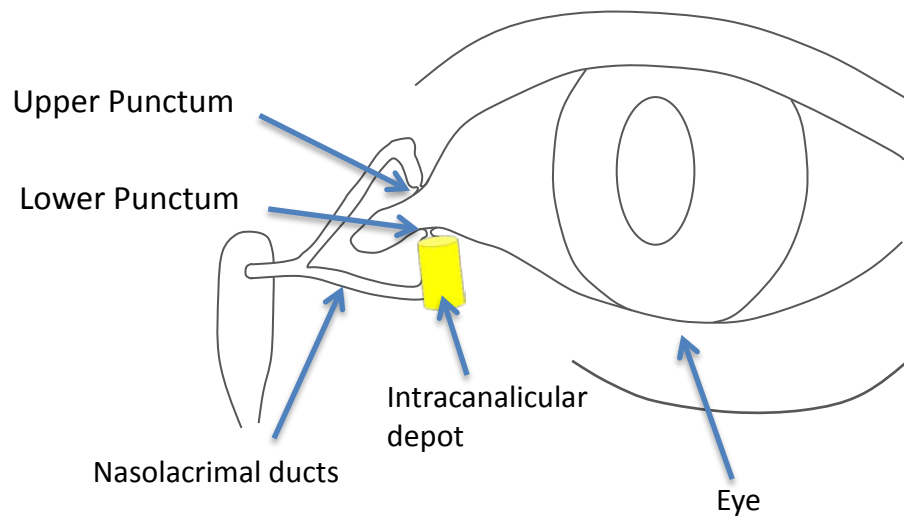
4.5.7.6.1. Intracanalicular Depot Insertion

Prior to insertion, it should be ensured that the area of the superior or inferior punctum including eyelids is clean using an eyelid wash, if necessary. The area should be anesthetized with either a topical anesthetic instilled into the conjunctival sac or an anesthetic soaked, cotton-tipped Weck-Cel™ spear or equivalent held against the conjunctival side of the eye lid in the area of the punctum for approximately 30 seconds. The punctum will be dilated as necessary prior to insertion of the intracanalicular depot. The intracanalicular depot will then be inserted using forceps as per the instructions for use. The intracanalicular depot should rest down within the canaliculus just below the punctal opening as shown in [Figure 1](#).

After insertion and exposure with tear film, the intracanalicular depot will rapidly hydrate and expand to fill the canaliculus; however, gentle irrigation of the eye with BSS solution or artificial tears may be used to ensure the intracanalicular depot is adequately hydrated.

If protrusion or partial extrusion occurs, the intracanalicular depot may be removed and insertion may be reattempted using a new depot.

Misalignment of the intracanalicular depot, failure to insert it into the canaliculus, or contact of the intracanalicular depot with other adnexa of the eye will result in discarding the intracanalicular depot, followed by replacement and re-attempt with a new, sterile intracanalicular depot.

Figure 1: Placement of Intracanalicular depot in the Inferior Canaliculus**4.5.7.6.2. Observations to be Recorded**

The following observations for the insertion of the intracanalicular depot will be recorded:

- Use of dilation
- Ease of insertion of the intracanalicular depot: The Investigator will be asked to grade the level of ease of insertion of the intracanalicular depot as “easy”, “moderate” or “difficult”.

4.5.7.6.3. Discharge Instructions

Subjects should be instructed to refrain from rubbing his/her eyes and to contact their Study Doctor in the event that they experience excessive pain, excessive discomfort, loss of vision, or increasing redness of the eye.

4.5.7.7. Concurrent Medications

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

4.5.7.8. Prohibited Medications/Treatments

The following restrictions related to medications and treatments apply:

- Topical or systemic ocular hypotensive medications may not be used for the duration of the study with the exception of the study treatment. The washout period for medications between the Screening and Baseline Visit 1 for subjects currently taking prostaglandin analogues for OAG/OHT, is 6 weeks (- 2 days/+ 3 days)
- Systemic beta blockers will be allowed, but any initiation of or alterations in systemic regimen of beta-blocker containing medications from 8 weeks prior to screening through the final study visit is excluded.
- Use of inhaled (using mouthpiece) and nasal corticosteroids and topical dermal steroids (except on the face) are allowed.
- Any medication or substance administered by any route and used on a chronic basis that has not been on a stable dose for 8 weeks prior to Screening and may not be changed for the duration of the study.
- Non-diagnostic topical ophthalmic solutions (other than the study treatment) may not be used from Baseline Visit 1 through the duration of the study. Note: Use of artificial tears or ocular lubricants should be avoided but if necessary, intermittent use may be allowed up to twice a day.
- Contact lenses may not be used at any point during the study after the Screening Visit including on the day of the Baseline Visits. In addition, contact lens wear must be discontinued prior to pachymetry a minimum of 3 days for soft contact lenses, or 14 days for rigid gas permeable contact lenses.

4.5.7.9. Follow-up Assessments

4.5.7.9.1. 4 Week (Day 29± 3 days), 8 Week (Day 57 ± 3 days), and 10 Week (Day 71 ± 3 days) Visits

The following will be performed for both eyes:

At 8AM only

- Medication and medical history update
- Subject ocular comfort assessment
- Assessment of Ocular complaints
- Assessment of BCVA
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Confirmation of intracanalicular depot presence by the Investigator
- Punctum exam
- IOP measurement
- Adverse event assessment

*If the intracanalicular depot has to be removed for subject discomfort or an undesirable reaction, the investigator will prescribe IOP lowering medication at his/her discretion, and the subject will be exited from the study.

