1. CLINICAL PROTOCOL

Clinical Protocol Number:	IPC-02-2015
Final Clinical Protocol Date:	1 December 2015
Clinical Protocol Version:	3.0
Clinical Protocol Amendment Date:	26 June 2016
Clinical Protocol Amendment:	2.0
Study Drug Identification:	Trabodenoson/Latanoprost Fixed-Dose Combination
Clinical Protocol Title (Long):	A Phase II, Randomized, Double-masked Study to Evaluate the Efficacy, Safety and Tolerability of Topical Ocular Administration of Fixed-Dose Combinations of Trabodenoson and Latanoprost in Subjects with Ocular Hypertension or Primary Open-Angle Glaucoma.
Clinical Protocol Title (Short):	A Phase II Investigation of Fixed-Dose Combinations of Trabodenoson and Latanoprost in Subjects with Ocular Hypertension or Primary Open-Angel Glaucoma.
Study Phase:	Phase II
U.S. IND NO.	10092
Sponsor:	Inotek Pharmaceuticals Corporation 91 Hartwell Avenue, Second Floor Lexington, MA 02421, US Tel: 781-676-2100 Fax: 781-676-2155
Sponsor Medical Monitor:	Cadmus C. Rich, M.D., MBA, CPE Inotek Pharmaceuticals Corporation VP of Medical Affairs and Clinical Development
Sponsor Signatory:	Rudolf Baumgartner, M.D. Executive Vice President and Chief Medical Officer

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

SIGNATURE PAGES

1.1. Clinical Signature Page

Clinical Protocol Number:	IPC-02-2015
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Cadmus C. Rich, M.D., MBA, CPE
VP of Medical Affairs and Clinical Development or designee

Signature: _____

Date: 28-JUN-16

Rudolf Baumgartner, M.D.
Executive Vice President & Chief Medical Officer or designee

Signature: _____

Date: 28 June 2016

1.2. Investigator Signature Page

Clinical Protocol Number:	IPC-02-2015
Final Clinical Protocol Date:	1 December 2015
Clinical Protocol Version:	3.0
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Clinical Protocol Amendment	2.0
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I have read and understand this protocol and concur with the study design. I agree to participate as an Investigator and to conduct the study in accordance with the protocol, the Food and Drug Administration (FDA) Code of Federal Regulations (CFR) for Good Clinical Practice (GCP), the International Conference on Harmonization (ICH) Guidelines and local regulations.

Site Number: _____

Investigator's Name: _____

Investigator's Signature: _____

Date: ____/_____/_____

dd mmm yyyy

2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Inotek Pharmaceuticals Corporation	
Name of Investigational Product: Trabodenoson (INO-8875) ophthalmic formulation	
Title of Study: A Phase II, Randomized, Double-masked Study to Evaluate the Efficacy, Safety and Tolerability of Topical Ocular Administration of Fixed-Dose Combinations of Trabodenoson and Latanoprost in Subjects with Ocular Hypertension or Primary Open-Angle Glaucoma.	
Study center(s): Multi-center, approximately 40 sites within the United States (US).	
Study Duration: ~17 Months	**Phase of development:** 2
Objectives: **Primary objective:** • To evaluate the efficacy of different topical ocular doses of trabodenoson (3.0% and 6.0%) when added to latanoprost (0.005% or 0.0025%), one drop daily to both eyes over two consecutive 4 week periods. **Secondary objectives:** • To evaluate the tolerability and safety of different doses of trabodenoson (3.0% and 6.0%) when added to latanoprost (0.005% or 0.0025%), one drop daily to both eyes over two consecutive 4 week periods.	
Study Design: This is a phase II, randomized, double-masked study to evaluate the efficacy and tolerability of topical ocular delivery of fixed-dosed combinations of trabodenoson and latanoprost in subjects with OHT or POAG. All subjects who meet the study's enrollment criteria following Screening will undergo washout of all prohibited medications (if washout is needed), including their routine glaucoma medications. During the Placebo Run-In Period, placebo (vehicle control matched to trabodenoson) is applied twice daily to both eyes in all subjects. During the Treatment Period, study drug is applied to both eyes for a total of 8 weeks. Each subject will be assigned 4 weeks of AM and 4 weeks of PM dosing in a masked manner. The Treatment Period will be followed by an Observation Period of approximately 7 days wherein no study eye drops are instilled. The purpose of the study is to assess the efficacy, tolerability, and safety of binocular topical application of different doses of trabodenoson (3.0% and 6.0%) when combined with latanoprost (0.005% or 0.0025%) one drop daily over two consecutive 4 week periods in subjects with POAG or OHT. Data collection will include efficacy (masked-IOPs), local (ophthalmic) and systemic tolerability and safety assessments.	
Number of subjects (planned): ~165	
Inclusion / Exclusion Criteria **Inclusion Criteria:** 1. Subject provides written informed consent prior to any study-related procedure not part of normal medical care.	

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2. Subject has the diagnosis of OHT or POAG (subjects with secondary, exfoliative, and/or pigmentary glaucomas are excluded from the trial).
3. Subject with at least 1 eye that meets each of the following criteria in the same eye: (1) mean 8AM IOP ≥25 and ≤34 on Placebo Run-In Visit, Day -1, and Day 1 (AM predose) mmHg; and (2) mean IOP ≥21 mmHg on Day -1 at 8 hours post-dose (~4PM). IOP is taken by Goldmann Applanation Tonometry and is not corrected for central corneal thickness. (If one eye fails this criterion but the second eye meets this criterion and all other enrollment criteria are met, the subject can be randomized).
4. Subject is aged 18 years or older;
   If female, subject must not be pregnant or nursing, and is either:
   a. Not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or
   b. Of childbearing potential and meets at least 1 of the following:
      i. Is practicing an effective method of contraception (e.g., a. double barrier method, b. oral/parenteral contraceptives plus barrier, c. intrauterine device plus barrier), or
      ii. Has a vasectomized partner (at least 90 days post vasectomy procedure), or
      iii. Is practicing abstinence from sexual intercourse.

   Subjects must be willing to practice the chosen contraceptive method or remain abstinent during the conduct of the study and for at least 1 month after last dose of study medication.

   Non-vasectomized males (with a partner of childbearing potential) are required to practice effective birth control methods (e.g., abstinence, use of condom [or other barrier device] along with partners oral/parenteral contraceptives) during the conduct of the study and for at least 1 month after last dose of study medication;

Exclusion Criteria:

1. Subject has clinically significant abnormalities in their medical history or from the results of the physical examinations, vital signs, or clinical laboratory tests performed at Screening or during the Placebo Run-in period that may put the subject at risk in this trial or cause the subject not to complete the trial per protocol by the Investigator's judgment (Examples of clinically significant laboratory results include: both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2 times upper limit of normal (ULN) or either >3.0 times ULN, Total bilirubin > 2.0 times ULN, BMI > 40 kg/M^2, Hemoglobin A1C > 8.0%, or creatinine clearance <50 ml/min).
   Note: Subject with creatinine clearance <50 ml/min may still be eligible upon review and written approval by the Inotek Medical Monitor or his designee (a Board-certified physician) following review of the current medications, laboratory values, and medical history.
2. Subject has any new clinically significant field loss within the past year in either eye, or any non-glaucomatous ophthalmologic disease that might exacerbate during the trial.

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3. Subject's ETDRS BCVA Snellen equivalent is worse than 20/80 in either eye.
4. Subject has a vertical cup-to-disc ratio >0.8 or an IOP in either eye above 34 mmHg at any examinations prior to Day 1 dosing in either eye.
5. Subject has a central corneal thickness <490 µm or >610 µm at Screening in both eyes. (If only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).
6. Subject is currently taking any drug that in the opinion of the Investigator might affect IOP including oral or ocular glucocorticoids. (Low to moderate stable doses [no change for 30 days] of nasal or dermatologic steroids are permitted).
7. Subject received oral/systemic beta-blocker within 28 days of screening.
8. Subject has history of clinically significant trauma to the globe of both eyes. (If only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).
9. Subject has had ocular or orbital surgery (conventional or laser, such as SLT or ALT) to both eyes (If only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).