4.5.7.9.2. 2 Week (Day 15 ± 3 days) and 6 Week (43 ± 3 days) Visits

The following will be performed for both eyes:

At 8AM (T₀)

- Medication and medical history update
- Subject ocular comfort assessment
- Assessment of Ocular complaints
- Assessment of BCVA
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Confirmation of intracanalicular depot presence by visual assessment
- Punctum exam

At 8AM (T₀), 10AM (T₀+2h) and 4PM (T₀+8h)

- IOP measurement
- Adverse event assessment

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

If the intracanalicular depot is still present in one or both eyes at the 12 Week Visit, the Investigator will attempt to remove the intracanalicular depot from the respective eye(s). If removal is successful bilaterally, the subject will be exited from the study. The subject may be prescribed IOP-lowering drops at the Investigator's discretion.

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

If the intracanalicular depot is not present bilaterally at the 12 Week Visit, the subject will be exited at the end of that visit. The subject may be prescribed IOP-lowering drops at the Investigator's discretion.

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

4.5.7.9.3. 12 Week (Day 85 ± 3 days) Visit

The following will be performed for both eyes:

At 8AM (T₀)

- Medication and medical history update
- Iris color

- Subject ocular comfort assessment
- Assessment of Ocular complaints
- Assessment of BCVA
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Confirmation of intracanalicular depot presence by visual assessment

- Punctum exam

At 8AM (T₀), 10AM (T₀+2h) and 4PM (T₀+8h)

- IOP measurement
- Adverse event assessment

At 4PM (T₀+8hr)

- Dilated fundus exam

For subjects who received a replacement intracanalicular depot prior to the 6 Week Visit:

If the intracanalicular depot is still present at the 12 Week Visit in one or both eyes, the Investigator will attempt to remove the intracanalicular depot from the respective eye(s). If removal is successful bilaterally, the subject will be exited from the study.

If removal is unsuccessful in one or both eyes, the subject will return at the 20 Week Visit.

If the intracanalicular depot is not present bilaterally at the 12 Week Visit, the subject will be exited at the end of the visit.

The subject may be prescribed IOP-lowering drops at the Investigator's discretion.

4.5.7.9.4. 20 Week (Day 141 ± 7 days) Visit

The following will be performed for both eyes:

At 8AM only

- Medication and medical history update
- Subject ocular comfort assessment
- Assessment of Ocular complaints
- Assessment of BCVA
- Slit lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Confirmation of intracanalicular depot presence by visual assessment
- Punctum exam
- IOP measurement
- Dilated fundus exam
- Adverse event assessment

For subjects who received a replacement intracanalicular depot starting at the 6 Week Visit and prior to the 12 Week Visit:

If the intracanalicular depot is still present in one or both eyes at the 20 Week Visit, the Investigator will attempt to remove the intracanalicular depot from the respective eye(s). If removal is successful bilaterally, the subject will be exited from the study.

If removal at the 20 Week Visit is not successful in one or both eyes, the subject will be required to return to the clinic every 30 (± 10) days until the intracanalicular depot is confirmed to be no longer present.

If the intracanalicular depot is not present bilaterally at the 20 Week Visit, the subject will be exited at the end of the visit.

The subject may be prescribed IOP-lowering drops at the Investigator's discretion.

4.5.7.9.5. Unscheduled Visits

For Unscheduled Visits, the reason for the visit should be clearly documented on the appropriate CRF, including findings from all evaluations that are completed. The following evaluations must be completed. Ocular assessments are required to be conducted on both eyes.

- Medication and Medical History Update
- Subject ocular comfort assessment
- Assessment of Ocular complaints
- Assessment of BCVA
- Slit Lamp biomicroscopy
- Assessment and grade of ocular hyperemia (at slit lamp)
- Confirmation of intracanalicular depot presence by visual assessment
- Punctum exam
- IOP measurement
- Adverse event assessment

4.6. Intracanalicular Depot Removal

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

Once OTX-TP has been removed, the subject may be prescribed IOP-lowering drops for the affected eye(s) at the Investigator's discretion. Intracanalicular depots that are removed due to subject withdrawal or an undesired reaction at any point in the study will not be replaced.

4.7. Potential Risks and Benefits

The potential risks and benefits associated with the use of OTX-TP Intracanalicular Depot are discussed in sections below.

4.7.1. Risks Associated with OTX-TP Intracanalicular Depot or PV

In general the following risks are associated with travoprost and/or could occur from the insertion and use of the intracanalicular depot:

- Visual changes
- Ocular pain and discomfort
- Conjunctivitis
- Keratitis
- Dacryocystitis
- Tearing with mucopurulent discharge

- Stenosis (narrowing/closing) of the punctum
- Ocular hyperemia
- Prostaglandin Associated Orbitopathy
- Blepharitis
- Epiphora
- Dry eye
- Iris discoloration
- Ocular pruritus
- Subconjunctival hemorrhage
- Cataract
- Macular edema
- Infection that if severe could lead temporary or permanent impairment of sight
- Perforation of or trauma to the punctum and/or surrounding tissues; or punctoplasty
- Allergic reaction
- Chemosis
- Inflammatory reaction
- Inability to remove the intracanalicular depot

4.7.2. Minimization of Risks

With any new product, there is always chance of developing complications. Not all risks of using OTX-TP are known. However, the risks associated with OTX-TP have been minimized by the use of iterative product design changes during the OTX-TP clinical development program as well as by formulating the intracanalicular depot with constituents that have a long history of safe use in ophthalmic drugs, medical devices and cosmetics. Furthermore, results of biocompatibility and preclinical testing when evaluated at a comparable dose, demonstrate OTX-TP does not invoke an inflammatory or toxic response from ocular tissues.

Subjects will be selected and enrolled using clearly defined inclusion and exclusion criteria to ensure that subjects with ocular or periocular anatomy and/or 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 use of rescue medication. If IOP is unreasonably high in the opinion of the Investigator, the protocol allows rescue medication to be administered to the subjects, at any point throughout the study. The specific medication regimen will be at the Principal Investigators' discretion. Safety checks will be conducted at every scheduled visit, however the investigator may initiate rescue therapy and any time during the study.

This study will be monitored by the Sponsor and/or its CRO designates to ensure the identification, documentation and analysis of all adverse events, compliance with the protocol, the terms of the participating IRB's to protect the safety and rights of all subjects, and applicable Federal regulations. To minimize safety risks to the subjects, only those investigators trained for

treating subjects with glaucoma or ocular hypertension will be considered for participation as investigators in this study. For all investigators who will use the intracanalicular depot, only those who are experienced in intracanalicular depot insertion will be considered and all investigators will be required to undergo training per the OTX-TP Instructions for Use by the Sponsor and/or its designates prior to initial use.

4.7.3. Potential Benefits

The benefits of OTX-TP are not yet known, but are thought to be the reduction of elevated intraocular pressure and improved treatment outcome through eliminating subject non-compliance with the use of daily drops.

4.8. Product Malfunctions

All malfunctions of OTX-TP or PV will be documented on the appropriate eCRF and reported to Ocular Therapeutix within 24 hours. Ocular Therapeutix will advise whether the intracanalicular depot(s) should be returned for analysis. The incidence of malfunctions will be included in the final analysis.

4.9. Subject Withdrawal

For any subject who withdraws their consent following randomization, to the extent possible, the reason(s) for withdrawal will be documented on the End of Study eCRF. Subjects will be asked, but not required, to return for removal of the intracanalicular depot (if still present) prior to withdrawing from the study. 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.

5. ADVERSE EVENTS (AES)

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

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

5.1. Definitions

Adverse Event (or Adverse Experience, AE)

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

Adverse Ocular Event

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

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

Treatment Emergent Adverse Ocular Event (or TEAE)

An adverse ocular event will be considered a treatment-emergent AE if it occurs or worsens on or after the initiation of the intracanalicular depot insertion.

Adverse Reaction (or Related Adverse Event or Adverse Effect)

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

Unexpected Adverse Reaction (Unanticipated Adverse Effect)

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

Serious Adverse Event (Serious Adverse Experience)

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

- results in death
- is life-threatening
(The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is sight threatening

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.⁸

5.2. Severity

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

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

⁸ The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations. (Severity of all adverse events, ocular and non-ocular, will be reported according to the terminology defined in the protocol.)

5.3. Relationship to OTX-TP or PV

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

NO RELATIONSHIP SUSPECTED	This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
RELATIONSHIP SUSPECTED	The following criteria should be applied in considering inclusion of an adverse event in this category: 1) It bears a reasonable temporal relationship to the insertion procedure or the presence of the intracanalicular depot. 2) It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. 3) It disappears or decreases on removal of the intracanalicular depot. 4) It follows a known pattern of response to the insertion procedure or the intracanalicular depot.
UNABLE TO DETERMINE*	The Investigator is unable to assess the relationship of the event to the insertion procedure or the intracanalicular depot.
*Where the causal relationship of the AE to the insertion procedure or the intracanalicular depot has not been determined or is unknown, the AE will be treated as if a relationship is suspected for the purposes of regulatory reporting.	

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the study drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the adverse event. Types of evidence that would suggest a causal relationship between the study drug and the adverse event include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure; one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

5.4. Expectedness

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

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

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

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

5.5. Procedures for Reporting Adverse Events

All adverse events that are "serious" and "unexpected" and related to the study drug are to be reported to Ocular Therapeutix and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities. All serious events, regardless of their expectedness or relatedness are to be reported to Ocular Therapeutix within 24 hours of site awareness.

All adverse events observed during the course of this study from the point of consent, regardless of severity or relationship to the study product will be recorded on the appropriate case report form(s). To the extent possible, the event to be recorded and reported is the event **diagnosis** as opposed to event **symptoms** (e.g., symptoms of vision loss or diplopia associated with intraocular lens dislocation; the event should be documented as intraocular lens dislocation). Details and symptomology associated with the event may be reported in the narrative section of the Adverse Event Case Report Form.

Any serious adverse experiences or any severe, sight-threatening adverse reactions, whether ascribed to the study treatment or not, will be communicated within 24 hours, by telephone, to Ocular Therapeutix, Inc. The Investigator must obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide OTX with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the adverse event within the IRB's guidelines for reporting SAEs. A written report detailing the event, signed by the Investigator, shall be submitted to the Sponsor within 5 working days. All subjects experiencing an SAE must be followed up and the outcome reported.

5.5.1. Specific Anticipated Adverse Ocular Events

Anticipated adverse ocular events that may be associated with OTX-TP or PV include, but are not necessarily limited to:

- Ocular hyperemia should be considered as an AE only if the subject complains of it or if the subject is discontinued because of ocular hyperemia
- Prostaglandin Associated Orbitopathy
- Iris discoloration
- Blepharitis
- Worsening in BCVA defined as ≥ 3 lines (≥ 15 letters)
- Subconjunctival hemorrhage
- Cataract
- Macular edema
- Conjunctivitis
- Keratitis
- Perforation of or trauma to the punctum and/or surrounding tissues
- Allergic reaction
- Chemosis

- Inflammatory reaction
- Epiphora, defined as clinically significant excessive tearing outside of normal limits
- Dacryocystitis
- Tearing with mucopurulent discharge
- Stenosis of the punctum
- Infection*

*Note: In the case of a suspected infection, a culture should be performed and the organism identified, if possible.