   However, the following procedures are not exclusionary:

   a. At least 1 year prior to Screening: retinal laser, cataract extraction (no surgical complications such as capsular rupture or vitreous loss), peripheral iridotomy (with otherwise open angle per Exclusion Criteria # 25), and other extraocular (e.g., tear duct, pterygial, or palpebral) surgeries.
   b. At least 180 days prior to Screening: uncomplicated YAG laser capsulotomy.
10. Subject has any ocular abnormality that in the opinion of the Investigator might preclude reliable applanation tonometry in either eye.
11. Subject has a fundus in either eye that in the opinion of the Investigator cannot be well-visualized with pupillary dilation.
12. Subject has a history of or current retinal condition that, in opinion of the Investigator, could affect BCVA (i.e., diabetic retinopathy, central or branch retinal vein occlusion, cystoid macular edema, etc).
13. Subject cannot, or is unwilling to, function without contact lenses from Placebo Run-In Visit through the completion of the End-of-Study Visit.
14. Subject uses oral sympathomimetics (e.g., pseudoephedrine) within 14 days of start of Placebo Run-In Period, or the Investigator feels may be required during the study.
15. Subject used inhaled bronchodilators and/or inhaled steroids more than once per week on the average in the past 90 days, or the Investigator feels may be required during the study.

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16. Subject uses dipyridamole, theophylline, or other adenosine antagonist medication within 4 days of the start of the Placebo Run-In Period, or the Investigator feels may be required during the study.
17. Subject used any of the following drugs (alone or in combination) for treatment of ophthalmologic illness:
    a. Parasympathomimetics or carbonic anhydrase inhibitors within 4 days of the start of the Placebo Run-In Period.
    b. Sympathomimetics or alpha adrenergic agonists within 14 days of the start of the Placebo Run-In Period.
    c. Topical ocular beta-blockers with 28 days of the start of the Placebo Run-In Period.
    d. Prostaglandins, prostamides or prostanoids within 35 days of the start of the Placebo Run-In Period.
18. Subject has any acute or chronic ophthalmologic illness requiring use of any non-IOP lowering ocular medication at screening and throughout study conduct (specific tear supplements are allowed as described in Section 9.3.9).
19. Subject has a history of significant cardiac rhythm disturbance or a complete left bundle branch block (LBBB). (Examples of significant rhythm disturbances include PR intervals above 220 msecs, history of 2nd or 3rd degree blocks, acquired or congenital long QT syndrome, atrial fibrillation or other atrial arrhythmia, ventricular arrhythmia, bradycardia (<50 bpm), or ventricular pre-excitation (WPW). Subjects with PR intervals between 221 msec and 240 msec (inclusive) may only be enrolled following receipt of the written approval of the Inotek Medical Monitor or his designee (a Board-certified physician) so as to ensure an opportunity to review, as necessary, the subject's ECG, medication and medical history with the study cardiologist.)
20. Subject has clinically significant corneal and/or conjunctival findings (including clinically significant hyperemia) related to any recurrent or chronic conditions including allergic conjunctivitis, blepharitis, pegueculae/pterygium, or keratoconjunctivitis sicca that might recur or worsen during the study and confound the ophthalmologic safety data.
21. Subject has a closed or occludable angle on gonioscopy (chamber angle less than 10 degrees), a history of angle-closure, or any non-POAG glaucoma (including neovascular glaucoma) in both eyes at Screening (if only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).
22. Subject has a history of, or current, uveitis or any other inflammatory intraocular disease of either eye, unless the inflammatory process was caused by a topical ophthalmic medication that was stopped and has been in full remission for at least 1 year.
23. Subject received any investigational device or product within 30 days prior to the start of the Placebo Run-In Period or has ever been rejected on medical or psycho-social grounds from participation in a clinical trial.

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24. Subject has a history of allergy to more than 3 structurally unrelated medications, unless approved in writing by the Sponsor Medical Monitor (or their designees, a Board-certified physician). 25. Subject has a history of significant sensitivity to latanoprost, trabodenoson, benzalkonium chloride, EDTA, or any of the other study drug excipients, or to local anesthetics or topical ophthalmic anesthetics such as lidocaine or to fluorescein. 26. Subject is unable to discontinue the use of prohibited medications delineated in Section 9.3.9 from the start of the Placebo Run-In Period through completion of the End-of-Study Visit. 27. Subject is unable to limit their daily consumption to ≤ 24 ounces of beer, ≤ 8 ounces of wine, or ≤ 4 ounces of liquor from the start of the Placebo Run-In Period through completion of the End-of-Study Visit. 28. Subject has any recent (acute) or chronic medical, psychiatric, drug or alcohol, or social problem that might in the opinion of the Investigator: (1) interfere with the subject's performance or completion of the trial; (2) obfuscate the subject's study data; or (3) render the subject unable to understand the nature, scope, and possible consequences of the study. Or subject is likely to be noncompliant with the protocol (e.g., uncooperative attitude; a history of significant mental depression, panic attacks, or manic episodes; inability to return for all planned visits, and/or unlikelihood of completing the study). 29. Subject is involved in any aspect of trial conduct including, Investigator, Sub-Investigator, other site staff, and/or immediate family members (first degree relative, spouse, adoptees, legal dependents) or employee of Inotek.
Investigational product: The latanoprost-only ophthalmic solutions for use in this trial are sterile, isotonic, buffered aqueous solutions of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL contains either 25 (0.0025%) or 50 (0.005%) micrograms of latanoprost. Benzalkonium chloride (BAC), 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection. Trabodenoson/latanoprost Fixed Dose Combinations (FDCs) are aqueous ophthalmic suspensions containing latanoprost and trabodenoson with a pH of approximately 6.5, containing 0.01% BAK and 0.03% Ethylenediaminetetraacetic acid (EDTA) as preservatives. The inactive ingredients are: carboxymethyl cellulose, polysorbate 80, monobasic sodium phosphate, boric acid, sodium chloride, and water for injection. The matched vehicle control/placebo (MVC/placebo) product is composed of the same inactive ingredients as the trabodenoson/latanoprost FDCs, but without trabodenoson and latanoprost.

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Study Endpoints:

Primary Efficacy Endpoint:

- Daily IOP-change from diurnal baseline (average of the 4 diurnal changes from baseline calculated during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.

Secondary Efficacy Endpoints:

- Daily IOP (average of the 4 serial IOPs taken during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.
- Daily IOP-change from study baseline (average of the 4 changes from study baseline calculated during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.
- Mean IOP at 8AM, 10AM, 12PM, and 4PM for the subject's 'study' eye calculated at the end of each of the 4 weeks of treatment for each of the doses/combinations tested.
- IOP change from diurnal baseline [this is the time-matched subtraction of each of the 4 IOP timepoints of the circadian curve post randomization from the pre-randomization circadian curve] calculated at the end of the 4 weeks of treatment for each of the doses/combinations tested.
- IOP change from study baseline [this calculates the change in IOP from the 8AM Day 1 baseline IOP] calculated at the end of the 4 weeks of treatment for each of the doses/combinations tested.

Statistical methods:

To address the primary objective of this trial, based on an assumed SD of 3.3 mmHg, a sample size of 30 subjects in each group will provide an estimate of the effect on IOP with a 95% Confidence Interval with a ½ width (precision) of no greater than 1.2 mmHg.

In order to compensate for an anticipated drop-out rate of 10%, approximately 33 subjects will be enrolled in each of the 5 treatment groups in order to complete the trial with approximately 165 enrolled subjects and a total of 150 evaluable subjects.

All analyses will be presented by treatment group. Continuous variables will be described as the mean, median, standard deviation and range of n observations. Categorical data will be described with contingency tables including frequency and percent. Statistical analysis and data descriptions will be carried out using SAS statistical analysis software (SAS Institute, Inc., Cary, NC) version 9.3 or higher.

Of note, the Statistical Analysis Plan (SAP) will supersede the protocol for all statistical purposes including endpoints, hierarchy, and comparisons of interest, subgroups and so forth.

SCHEDULE OF ASSESSMENTS

Note: In the tables below, the number preceding a check denotes the number of times that a procedure is performed during that visit. For example, 3√ means that procedure is performed 3 times during that visit (specific timepoints are described in Section 9.2). If no number appears, then the procedure is performed only once.

The order of the assessments listed in Table 7, is random. However, throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any of the external eye assessments. Masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs, or blood sampling) so as not to affect the IOP results. Investigators and site personnel will perform study procedures in their appropriate order, as delineated in the clinical protocol.

Table 7: Schedule of Assessments

Study Period:	Screening Period Range	Washout and Placebo Run-in Period: Washout Range: 4 to 39 Days [f] Placebo Run-in Range: 5 to 9 Days			Treatment Period: Day 1 to Day 56 (± 2)			Observation Period: 7 Days (± 1) after EOT
Visit: **Procedure:**	1 to 14 Days	Washout Visit [e]	Placebo Run-In Visit [a]	Day -1 [a]	Day 1 [a]	Day 28 [a] (± 2)	End-of- Treatment (EOT) Visit Day 56 [a] (± 2)	End-of-Study (EOS) Visit [g] 7 Days (± 1) after EOT
Informed consent procedures	√							
Demographics and medical history	√							
Medication History / Concomitant medications	√	√	√	√	√	√	√	√
Enrollment criteria and/or safety data review	√	√	√	√	√			
Subject randomization					√			
Physical examination, complete (C) or directed (D)	√C				√D			√C
Height / weight	√							
Clinical laboratory tests (Central Lab)	√		√			√		√
Pregnancy test for females, central (C) or at the site (S)	√C Serum			√S Urine			√S Urine	
Adverse events review /reporting	√	√	√	√	√	√	√	√
Modified ETDRS-BCVA	√		√	√	√	√	√	√
External eye examination [h]	√		√ [h]	√ [h]	√	√ [h]	√ [h]	√
Slit Lamp examination	√		√	√	√	√	√	√
Masked-IOPs	√		√	4√	√	4√	4√	√
Dilated Fundus examination	√							√
Vital signs	√		√	√	√	√	√	√
12-Lead ECG	√		√					√
Gonioscopy [c]	√							

Study Period:	Screening Period Range	Washout and Placebo Run-in Period: Washout Range: 4 to 39 Days [f] Placebo Run-in Range: 5 to 9 Days			Treatment Period: Day 1 to Day 56 (± 2)			Observation Period: 7 Days (± 1) after EOT
Visit: / Procedure:	1 to 14 Days	Washout Visit [e]	Placebo Run-In Visit [a]	Day -1 [a]	Day 1 [a]	Day 28 [a] (± 2)	End-of- Treatment (EOT) Visit Day 56 [a] (± 2)	End-of-Study (EOS) Visit [g] 7 Days (± 1) after EOT
Central corneal thickness [d]	√							
Visual field test [b]	√							√
Drug/Dosing accountability				√	√	√	√	
Washout prohibited medication		√	√	√				
Study drug dosing					BID	BID	QAM	
Placebo Run-In dosing			BID	BID				

[a] On Placebo Run-In Visit and Days -1, 1, 28, and 56 all procedures will take place at the Investigational site.
[b] Measurements can be historical values within 90 days.
[c] Measurements can be historical values within 180 days.
[d] Measurements can be historical values within 1 year.
[e] Upon conclusion of all Screening Period activities, subjects who still meet the study enrollment criteria are invited to attend a Washout Period Visit (if washout is needed). This visit may be accomplished in person at the investigative site or by phone.
[f] Minimum length of washout required is described in Table 5.
[g] End-of-Study Visit is calculated as 7 Days (± 1) after the actual occurrence of the EOT Visit.
[h] Hyperemia assessments performed on Placebo Run-in Visit, Day -1, Day 28, and Day 56.

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4. LIST OF ABBREVIATIONS

Abbreviation	Definition
ß	Beta
°C	Degrees Celsius
µg	Microgram
µm	Micron
A_1	Adenosine receptor sub-type 1
A_{2A}	Adenosine receptor sub-type 2a
A_{2B}	Adenosine receptor sub-type 2b
A_3	Adenosine receptor sub-type 3
AE	Adverse event
ALT	Alanine aminotransferase
AM	Morning
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from time zero (t_0) to the time of the last measured sample (t_{last})
$AUC_{0-\tau}$	Area under the plasma concentration-time curve from time zero to the last measurable concentration
BCVA	Best-Corrected Visual Acuity
BID	Twice daily
BL	Baseline
CFR	Code of Federal Regulations
C_{max}	Peak plasma concentration
COA	Certified Ophthalmic Assistant
COT	Certified Ophthalmic Technician
CPK	Creatinine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curricula Vitae
D5W	5% Dextrose
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
e.g.	Exempli gratia, for example
EP	Electrophysiology

Abbreviation	Definition
ERK	Extracellular Signal-Regulated kinase
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
GCP	Good Clinical Practice
GFR	estimated glomerular filtration rate
HED	Human Equivalent Doses
hr	Hour
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
i.e.	Id est, in other words
IND	Investigational New Drug
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
kg	Kilogram
LOCF	Last observation carried forward
µg	Microgram(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minutes
mL	Milliliter
mmHg	Millimeters of mercury
MMRM	Mixed Model Repeated Measures
N/A	Not applicable
nM	Nanomoles
NOAEL	No observed adverse effect limit
OD	Right eye
OHT	Ocular hypertension
OS	Left eye
OU	Each eye
PBS	Phosphate buffered saline
pg	Picogram

Abbreviation	Definition
PG	prostaglandin
PI	Principal Investigator
pH	hydrogen ion concentration
PK	Pharmacokinetic
PM	Evening
POAG	Primary open-angle glaucoma
QAM	Each morning
QD	Once daily
QPM	Each evening
QS	Quantum statis, the amount which is needed.
QTcB	QTc interval corrected using Bazett's formula
QTcF	QTc interval corrected using Fridericia's formula
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
$t_{½}$	Terminal plasma half-life
T_{max}	Time of the peak plasma concentration
TVC	Trabodenoson vehicle-matched placebo control
US	United States

5. BACKGROUND AND RATIONALE

5.1. Indication

Trabodenoson, a highly selective adenosine mimetic that targets the A_1 receptor, is under development for the reduction of elevated intraocular pressure (IOP) in subjects with Ocular hypertension (OHT) or Primary Open-Angle Glaucoma (POAG). Latanoprost, a prostaglandin F-2α analogue, is currently approved for the reduction of elevated intraocular pressure (IOP) in subjects with Ocular hypertension (OHT) or Primary Open-Angle Glaucoma (POAG).

5.2. Ocular Hypertension, Glaucoma, and Medical Need

5.2.1. Ocular Hypertension

Ocular hypertension is a condition in which IOP is elevated but no glaucomatous findings (e.g., structural changes in cup-to disc-ratio or visual field loss) have been observed. The National Eye Institute estimates that 3 to 6 million Americans have elevated IOP [1, 2] The Ocular Hypertension Study demonstrated that subjects with OHT have an overall risk of developing glaucoma of 10% over 5 years and that this risk can be cut in half by medical treatment [3].

5.2.2. Primary Open-Angle Glaucoma

Glaucoma refers to a group of optic neuropathies that are characterized by loss of retinal ganglion cells and atrophy of the optic nerve with resultant visual field loss [4]. The disease is the leading cause of irreversible blindness worldwide and the second leading cause of blindness, behind cataracts [5]. Clinical trials have demonstrated that elevated IOP is a major risk factor for glaucoma and have validated the role of IOP lowering in the management of this disease. However, despite the use of current medical and surgical therapies that reduce IOP, progressive vision loss is common among glaucoma subjects. The most common form of glaucoma is POAG. In 2004 the World Health Organization estimated that 7 million people in the world were blind due to POAG and this disease accounts for >90% of the more than 3 million cases of glaucoma in the United States [6-8].

5.2.3. Unmet Medical Need

The ideal glaucoma medication would be one that has once daily dosing, reduced IOP in all subjects, has negligible ocular and no systemic side effects or contraindications, is neuro-protective, and increases blood flow to the optic nerve. No current glaucoma drug or drug combination fulfills all these criteria; few meet most of these criteria. Considering the enormity of the number of subjects with increased IOP, the impact visual loss has on the quality of life, and the absence of even a nearly-ideal drug, an unmet medical need clearly exists in the treatment of OHT and POAG.

5.2.4. Pharmacology

Adenosine is an endogenous purine nucleoside that modulates many physiologic processes. Cellular signaling by adenosine occurs through the adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3). Trabodenoson has a high binding affinity to the adenosine A_1 receptor subtype (K_i=0.97 nM) and a high selectivity for A_1 receptors over the other adenosine subtypes, the

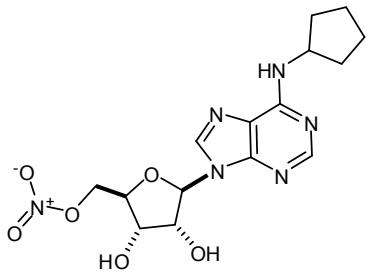
stimulation of which has been shown to increase IOP in animal models [11]. Trabodenoson reduces IOP following topical instillation in the eye in rabbits and monkeys. Studies in human primary trabecular meshwork cells, the proposed site of action of adenosine A_1 receptor agonists in the eye, demonstrated that trabodenoson (0.1 µm) activated extracellular signal-regulated kinase (ERK) 1/2 phosphorylation and increased MMP-2 release, and effect inhibited by cyclopentyltheophylline, a selective adenosine A_1 receptor antagonist [12].