5.6. Procedures for Unmasking

When medically necessary, the Investigator may need to determine the treatment that has been assigned to a subject. The Investigator will contact the Sponsor with the details of the emergency unmasking request. Ocular Therapeutix will make the final determination if the unmasking request will be granted. If granted, the Investigator will be permitted to use the unmasking instructions available on site.

At the conclusion of the 12 Week visit, if both eyes no longer have the depot present or depots have been removed bilaterally, the Investigator may be unmasked to the treatment assignment of the subjects who were assigned to OTX-TP or PV as those subjects may require IOP-lowering drops.

5.7. Type and Duration of the Follow-up of Subjects after Adverse Events

Adverse Events (AEs) will be followed until:

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

Adverse events will be documented on the appropriate Case Report Form.

6. STATISTICAL ANALYSIS

6.1. Study Populations

Intent-to-Treat (ITT): The ITT population will include all randomized subjects with a primary study eye in which an intracanalicular depot was inserted. Analysis on the ITT population will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.

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

Safety: The Safety population will include all subjects who received any investigation study medication (OTX-TP or PV). Analyses performed on the Safety population will be according to the treatment the subjects actually received.

6.2. Unit of Analysis

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

6.3. Imputation Methods

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

Sensitivity analyses, to determine robustness of results, will be performed using Monte Carlo Markov Chain approach to impute non-monotone missing information and pattern mixture models control-based pattern imputation for monotone missing information (including subjects who drop out and data for time points after a subject's primary study eye is prescribed IOP-lowering drops), LOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops, and baseline time-consistent observation carried forward to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops and observed data only. Additionally, sensitivity analyses will be performed on the per protocol population using observed data only.

6.4. Hypotheses

H₀: The difference between study eyes that received OTX-TP and study eyes that received PV (OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is ≥ 0 mmHg for at least one time point over all visits.

H₁: The difference between study eyes that received OTX-TP and study eyes that received PV (OTX-TP minus PV), in mean IOP at the following time points: 8AM, 10AM, and 4PM at the 2 Week, 6 Week, and 12 Week Visits, is < 0 mmHg for all time points over all visits.

6.5. Efficacy Variables

6.5.1. Primary

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

6.5.2. Secondary

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

6.6. Safety Variables

The safety variables are:

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

6.7. Sample Size

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

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

6.8. Interim Analyses

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

- 1) All efficacy data will be cleaned and monitored prior to unmasking and conducting the interim analysis
- 2) No alpha adjustments for multiplicity will be made.

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

6.9. Methods of Analyses

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, standard deviations, and medians will be presented to one additional decimal place than reported in the raw values. Summaries for discrete variables will include frequencies and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between treatment groups will be calculated as OTX-TP minus PV and change from baseline will be calculated as follow-up visit minus baseline. The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment. For IOP the baseline time point will be defined as the last non-missing time equivalent measure prior to initiation of investigational treatment and after washout of previous IOP medication. All efficacy summaries will be presented for the primary study eye. Additional analyses may be reported for secondary study eyes.

All summaries will be presented by treatment group and where appropriate by visit.

6.10. Demographic and Baseline Medical History

Subject demographics: gender, ethnicity, race, age category (< 65 years and \geq 65 years), and iris color will be presented using discrete summary statistics. Age will also be presented using continuous summary statistics.

Non-ocular and ocular medical history will be summarized by treatment group using discrete summaries.

6.11. Efficacy Analyses

The primary analysis of the primary efficacy outcome will employ a linear model with IOP at the given visit (2 Week, 6 Week, and 12 Week) and time point (8AM, 10AM, and 4PM) as the response, time point specific baseline IOP as a covariate, and treatment as a main effect factor, using the ITT population with multiple imputation methods using Monte Carlo Markov Chain approach to impute missing data and using LOCF to impute data for time points after a subject's study eye is prescribed IOP-lowering drops. Each time point within each visit will be modeled separately. The least squares mean differences (test – control) between OTX-TP and PV will be presented along with 2-sided 95% confidence intervals (CIs) around the difference and 2-sided p-values testing the difference equal to 0. Inference will be made on the 2-sided p-value at a 2-sided alpha = 0.05 at each time point and visit. The study will be considered a success if the 2-sided p-value < 0.05 (demonstrating statistical superiority) and the point estimate of the difference is < 0 at all time points over the three visits.

Similar analyses will be conducted on the ITT data obtained after using each of the imputation methods as described in [Section 7.3](#) to assess the sensitivity of results.

Additional sensitivity analyses will be performed on the per protocol population using observed data only.

Two-sample t-test p-values and two-sided 95% t-distribution CI's will also be computed around the difference in mean IOP between treatment groups at each time point and visit for the primary analysis data (ITT population employing multiple imputation methods using Monte Carlo Markov Chain approach to impute missing data and using LOCF to impute data for time points after a subject's study eye is prescribed IOP-lowering drops as rescue therapy). Similar summaries will be presented on the ITT population using LOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy and for the ITT and per protocol populations using observed data only.

Mean change from baseline IOP will be analyzed similarly to the primary endpoint analysis, including all sensitivity analyses.