5.3. Chemistry and Formulated Drug Products (Latanoprost Ophthalmic Solutions, Trabodenoson-Latanoprost Fixed Dose Combinations[FDCs], and Trabodenoson-Matched Vehicle Control/Placebo)

Trabodenoson, an adenosine mimetic selectively targeting the A_1 receptor, is 5'-O-nitro-N6-cyclopentyladenosine. Synonyms include INO-8875, PJ-875, N6-cyclopentyl-5'-O-nitro-adenosine; 5'-Nitrate-N6-cyclopentyl adenosine; N6-Cyclopentyladenosine-5'-nitrate; N6-Cyclopentyl-5'-nitrateadenosine; N6-Cyclopentyl-9-(5-nitrate-ß-D-ribofuranosyl)-purine; N6-Cyclopentyl-9-(5-nitrate-ß-D-ribofuranosyl)-purine. Its molecular weight is 380.4 grams.

The chemical structure of trabodenoson is shown in Figure 1.

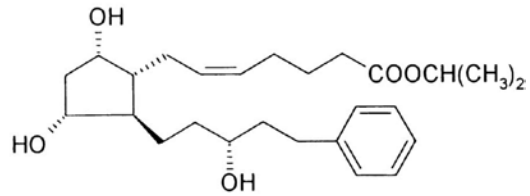
Figure 1: Chemical Structure of Trabodenoson (INO-8875)



Latanoprost is a prostaglandin F2α analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5- heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its molecular weight is 432.58 grams.

The chemical structure of latanoprost is shown in Figure 2.

Figure 2: Chemical Structure of Latanoprost



The latanoprost-only ophthalmic solutions for use in this trial are sterile, isotonic, buffered aqueous solutions of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL contains either 25 (0.0025%) or 50 (0.005%) micrograms of latanoprost. Benzalkonium chloride (BAC), 0.02% is added as a preservative. The

inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection.

Trabodenoson/latanoprost Fixed Dose Combinations (FDCs) are aqueous a trabodenoson ophthalmic suspensions in a buffered, isotonic aqueous solution of containing latanoprost and trabodenoson with a pH of approximately 6.5, and containing 0.01% BAK and 0.03% Ethylenediamine tetraacetic acid (EDTA) as preservatives. The inactive ingredients are: carboxymethyl cellulose, polysorbate 80, monobasic sodium phosphate, boric acid, sodium chloride, and water for injection.

The trabodenoson-matched vehicle control/placebo (MVC/placebo) product is composed of the same inactive ingredients as the active trabodenoson/latanoprost drug product FDCs, but without trabodenoson and latanoprost.

The drug products prepared for use in the trial are shown in Table 1 below.

Table 1: Drug Products for Trial

	% Active w/w	
Dosage Form	**Trabodenoson**	**Latanoprost**
Latanoprost Low	-	0.0025%
Latanoprost High	-	0.005%
Trabodenoson Low/ Latanoprost High	3%	0.005%
Trabodenoson High/ Latanoprost Low	6%	0.0025%
Trabodenoson High/ Latanoprost High	6%	0.005%

All drug products, are packaged in identical sterile low density polyethylene eye dropper bottles that contain approximately 3.5 mL. The dosing volume is one drop.

5.4. Overview of Clinical Investigations Involving Trabodenoson Ophthalmic Formulations

Trabodenoson has been investigated in 2 completed Phase 1 trials and 2 completed Phase 2 trials. Approximately 230 subjects have received trabodenoson in these trials. The findings from these trials demonstrate that trabodenoson is well-tolerated at all doses tested. In addition, treatment with trabodenoson lowered IOP in a dose-dependent fashion.

After 28 days of dosing in the Phase 2 Monotherapy trial (IPC-10-2009), the trabodenoson 500 µg twice daily (BID) dose demonstrated the most consistent response over the dosing interval,

with statistically significant reductions in IOP from the placebo group at all timepoints. In a Prostaglandin (PG)-Additivity trial (IPC-01-2013), trabodenoson 500 µg BID co-administered with latanoprost in prostaglandin poor-responders (defined as an IOP>24 mmHg on latanoprost), demonstrated a statistically significant reduction in IOP compared with latanoprost alone. Further, trabodenoson once daily (QD) dosing with 1000 µg for 4 weeks resulted in similar, if not greater, reduction in IOP compared with 500 µg BID dosing, indicating that once daily dosing with trabodenoson is achievable.

The first confirmatory (Phase 3) trial of trabodenoson monotherapy is ongoing. This is a randomized, double masked, active and placebo-controlled trial involving the binocular topical application of trabodenoson ophthalmic formulation 3.0% (1000 mcg) or 6.0% (2,000 mcg) QD or 4.5% (1500 mcg) BID, placebo BID or timolol 0.5% BID for 12 weeks in adult subjects with OHT and POAG. Results for this trial are anticipated in the fourth quarter of 2016.

Refer to the Investigator's Brochure (IB) for additional information on the clinical experience with trabodenoson.

5.5. Study Rationale

The current trial is designed to inform internal decision making regarding various trabodenoson/latanoprost fixed-dose combination products comprised of differing amounts of trabodenoson and latanoprost, with the objective of identifying an Fixed Dose Combination (FDC) with an appropriate benefit/risk profile for further clinical study. The trial will examine both high and low doses of trabodenoson with high and low doses of latanoprost. The efficacy as well as the safety profile of the different FDC products will be assessed. The trial is designed and powered to produce a precision-estimate of IOP-lowering efficacy of the various treatments, but not a defined detectable difference between treatment arms.

5.5.1. Role of Study in Development and Registration of Trabodenoson

The completed clinical ophthalmic trials described in the IB demonstrated that trabodenoson: (1) was well-tolerated both locally in the eye as well as systemically in subjects with increased IOPs at doses as high as 500 µg BID when applied to 1 eye for 4 weeks; (2) after 14 and 28 days of BID treatment, significantly reduced the mean IOP of subjects enrolled in the 200 and 500 µg cohorts, respectively; and (3) the IOP reduction lasted 24 hours after the final dose of the study. In addition, trabodenoson was well-tolerated in healthy adult volunteers at doses as high as 3200 µg BID when applied for 14 days to the 1 study eye and up to at least a single dose of 3200 µg in each eye (6400 µg total dose). Furthermore, in a trial conducted in patients who were prostaglandin-poor responders maintained on prostaglandin therapy, addition of concomitant trabodenoson (500 mcg BID or 1000 mcg QD), while being well-tolerated, further reduced their IOP indicating that the mechanism of IOP lowering of trabodenoson is complimentary to that of prostaglandin analogues.

Pharmacokinetic data from these trials demonstrated that trabodenoson and its major metabolite: (1) had short plasma half-lives; (2) did not accumulate in plasma; and (3) developed plasma concentrations that were dose-proportional at low doses, dose-dependent at moderate doses, but plateaued at doses at or above 2400 µg.

Therefore, based upon these safety and efficacy data, we propose herein to administer trabodenoson ophthalmic formulation to subjects with OHT or POAG who, off all glaucoma medications, have IOPs between 25 and 34 mmHg. The goals of this proposed clinical trial are to understand in subjects with OHT or POAG the effectiveness, safety, and tolerability of several fixed-dose combinations of trabodenoson/latanoprost when applied to both eyes for 8 weeks.

5.5.2. Dose and Posology Justification

This trial will investigate five different treatments dosed once daily, QAM for 4 weeks of the treatment period and QPM for 4 weeks of the treatment period. Therefore the total double-masked treatment period in this study will be 8 weeks. AM vs PM Dosing is masked utilizing placebo in addition to the active drug product. The five different treatments to be investigated are as follows:

1. Trabodenoson 6%/Latanoprost 0.005%
2. Trabodenoson 3%/Latanoprost 0.005%
3. Trabodenoson 6%/Latanoprost 0.0025%
4. Latanoprost 0.005%
5. Latanoprost 0.0025%

5.5.2.1. Justification for Dose Selection

The trabodenoson doses for this Phase 2 trial were chosen based on the data obtained from the completed clinical trials, specifically the Phase 2 Monotherapy (IPC-10-2009) and PG-Additivity (IPC-01-2013) trials. All trabodenoson doses administered to date have been well-tolerated.

Because dose increases continue to result in additional efficacy and dose-limiting tolerability (ocular or systemic) has not been observed, it is proposed to study 3% / 1000 µg (which was observed to have a tolerability profile similar to placebo in the PG-Additivity trial [IPC-01-2013 see IB]) and additional doses up to 6% / 2000 µg.

The results of Study IPC-09-2009 have shown that the percent increase in plasma $AUC_{0\text{-last}}$ and C_{max} ranged from 14% to 44% when doubling the whole body dose by dosing both eyes (Table 2).

Table 2: Mean Percent Change in Exposure from Monocular to Binocular Application of Trabodenoson (Study IPC-09-2009)

Dose	Change in $AUC_{0\text{-last}}$ (%)	Change in C_{max} (%)
1600 µg	44	44
2400 µg	26	28
3200 µg	14	15

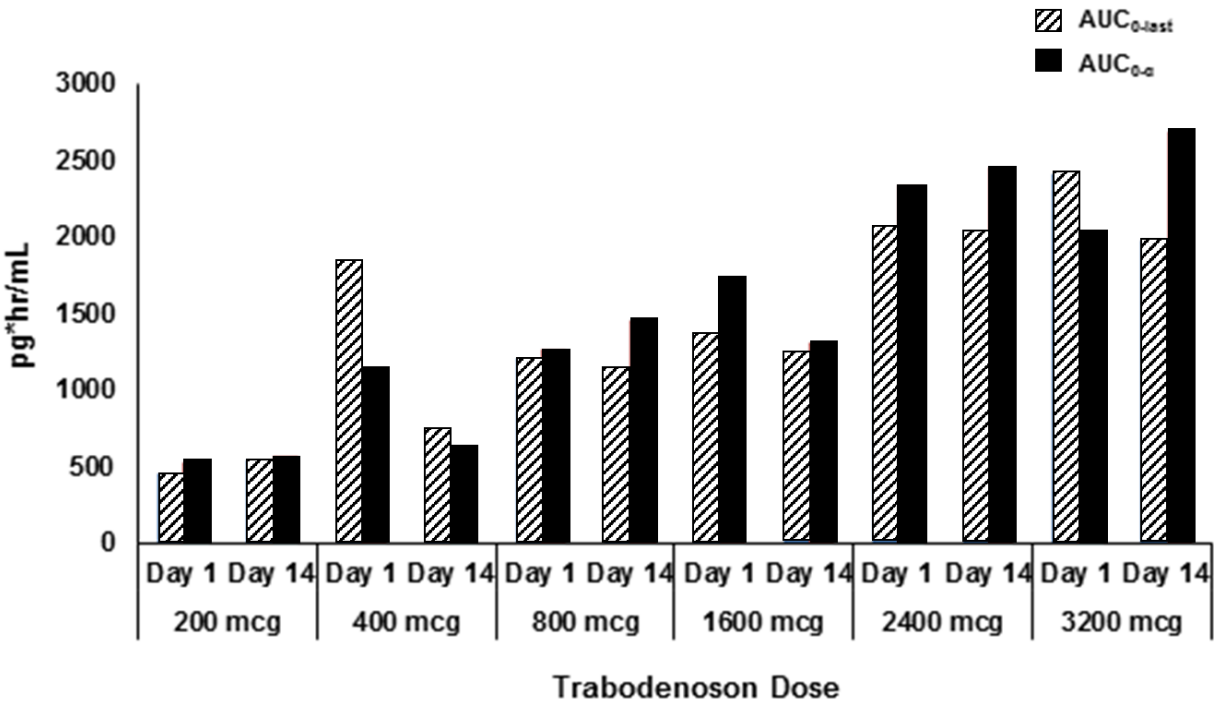
$AUC_{0\text{-last}}$=area under the plasma concentration-time curve from time zero to the last timepoint; C_{max}=peak plasma concentration

The impact on exposure of increasing the dose was also evaluated in order to project the exposure when the 3% / 1000 µg dose is increased to 4.5% / 1500 µg or doubled to 6% / 2000

µg. In all clinical trials to date, it has been observed that exposure, measured by AUC or C_{max} of the drug in plasma, increases with increasing dose. However, as the dose increases, it has been found that the exposure increases are dose-dependent, but smaller than dose-proportional. This is shown in Figure 3 which presents the relationship between increasing doses and AUC in Study IPC-09-2009. Note that doses of 2400 µg and above have similar AUCs.

A similar plateau effect was also observed in the single dose portion of Study IPC-09-2009 when the single-eye doses rose above 6% / 2000 µg (total doses greater than 4000 µg) as shown by $AUC_{0\text{-last}}$ and C_{max} (see Trabodenoson IB).

Figure 3: Relationship Between AUC and Dose in Study IPC-09-2009 (Cohorts 1 through 6)



Based on the observed increases in exposure when doses are increased in the range of the proposed Phase 3 doses, a 6% / 2000 µg dose is projected (estimated) to result in an exposure of 1200 pg•hr/mL for $AUC_{0\text{-t}}$ and a C_{max} of 800 pg/mL.

Safety factors were calculated by assessing the plasma exposures in the 13-week monkey and dog studies at the respective no observed adverse effect levels (NOAELs), measured as C_{max} of $AUC_{0\text{-t}}$, and comparing them to the projected exposures for the planned Phase 3 doses. Please see Table 3 and Table 4 below. The dose exposures for a 1000 µg/3% single-eye dose from study IPC-01-2013 are included for comparison.

Table 3: Safety Factors Between Exposure (Steady State Plasma C_{max}) at the NOAEL in the Monkey and Dog 13-Week Ocular Toxicity Studies and the Projected Exposure for the Proposed Phase 3 Doses

NOAELs	Exposure (C_{max})	Human Dose (Study IPC-01-2013)	*Projected* Human Exposure at Highest Proposed Phase 3 Dose
From 13-week Ocular Toxicity Studies[1]		**1000 µg/3% QD**	**2000 µg/6% QD**
		351 pg/mL (C_{max} at Day 84)	800 pg/mL[2] (C_{max})
		Safety Factors	
Monkey (500 µg BID/ 1000 µg/day)	4,857 pg/mL (Day 91)	14	6.1
Dog (3000 µg BID/ 6000 µg/day)	36,200 pg/mL (Day 93)	103	45

Abbreviations: C_{max} = maximum plasma concentration; BID = twice daily; NOAEL = no observed adverse effect level; QD = once daily
[1] Males
[2] Projected

Table 4: Safety Factors Between Exposure (Steady State Plasma AUC_{0-t}) at the NOAEL in the Monkey and Dog 13-Week Ocular Toxicity Studies and the Projected Exposure for the Proposed Phase 3 Doses

NOAELs	Exposure (AUC_{0-last})	Human Dose (Study IPC-01-2013)	*Projected* Human Exposure at Highest Proposed Phase 3 Dose
From 13-week Ocular Toxicity Studies[1]		1000 µg/3% QD	2000 µg/6% QD
		527 pg•hr/mL (AUC_{0-last} at Day 84)	1200 pg•hr/mL[2] (AUC_{0-last})
		Safety Factors	
Monkey (500 µg BID/ 1000 µg/day)	5,611 pg•hr/mL (Day 91)	11	4.7
Dog (3000 µg BID/ 6000 µg/day)	16,300 pg•hr/mL (Day 93)	31	14

Abbreviations: AUC_{0-last} = area under the concentration x time curve through last timepoint; BID = twice daily; NOAEL = no observed adverse effect level; QD = once daily
[1] Males
[2] Projected

The comparison of the animal exposure data and the projected human exposures indicate robust safety factors between no-effect doses in both safety species, and the projected levels of drug in plasma at the planned Phase 3 doses.

The latanoprost doses selected in this trial include the approved commercial dose (0.005%) and, for purposes of dose-ranging, half the approved latanoprost dose of 0.0025%. The safety of the 'half-dose' of latanoprost is assumed to be better than or equal to the safety profile of the higher approved dose.