Mean percent change from baseline IOP will be analyzed using two-sample t-tests and two-sided 95% t-distribution CI's for the primary analysis data (ITT population employing multiple imputation methods using Monte Carlo Markov Chain approach to impute missing data and using LOCF to impute data for time points after a subject's study eye is prescribed IOP-lowering drops as rescue therapy). Similar summaries will be presented on the ITT population using LOCF to impute both missing data and data after a subject's primary study eye is prescribed IOP-lowering drops as rescue therapy and for the ITT and per protocol populations using observed data only.

IOP measures and change from baseline IOP measures from non-primary visits will be analyzed and summarized similarly to the mean percent change from baseline IOP.

Additionally, as secondary analyses to further understand efficacy within each previous ocular anti-hypertensive therapy category, the primary analysis strategy will be completed separately for the subgroups of subjects within each previous ocular anti-hypertensive therapy category.

6.12. Other Analyses

Visualization of the intracanalicular depot by the Investigator and by the subject will be summarized at each time point using discrete summary statistics.

Ocular complaints will be summarized using discrete summary statistics at the eye level as well as at the subject level for all eyes that received a depot.

6.13. Safety Analyses

The primary safety analysis will summarize treatment emergent ocular AEs (TEAE) separately for primary study eyes and secondary study eyes using discrete summaries at the eye and event level by system organ class and preferred term for each treatment group. A TEAE will be defined as occurring on or after the day treatment is initiated. Treatment emergent non-ocular AEs will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each treatment group. Treatment related treatment emergent ocular and non-ocular AEs will be summarized similarly. Treatment emergent ocular and non-ocular AEs will also be summarized by severity.

Slit lamp biomicroscopy and dilated funduscopy measures will be summarized at each time point using discrete summary statistics.

Visual acuity data will be summarized at each time point using both continuous summaries, including change from baseline, and discrete summaries, including change from baseline in the number of lines and the proportion of subjects with a worsening of ≥ 3 lines from baseline. Ocular hyperemia and ocular comfort will be summarized at each time point using discrete summary statistics.

7. GENERAL INFORMATION

7.1. Study Termination

Ocular Therapeutix reserves the right to discontinue the study at any stage, with suitable written notice to the Investigator and the local research ethics committee or regulatory authority. Similarly, the Investigator may withdraw from the study subject to providing written notification to Ocular Therapeutix within 30 days of their intent to withdraw. However, Ocular Therapeutix and the Investigator will be bound by their obligation to complete the follow up of subjects already randomized in the trial. The subjects must be followed according to the clinical protocol and information obtained during subject follow-up shall be reported to Ocular Therapeutix on follow-up CRFs.

All serious adverse events will be evaluated and if the Sponsor determines that unreasonable risk to the subject is possible, the study will be terminated, and all regulating authorities and participating Investigators will be notified. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect.

A terminated investigation may not be resumed without the local research ethics committee or regulatory authority approval, as required.

7.2. Monitoring

The Investigator and the investigating center will permit authorized clinical research personnel and clinical monitors from Ocular Therapeutix and/or designee(s) employed by Ocular Therapeutix to review completed CRFs, IRB decisions, and Investigator and clinical site records at regular intervals throughout the study. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations and/or hospital policies prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor. Further details of the study monitoring will be outlined in a Monitoring Plan.

If the monitor discovers that the Investigator is not complying with the signed Investigator Agreement, the investigational plan, or other applicable regulations, or any conditions of approval imposed by the reviewing IRB, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, investigational product shipments to the Investigator may be discontinued and the Investigator's participation in the investigation terminated. The monitor shall also require such an Investigator to dispose of or return the product, unless this action would jeopardize the rights, safety, or welfare of a subject.

7.3. Retention of Documentation

The Investigator will maintain all study related documentation including all correspondence, records of financial interest, individual subject records, informed consent forms, all intracanalicular depot accountability records, the protocol with any/all amendments, all correspondence with and approval from the IRB, the budget agreement, the Investigator agreement, and copies of electronic case report forms for 2 years after the latter of the following two dates:

- a. The date on which the investigation is terminated or completed, or
- b. The date that the records are no longer required for purposes of supporting an application to a regulatory agency.

The files may be discarded only upon notification from OTX. To avoid error, the Investigator should contact Ocular Therapeutix before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, in accordance with the Clinical Trial Agreement (CTA), Ocular Therapeutix should be contacted if the Investigator plans to leave the investigational site so that appropriate arrangements can be made for the transfer of the records to the appropriate designee at the study site.

7.4. Photos and Videos

The Investigator may be asked to record the insertion procedure and follow-up assessments, and to collect photographs of the eye. The videos and photographs should be identified only using the subject number and subject initials and should not contain any identifiers such as the subject's name or birth date. The video and photographs will be used for training, advertising or in scientific conferences, journals or magazines.

8. COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS AND ADMINISTRATIVE ISSUES

The study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines, and consistent with the 2013 version of the Declaration of Helsinki. In addition, all applicable local, state and federal requirements relevant to the use of intracanalicular depots will be adhered to.

8.1. Protection of Human Subjects

8.1.1. Compliance with Informed Consent Regulations

An IRB approved consent form, signed and dated by both the subject and the approved study staff presenting the consent, is required from each subject prior to enrollment into the study, and before any study specific procedures are initiated.