5.5.2.2. Justification for Posology Selection

The IOP lowering from Study IPC-01-2013 showed an increase in efficacy when the same subjects were switched from a 1.5% / 500 µg BID dose to a 3% / 1000 µg QD dose. These data indicate that trabodenoson given once-daily (QD) was effective. Latanoprost has also been shown to be effective when given once–daily (QD), supporting the once-daily posology of the fixed-dose combinations to be investigated in this trial. Additionally, because latanoprost is typically administered at night and trabodenoson once-daily has only been administered in the morning, the difference in night time versus morning dosing is also being investigated in this trial.

5.6. General and Specific Risks

5.6.1. General Risks

Trabodenoson is a new drug and its effects on the unborn child, the reproductive system, and the fetus are unknown. The effects of latanoprost on the unborn child, the reproductive system and the fetus are also unknown. In the proposed study, women who are pregnant or are nursing are to be excluded. Female subjects who enroll in the study and male subjects and their female partners must use a medically-accepted contraceptive regimen from the time of enrollment to 1 month following study drug application, as described in the inclusion criteria.

Blood collection can cause local pain, swelling, and/or discoloration of the skin, mild lightheadedness, a feeling of weakness, sweating, slowing of the heartbeat, a decrease in blood pressure, or, sometimes, fainting. Approximately 40 mL of blood for central laboratory testing (~3 tablespoons or ~10% of a routine Red Cross blood donation) will be collected. No samples for genetic testing will be collected.

5.6.2. Trabodenoson Risks

With treatment of OHT or POAG there is a risk that subjects may not achieve adequate control of their IOP. Subject withdrawal procedures and a rescue plan have been incorporated in the protocol to ensure safe treatment of subjects (see Sections 9.4 and 9.5). Hyperemia of the conjunctiva, reported to date following administration of the drug, was short-lived and self-limited. No underlying inflammation or tissue damage was seen in any eye treated.

When trabodenoson was administered to older-adult healthy volunteers at daily and single-eye doses higher than those proposed in this protocol (3200 µg BID for 14 days to one eye in Study IPC-09-2009) and to subjects with POAG or OHT at single-eye doses of 500 µg/1.5% BID for 8 weeks and 1000 µg/3% QD for 4 weeks, systemic AEs were generally mild, short-lived, self-limited, and appeared to be un-related to adenosine-associated effects in the body. Please refer to the IB for further details.

Safety findings from Inotek's pre-clinical toxicology studies (performed in animals administered trabodenoson) and from clinical trials reported by other pharmaceutical companies (in human subjects exposed to adenosine agonists less selective than trabodenoson) are discussed below. The specific systemic risks, and in particular those thought to be associated with adenosine-related systemic effects, observed in these studies were not observed in the completed Phase 1 or Phase 2 clinical trials described above, but will be monitored for in the proposed clinical trial.

Humans enrolled in the Phase 1 clinical study (IPC-09-2009) and administered total daily doses as high as 6400 µg of trabodenoson 3200 ug OU) for 14 days experienced no significant AEs. Nonetheless, as with all new drugs and formulations being developed, these or other previously unknown side-effects could occur, including life-threatening problems.

In a previous Phase Ia study (IPC-11-2006) conducted at the Royal Adelaide Hospital in Australia (not under a US IND), 5 adults received 1 µg/kg of trabodenoson as a 5-minute IV bolus in an electrophysiology (EP) laboratory following an elective EP study and/or procedure. The extensive cardiac electrophysiologic data collected showed no consistent drug effects. However, 1 subject might have had detectable effects consistent with adenosine receptor agonism (i.e., slowing of the conduction of the sinus node and the atrioventricular node). While similar observations were not observed in the other 4 subjects, a drug effect in this 1 subject could not be ruled out. There were no serious adverse events (SAEs) or dose-limiting toxicities observed. Despite extensive cardiac, renal, pulmonary and central nervous system monitoring, and assessments in Studies IPC-09-2009 and IPC-10-2009, no effects on these or any other organ system were detected.

As plasma exposure following topical ophthalmic application plateaus at doses above 2400 µg, high systemic exposures are unlikely even in the case of accidental overdose. However, in a rare event of a high systemic exposure that resembles the exposure observed following a rapid bolus IV administration, cardiovascular symptoms similar to other adenosine agonists may be expected. These include non-selective adenosine agonists to humans (marketed as Adenocard IV and Adenoscan by Fujisawa Healthcare, Inc.) that may cause systemic findings, most notably slowed atrioventricular node conduction or atrioventricular block, chest pain, bronchoconstriction, nausea, hypotension, flushing, and headache.

In the Phase 2 and 3 trials conducted with tecadenoson administered as an IV bolus, the adenosine agonist with a chemical structure most closely resembling that of trabodenoson, recurrent tachycardia, paresthesias (e.g., heaviness or burning sensation of the extremities), and dyspnea were events considered possibly or probably attributable to the drug. Subjects with a history of asthma or chronic obstructive lung disease tolerated the drug without developing bronchospasm.

Based upon the clinical safety finding with topical ocular trabodenoson administered as a single total dose of 6400 µg, or doses of 3200 µg BID for 14 days, it is unlikely to expect cardiac effects similar to those described with other adenosine-like agents. Subjects in the clinical trial under discussion in this protocol (IPC-01-2015) will receive doses of 1500 µg/4.5% BID, 1000 µg/3.0% and 2000 µg/6.0% QD. Other safety precautions include careful ophthalmic and systemic monitoring (including particular attention to cardiac assessments) at the time of the anticipated trabodenoson T_{max} and selection of experienced investigative sites.

5.6.3. Latanoprost Risks

Latanoprost 0.005% ophthalmic solution is a commercially available product currently marketed in the United States, Canada and European Union as branded latanoprost and as generic latanoprost. Latanoprost is available as a 0.005% ophthalmic solution that has a well-defined risk profile based on multiple clinical trials and post-marketing/clinical experience. Adverse events in the latanoprost product insert (PI) that occurred at a rate of 5-15%that includes: blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris and punctate epithelial keratopathy. Adverse events that were reported in 1 to 4% of subjects were dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema and photophobia. In addition, conjunctivitis, diplopia and discharge from the eye were reported in less than 1% of subjects.

Hyperemia with latanoprost was recently evaluated in a meta-analysis and the percent of subjects reported with hyperemia was 19.7% (271 subjects with hyperemia out of 1379 subjects) and, when available, the percent of subjects reported with hyperemia greater than mild was 13.1% (160 subjects out of 1219 total subjects)[9]. Hyperemia is reversible and does resolve after discontinuation of latanoprost and a discontinuation rate due to hyperemia in the latanoprost PI is less than 1%.

Iris pigmentation with latanoprost was also recently evaluated in a second meta-analysis and the percent of subjects reported to have an increase in pigmentation by 12 months was 4.3% (21 subjects out of a total of 478 subjects) and the range in the individual trials was 4.8% to 18.4%. This is a particularly important adverse event because iris pigmentary changes may persist after discontinuation of latanoprost. [10]

Post-marketing surveillance/clinical use reporting included in the latanoprost PI due to seriousness, frequency of reporting, possible causal connection to latanoprost or a combination of these factors include: asthma and exacerbation of asthma,; corneal edema and erosions; dyspnea,; eyelash and vellus hair changes(increased length, thickness, pigmentation, and number); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; dizziness, headache and toxic epidermal necrolysis; periorbital and lid changes resulting in deepening of the eyelid sulcus.

Latanoprost has not been associated with systemic adverse effects and has not been reported to alter routine blood analyses.

In the IPC-01-2013 trial trabodenoson and latanoprost were studied as an unfixed combination with latanoprost 0.005% co-administered (concomitant administration) with either trabodenoson 1.5% or trabodenoson 3%. No unexpected adverse events were noted with co-administration and the incidence of adverse events was in the range that would be expected based on current data with both drugs.

In this trial latanoprost will be investigated at both 0.005% and 0.0025% and the risks of both doses should be contained in the risk information above related to the higher commercially available 0.005% dose.

6. STUDY DESIGN

6.1. Study Plan, Purpose and Duration

This is a phase II, randomized, double-masked study to evaluate the efficacy and tolerability of topical ocular delivery of fixed-dose combinations of trabodenoson and latanoprost in subjects with OHT or POAG.

All subjects who meet the study's enrollment criteria following Screening will undergo washout of all prohibited medications (if washout is needed), including their routine glaucoma medications. During the Placebo Run-In Period, placebo (vehicle control matched to trabodenoson) is applied twice daily to both eyes in all subjects. During the Treatment Period, study drug is applied to both eyes for a total of 8 weeks. Each subject will be assigned 4 weeks of AM and 4 weeks of PM dosing in a masked manner. The Treatment Period will be followed by an Observation Period of approximately 7 days wherein no study eye drops are instilled.

To mimic what is generally seen in clinical trials, the number of subjects with ocular hypertension as their diagnosis will be limited to approximately 30% of the total subjects enrolled. Additionally, so the trial mirrors the general population demographics (so as to improve generalizability of the results) the proportion of African American subjects will be approximately 25% or less but not less than 12% of the total subjects enrolled.

The purpose of the study is to assess the efficacy, tolerability, and safety of binocular topical application of different doses of trabodenoson (3.0% and 6.0%) when combined with latanoprost (0.005% or 0.0025%) one drop daily over two consecutive 4 week periods in subjects with POAG or OHT. Data collection will include efficacy (masked-IOPs), local (ophthalmic) and systemic tolerability and safety assessments

Approximately 40 sites in the United States (US) will participate in this trial.

6.2. Objectives

6.2.1. Primary Objective

- To evaluate the efficacy of different topical ocular doses of trabodenoson (3.0% and 6.0%) when added to latanoprost (0.005% or 0.0025%), one drop daily to both eyes over two consecutive 4 week periods.

6.2.2. Secondary Objective

- To evaluate the tolerability and safety of different doses of trabodenoson (3.0% and 6.0%) when added to latanoprost (0.005% or 0.0025%), one drop daily to both eyes over two consecutive 4 week periods.

6.3. Hypotheses

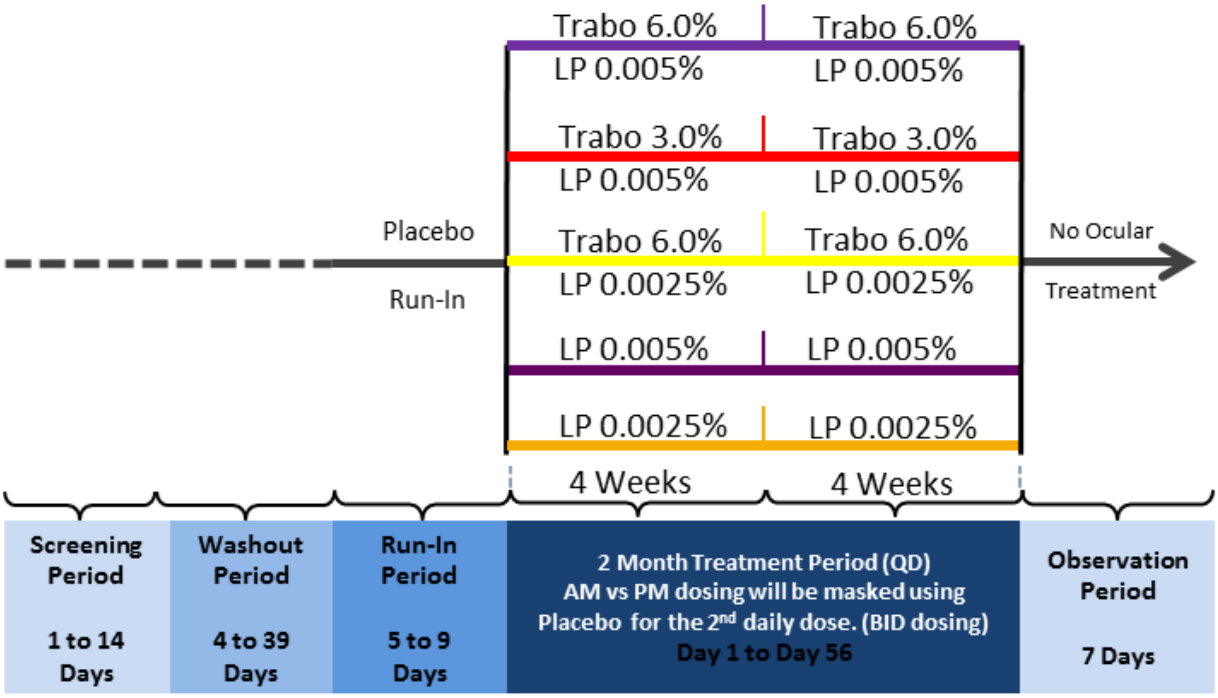
- Topical ocular co-administration of 3.0% or 6.0% trabodenoson plus latanoprost 0.0025% or 0.005% ophthalmic formulation will reduce IOP and be well-tolerated.

6.4. Study Period and Visit Schematics

6.4.1. Period Schematic and Goals

The following is a high-level schematic of the trial treatment plan. Please note that Screening, Washout, and Placebo Run-In Periods can vary in length and therefore are presented as ranges throughout the protocol instead of specific days.

Figure 4: Trial Schematic



6.5. Dosage, Dosage Form, Route, and Dose Regimen

6.5.1. Dosing Regimen for Each Period

- **Screening Period:** Subject eligibility is assessed and if found appropriate, baseline safety assessment is performed. Subjects remain on their routine medications during this period.
- **Washout Period:** This period begins with the conclusion of the Screening Period. The need for and duration of the Washout Period will vary from subject to subject based upon their ophthalmologic medication history at Screening, as depicted in Table 5. Once Screening results have been received and approved by the Investigator, subjects are notified that they have passed Screening and may proceed into the Washout Period. Washout Period procedures may be performed during a phone conversation. Maximum duration of washout is 39 days. Subjects requiring no washout must remain in Screening until all the Screening safety results have been

reviewed by the Investigator and will then proceed directly to the Placebo-Run-In Period.

Table 5: Minimum Washout Requirements Prior to Placebo Run-In Visit as a Function of Screening Medication History

Drug Class	Minimum Length of Washout Required Prior to Placebo Run-In Period
Topical ophthalmic prostaglandins, prostamides, or combination drugs containing any of these medications	35 days
Topical or oral β-blockers or combination drugs containing these medications	28 days
Sympathomimetics, topical α-agonists, or combination drugs containing any of these medications	14 days
Parasympathomimetics, (topical or oral) carbonic anhydrase inhibitors, dipyridamole, theophylline, or combination drugs containing any of these medications	4 days
None of the above drugs	No washout needed.

Note: Subjects receiving glaucoma medications requiring a long washout period may be placed on glaucoma medications with short washouts so long as adequate time is given for the washout of the second medication based upon the washout period required in Table 5.

- **Placebo Run-in Period:** For 5 to 9 days, subjects will receive 1 drop of placebo in the morning and in the evening to **both** eyes. In general, during this period, morning eye drop applications will occur between 7:00 AM and 9:00 AM while evening doses will be instilled between 7:00 PM and 9:00 PM. Washout of all prohibited medications (if needed) will continue during this period.

  Treatment Period: Subjects who continue to meet the study enrollment criteria on Day 1 AM will be randomized to 1 of 5 treatment arms. AM vs PM Dosing is masked utilizing Placebo in addition to the active drug product. During the Treatment Period, study drug (Active and Placebo) eye drop applications will occur twice daily, in the morning (between 7:00 AM – 9:00 AM) and in the evening (between 7:00 PM – 9:00 PM).

  - (1) trabodenoson 6.0% / latanoprost 0.005% QD and Placebo QD, instilled OU for a total of 8 weeks;
  - (2) trabodenoson 3.0% / latanoprost 0.005% QD and Placebo QD, instilled OU for a total of 8 weeks;
  - (3) trabodenoson 6.0% / latanoprost .0025% QD and Placebo QD, instilled OU for a total of 8 weeks;
  - (4) latanoprost 0.005% QD and Placebo QD, instilled OU for a total of 8 weeks;
  - (5) latanoprost 0.0025% QD and Placebo QD, instilled OU for a total of 8 weeks;

From Day 1 through Day 56, subjects will receive 1 drop of study drug, twice daily, in each eye (OU). No prohibited medications are permitted during this period. Of note, the **one** study eye will be determined on Day 1 (6.5.4 Definition of Study Eye).

- **Observation Period:** During this 7-day period no study medications are administered and all prohibited medications remain restricted.

The dosing regimen for each treatment group is depicted in Table 6.