If at any point during the subject's participation in the study the Informed Consent Form requires revision (e.g., due to a protocol amendment or significant new safety information) it is the Investigator's responsibility to ensure that the revised ICF is approved by Ocular Therapeutix and the IRB. The updated and IRB approved ICF must be presented to the subject, and signed and dated by both the subject, and the study staff presenting the consent as per IRB requirements.

8.1.2. Compliance with Institutional Review Board Regulations

The Investigator must obtain approval from appropriate the IRB prior to initiating the study and re-approval at least annually.

8.2. Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure the confidentiality of the data in accordance with local, state and federal laws and regulations. Monitors, auditors and other authorized representatives of Ocular Therapeutix, the IRB approving this study, the Food and Drug Administration, and other regulatory agencies, as appropriate, will be granted direct access to the study subjects' original medical and study records for verification of the data and/or clinical trial procedures.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the intracanalicular depot may ultimately be marketed, but the subjects' identity will not be disclosed in these documents.

9. LABELING, PACKAGING, STORAGE AND ACCOUNTABILITY OF INTRACANALICULAR DEPOT

9.1. Labeling/Packaging

OTX-TP and the PV will be identical in appearance and will be supplied in identical packaging. The packages will be labeled with a unique number based on the randomization scheme such that the identity of the intracanalicular depot cannot be identified by the study site.

9.2. Product Storage

OTX-TP and PV must be stored in a secure area accessible only to the Investigator and their designee(s) and in accordance with the conditions specified in the IFU (between 2°C and 8°C).

9.3. Product Accountability

The intracanalicular depot is to be administered only by the Principal Investigator or Sub-Investigator, in accordance with the protocol, and only to subjects enrolled in the study. The Investigator must keep an accurate accounting of all OTX-TP and PV received from Ocular Therapeutix on the provided accountability forms. Accountability will include details of receipt of investigational product from the Sponsor, administration of the investigational product to study subjects, and return of investigational product.

9.3.1. Product Return or Disposal

All unused intracanalicular depots will be returned to the Ocular Therapeutix upon request by the Sponsor and documented on the accountability form. All product shipment will be accompanied by a completed Ocular Therapeutix Product Return Log.

10. APPENDICES

[Appendix A](#) : Instructions for Determining Eligibility of Subjects Exiting From Prior Ophthalmic Investigational Research Studies

[Appendix B](#) : Procedures for Study Assessments

[Appendix C](#) : Instructions for Removal of OTX-TP or PV

APPENDIX A. INSTRUCTIONS FOR DETERMINING ELIGIBILITY OF SUBJECTS EXITING FROM PRIOR OPHTHALMIC INVESTIGATIONAL RESEARCH STUDIES

Please refer to the table below for determining eligibility and Visit Schedule for subjects who have exited an ophthalmic investigational research studies within 8 weeks of the Screening Visit. Please consult the Medical Monitor (MM) after obtaining informed consent. Written approval from the Medical Monitor will be required for the subject to continue in the Study after the Screening Visit.

Subject has just exited a study for <i>any</i> ophthalmic indication and may be interested in the Ocular Therapeutix (OTX) investigational research study			
→ Complete Informed Consent and Screening Visit for OTX investigational research study			
→ Begin 6 week prior trial recovery period <i>and</i> stop all glaucoma/ocular hypertension (OHT) medications			
Was this an investigational research study for ocular anti-hypertensive therapy?			
YES: was subject stable and IOP controlled on ocular anti-hypertensive medication for 8 weeks prior to start of non-OTX ophthalmic investigational research study?		NO: i.e., investigational research study was for another ocular indication that is not excluded by protocol. Was subject stable and IOP controlled on ocular anti-hypertensive medication for 8 weeks prior to start of non-OTX ophthalmic investigational research study?	
Is there history of monotherapy with a Prostaglandin Analogue (PGA) and a response?		Is there history of monotherapy with a Prostaglandin Analogue (PGA) and a response?*	
<p>YES: was there a 5 mm Hg or greater increase in IOP after PGA washout prior to or during non-OTX ophthalmic investigational research study? Documentation of Med History confirmed by MM?</p> <p style="text-align: center;">↳ If Yes: Proceed to IOP Confirmation Visit at the end of the 6 week prior trial recovery period. (8 AM IOP must be ≥ 24 and ≤ 34 mm Hg).</p> <p style="text-align: center;">↳ If Yes: return in 2 weeks for Baseline Visit 1. (Stratum C).</p> <p>If No: Screen Failure</p>	<p>NO: is subject PGA naïve or on therapy with a PGA plus a second agent at time of entry to non-OTX ophthalmic investigational research study?</p> <p style="text-align: center;">↳ If Yes: At the end of the 6 week prior trial recovery period, perform IOP Confirmation Visit and start 2 week run-in period with PGA. If adequate response at Run-in Visits 1 and 2, then 6-week washout period and proceed to Baseline Visit 1 (Stratum B).</p> <p>If No: Screen Failure.</p>	<p>YES: was there a 5 mm Hg or greater increase in IOP after PGA washout prior to or during non-OTX ophthalmic investigational research study? Documentation of Med History confirmed by MM?</p> <p style="text-align: center;">↳ If Yes: Proceed to IOP Confirmation Visit at the end of the 6 week prior trial recovery period. (8 AM IOP must be ≥ 24 and ≤ 34 mm Hg).</p> <p style="text-align: center;">↳ If Yes: return in 2 weeks for Baseline Visit 1. (Stratum C).</p> <p>If No: Screen Failure</p>	<p>NO: is subject PGA naïve or on therapy with a PGA plus a second agent at time of entry to prior non-OTX ophthalmic investigational research study?</p> <p style="text-align: center;">↳ If Yes: At the end of the 6 week prior trial recovery period, perform the IOP Confirmation Visit and start 2 week run-in period with PGA. If adequate response at Run-in Visits 1 and 2 is demonstrated, then start 6-week washout period and proceed to Baseline Visit 1 (Stratum B).</p> <p>If No: Screen Failure.</p>

*If subject is exiting a prior non-OTX ophthalmic investigational research study for an allowed indication other than ocular anti-hypertensive therapy and has continued PGA monotherapy during the study, subject (again, with Medical Monitor approval) should discontinue PGA therapy and proceed to Baseline Visit 1 at the end of the 6 week prior trial recovery period (Stratum A).

APPENDIX B. RECOMMENDED PROCEDURES FOR STUDY EXAMINATIONS

A. Best Corrected Visual Acuity

BCVA will be measured without refraction using a pinhole or while the subject is wearing his/her glasses, if the subject normally wears glasses or contact lenses.

Visual acuity is to be measured using an ETDRS (i.e., logMAR) chart at a viewing distance of 4 meters. Subjects are required to read the chart from the top to the bottom until he or she can no longer make a meaningful attempt. The visual score is to be calculated based on an assigned value of 0.02 logMAR per letter.

If visual acuity is so poor that the subject cannot read any of the largest letters at 4 meters, than acuity is to be measured at 2 meters and the appropriate conversions made.

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

B. Slit Lamp Biomicroscopy Examination

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

The clinician will use a slit lamp, which is a table-mounted binocular microscope to assess the following as normal, abnormal clinically significant or abnormal not clinically significant:

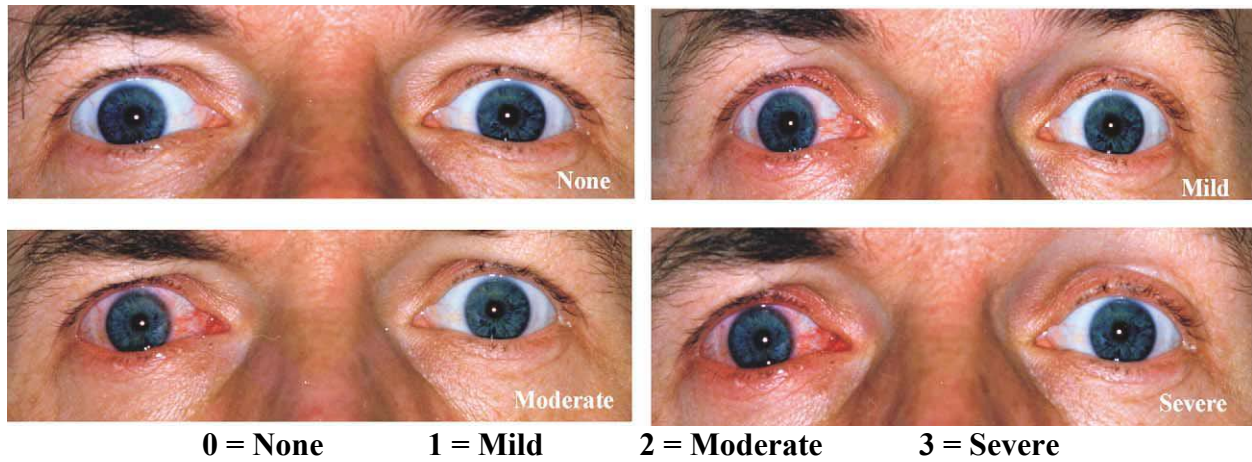
- Eyelids
- Conjunctiva
- Iris
- Cornea
- Anterior Chamber
- Lens
- Vitreous

Explanation/comments should be provided on the case report form for any abnormal observations.

C. Ocular Hyperemia Grading

The following scale⁹ will be used to grade the ocular hyperemia:

Figure 2: Scale for Grading Ocular Hyperemia



Using the slit lamp biomicroscope, the subject's eye(s) should be examined and compared to the images depicted in Figure 2. A grade (0-3) should be assigned and noted on the appropriate CRF based on the images. 0.5 increments may be used if the subject's hyperemia is between 2 images.

D. Pachymetry

The following procedure is recommended for conducting pachymetry:

Central corneal thickness measurements of each eye will be made at the screening visit using an ultrasonic pachymeter. Measurements will be made after IOP is taken. For ultrasound probes, the Probe Quality Factor must be greater than or equal to 85% (if applicable). With the subject seated and visualizing a consistent fixation target, position the probe tip on the cornea, perpendicular to the corneal surface, on the visual axis (i.e., centered on the pupil). Once the probe tip is positioned properly, take a measurement. A total of 3 acceptable measurements, as described above, should be made for each eye, and the 3 measurements will be recorded in microns. The average of the 3 measurements will be calculated to determine subject eligibility.

⁹ Parrish, R. K., Palmberg, P., and Sheu, W-P. A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients With Elevated Intraocular Pressure: A 12-week, Randomized, Masked-evaluator Multicenter Study, *Am J Ophthalmol.*, Vol. 135, No.5, p. 688-703, May 2003.

E. IOP Measurement

Goldmann tonometry as the international gold standard for tonometry is quite accurate and reproducible if proper technique is used. When performing Goldmann tonometry the following procedures should be followed:

1. Pre-tonometry procedures: Set tonometer in the correct position and make sure the prism is in the horizontal position on the slit lamp. Set the tension at 1 mmHg. Use Cobalt filter with slit beam open maximally with the angle between the illumination and the microscope at approximately 60 degrees.
2. Instill one drop of a topical anesthetic and a moistened fluorescein strip may be lightly touched against the tarsal conjunctiva of the lower lid of each eye, taking care not to flood the ocular surface with fluorescein dye. Alternatively a drop of topical anesthetic-fluorescein (e.g., Fluress) solution may be instilled into the lower conjunctival fornix of each eye, taking care not to flood the ocular surface with fluorescein dye. Ask subject to blink a few times just prior to tonometry.
3. Place subject in adjustable chair so chin can fit comfortably on the slit lamp chin rest and the forehead can be snug against the forehead bar.
4. Apply tonometer to the subject's eye while subject looks straight ahead and increase the force of applanation until the observer sees the inner portion of the two half fluorescein circles are touching. Record pressure on the case report form.

IOP measurement will be masked based on the following procedure:

Measurements will be taken by two qualified independent study site personnel using a Goldmann applanation tonometer affixed to a slit lamp with the subject seated. One person will adjust the dial in masked fashion and a second person will read and record the value. The subject and slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Both eyes will be tested, with the right eye preceding the left eye. Each IOP measurement is to be recorded.

One person ("the measurer") looks through the binocular viewer of the slit lamp at low power. The tension knob is pre-set at a low pressure value (4 to 6 mmHg). The measurer follows the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the measurer takes his/her fingers off the tension knob and the second person ("the reader") reads and records the IOP reading along with the date and time of day in the source document, thus maintaining a masked IOP reading. Two measurements should be performed, and if the IOP is within 1 mm Hg, the average of the first two measurements should be recorded. If the IOP from the first two readings shows a greater than 1 mm Hg difference, a third reading should be taken and the average of all three readings recorded.

F. Dilated Fundus Exam

Assessments should be conducted using indirect ophthalmoscopy. It is acceptable to perform the indirect ophthalmoscopy examination without scleral depression. Each of the following will be evaluated and documented as normal, abnormal clinically significant or abnormal not clinically significant: macula, peripheral retina and optic nerve. The cup to disc (C/D) ratio will also be measured. Explanation/comment should be provided on the case report form for any abnormal pathology.

G. Gonioscopy

The following procedure is recommended for conducting gonioscopy:

Clean and sterilize the front (curved) surface of the goniolens. Apply lubricating fluid to the front surface. Anaesthetize the subject's cornea with topical anesthetic. Prepare the slit lamp for viewing through the goniolens. Gently move the subject's eyelids away from the cornea. Slowly apply the goniolens to the ocular surface, forming suction. Fine-tune the slit lamp to optimize the view. The angle can now be viewed by rotating the lens gently through 360 degrees. Grade the angle based on the Shaffer System as follows. Subjects with a Grade 2 or lower should be excluded for angle closure glaucoma.

Grade 4 - 45° to 35° angle Wide open

Grade 3 - 35° to 20° angle Wide open

Grade 2 - 20° angle Narrow

Grade 1 - ≤ 10° angle Extremely narrow

Slit - 0° angle Narrowed to slit

H. Automated Perimetry

The following procedure is recommended for conducting automated perimetry.

Measure the subject's pupils (to the nearest 0.5 mm). If they are less than 3 mm in diameter, dilate them with 2.5% phenylephrine drops, unless contraindicated. If the brow is heavy or the upper lid is drooping, tape accordingly. Visual field results must be reliable (i.e., 33% fixation losses, false positive or false negative errors) or the field should be repeated within two weeks. Visual field examinations will be performed using a Humphrey automated perimetry test (full threshold 24-2 program or SITA standard or FAST assessment). Preferred equipment is the Humphrey 700 HFA-2 series machines (e.g., 740 or 750). Visual fields will be reported as normal or abnormal and the mean deviation will also be recorded in decibels (dB).

Begin by testing the right eye. Adjust the chin rest and the table height as needed to achieve proper alignment as well as to maintain the subject in a comfortable seated position throughout the test. It is permissible to encourage the subject occasionally if the subject seems to be fatigued or losing concentration, and to allow the subject to pause and rest if necessary. The subject should also be informed that a good time to blink is when the response button is pushed so as not to affect the results of the test. Repeat for the left eye.

I. Punctum Examination

The punctum and surrounding area is to be examined and the following assessed:

- Punctal appearance: score as normal or abnormal
- Lid apposition: score as normal or abnormal
- Tear meniscus: score as normal or abnormal

All abnormal findings will be graded as clinically significant or not clinically significant.

Explanation/comments should be provided on the case report form for any abnormal observations.

APPENDIX C. INSTRUCTIONS FOR REMOVAL OF THE INTRACANALICULAR DEPOT

The intracanalicular depot can be removed either via saline irrigation or application of manual pressure, as described below.

Application of Manual Pressure

1. Identify the intracanalicular depot visually through the punctal tissue.
2. Place the blunt end of an instrument, e.g. punctum dilator or equivalent, next to the distal end of the intracanalicular depot.
3. Apply gentle pressure by pressing on the instrument in an outward motion towards the punctum, until the intracanalicular depot is expressed out of the punctum.

Saline Irrigation

1. Ensure the punctum and canaliculus is sufficiently dilated.
2. Fill a sterile syringe and fixed cannula with sterile saline.
3. Insert the cannula into the canaliculus.
4. Insert until it stops, and simultaneously rotate the syringe horizontally.
5. Press slowly on the syringe plunger to flush the intracanalicular depot.
6. In order to help assess whether the flush is complete, it may be helpful to ask the subject to report when they taste saline or feel it in their nose.