Table 6: Binocular Dosing Regimen of Each Treatment Group

	Study Period					
	Screening	**Washout Period**	**Placebo Run-In**	**Treatment Period**		**Observation Period**
Randomized Group: BID Dosing	Range: 1 to 14 days	Range: 4 to 39 days	Range: 5 to 9 days	28 Days ±2 days (Day 1 to Day 28)	28 Days ± 2 days (Day 29 to Day 56)	7 ±1 days
Trabo 6.0% / LP 0.005% QD & Placebo QD	Continue routine medications & ensure subject meets general study entry criteria.	No prohibited medications are allowed.	Placebo BID No prohibited medications are allowed.	**Study Drug Dosing BID (Active or Placebo)**	**Study Drug Dosing BID (Active or Placebo)**	No prohibited medications are allowed.
Trabo 3.0% / LP 0.005% QD & Placebo QD						
Trabo 6.0% / LP .0025% QD & Placebo QD						
LP 0.005% QD & Placebo QD						
LP 0.0025% QD & Placebo QD						

6.5.2. Study Drug Administration and Drug Accountability

During scheduled visit days, study drug will be administered at the investigative site. On all other days, upon approval of the Investigator, qualified subjects may be dosed at home by themselves or by their caregiver.

Drug/Dosing accountability will be performed at all visits beginning with the Placebo Run-In Visit.

Study drug eye drop will be applied to the inferior conjunctival sac (fornix) of the study eye. Following administration of the drop, subjects will be instructed to gently close their eye for at least 1 minute. **No punctal occlusion pressure will be applied.**

6.5.3. Self-Dosing

Subjects (or caregiver) who demonstrate proper self-dosing technique may self-dose at home for a majority of study days. In order to demonstrate appropriate self-dosing technique, the Placebo Run-In Visit AM applications of the eye drops by the subject (or caregiver) must be observed by site personnel trained and experienced in ophthalmic drop administration and instruction. Subjects approved for self-dosing at Placebo Run-In Visit are permitted to administer the study drug at home on all the remaining days of the trial except for the dosing at the investigative sites by site personnel on Day -1, Day 1, Day 28 and Day 56. Subjects (or caregiver) incapable of proper self-dosing must either be dosed daily by site personnel or withdrawn from the study.

6.5.4. Definition of the Study Eye

The study eye will be an eye that meets all the following criteria: (1) mean 8AM IOP on Placebo Run-In Visit, Day -1, and Day 1 (AM predose) of ≥25 and ≤34 mmHg; and (2) mean IOP ≥21 mmHg on Day -1 at 8 hours post-dose (~4PM). If both eyes meet the above IOP criteria, then the eye with the highest mean 8AM IOP on Day 1 will be designated as the 'study' eye. In the event that the mean IOPs in both eyes are equivalent, the right eye will arbitrarily be designated as the 'study' eye. If only 1 eye meets all the Study Enrollment Criteria, that eye will automatically be designated as the 'study' eye.

6.6. Study Population

Application of the Inclusion and Exclusion (Enrollment) Criteria and definitions will give rise to a study population on Day 1 characterized by subjects who:

- Have OHT or POAG, are aged 18 years or older, and have signed the approved written informed consent form.
- Have appropriately washed out all prohibited medications.
- Have at least 1 eye that meets the following criteria: (1) mean 8AM IOP on Placebo Run-In Visit, Day -1, and Day 1 (AM predose) of ≥25 and ≤34 mmHg; and (2) mean IOP ≥21 mmHg on Day -1 at 8 hours post-dose (~4PM). (If one eye fails this criterion but the second eye meets this criterion and all other enrollment criteria are met, the subject can be randomized).
- Do not have ongoing medical, psychiatric, or social problems that might interfere with the performance, completion, and/or interpretation of the trial assessments or threaten subject safety.
- By Day 1 have received 1 drop of placebo to each eye BID for a minimum of 5 days.

6.7. Sample Size Justification

The sample size was chosen to provide a desired level of precision. Specifically, it was selected so the ½ width of the 95% CI for the primary endpoint of IOP would be no greater than 1.2 mmHg.

6.8. Safety Monitoring and Reporting

All randomized subjects will undergo adverse event (AE) and concomitant medication reviews, vital signs, Best-Corrected Visual Acuity (BCVA) testing, complete eye examinations and IOP measurements on Days 28 and 56.

As part of the rescue plan in Section 9.5, any subject whose mean IOP in either eye exceeds 34 mmHg, at any timepoint or who an investigator judges there being significant clinical risk will be withdrawn from the study. Please refer to Section 9.4 for complete instructions on withdrawal of subjects from the trial.

Board-certified consulting cardiologists will over-read the masked ECG data and, when necessary, inform the sites of any alerts.

Inotek will ensure that all federal (Code of Federal Regulations and International Conference on Harmonization-Good Clinical Practice and local (Institutional Review Board [IRB]) reporting requirements are met within applicable timelines.

Any SAEs, including death due to any cause, which occurs in any subject entered into treatment in this study or within 30 days following cessation of treatment, whether or not related to the investigational product, must be reported to the Sponsor within 24 hours. All subjects with SAEs must be followed-up for outcome.

7. STUDY ASSESMENTS

7.1. Study Assessments

7.1.1. Primary Endpoint, Efficacy

- Daily IOP-change from diurnal baseline (average of the 4 diurnal changes from baseline calculated during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.

7.1.2. Secondary Endpoints, Efficacy

- Daily IOP (average of the 4 serial IOPs taken during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.
- Daily IOP-change from study baseline (average of the 4 changes from study baseline calculated during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.
- Mean IOP at 8AM, 10AM, 12PM, and 4PM for the subject's ‘study' eye calculated at the end of each of the 4 weeks of treatment for each of the doses/combinations tested.
- IOP change from diurnal baseline [this is the time-matched subtraction of each of the 4 IOP timepoints of the circadian curve post randomization from the pre-randomization circadian curve] calculated at the end of the 4 weeks of treatment for each of the doses/combinations tested.
- IOP change from study baseline [this calculates the change in IOP from the 8AM Day 1 baseline IOP] calculated at the end of the 4 weeks of treatment for each of the doses/combinations tested.

7.1.3. Secondary Parameters, including Safety

- Clinical and laboratory evaluations including results of the bilateral eye examinations tests (e.g., IOPs, BCVA, visual fields, central corneal thickness, and conjunctival hyperemia grading), vital signs, physical examinations, clinical laboratory tests, 12-lead ECGs, AEs, concomitant medications, withdrawals/ terminations, and drug exposure will be used to assess tolerability and safety.

8. STUDY POPULATION

8.1. Number of Subjects

In order to assess 150 evaluable subjects, approximately 33 adults who meet the study enrollment criteria will be enrolled in each of the 5 treatment groups in order to complete the trial with approximately 165 enrolled and a total of 150 evaluable subjects.

8.2. Study Enrollment Criteria

8.2.1. Inclusion Criteria

1. Subject provides written informed consent prior to any study-related procedure not part of normal medical care.
2. Subject has the diagnosis of OHT or POAG (subjects with secondary, exfoliative, and/or pigmentary glaucomas are excluded from the trial).
3. Subject with at least 1 eye that meets each of the following criteria in the same eye: (1) mean 8AM IOP ≥25 and ≤34 on Placebo Run-In Visit, Day -1, and Day 1 (AM predose) mmHg; and (2) mean IOP ≥21 mmHg on Day -1 at 8 hours post-dose (~4PM). IOP is taken by Goldmann Applanation Tonometry and is not corrected for central corneal thickness. (If one eye fails this criterion but the second eye meets this criterion and all other enrollment criteria are met, the subject can be randomized).
4. Subject is aged 18 years or older;
   If female, subject must not be pregnant or nursing, and is either:
   a. Not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or
   b. Of childbearing potential and meets at least 1 of the following:
      iv. Is practicing an effective method of contraception (e.g., a. double barrier method, b. oral/parenteral contraceptives plus barrier, c. intrauterine device plus barrier), or
      v. Has a vasectomized partner (at least 90 days post vasectomy procedure), or
      vi. Is practicing abstinence from sexual intercourse.

   Subjects must be willing to practice the chosen contraceptive method or remain abstinent during the conduct of the study and for at least 1 month after last dose of study medication.

   Non-vasectomized males (with a partner of childbearing potential) are required to practice effective birth control methods (e.g., abstinence, use of condom [or other barrier device] along with partners oral/parenteral contraceptives) during the conduct of the study and for at least 1 month after last dose of study medication;

8.2.2. Exclusion Criteria

1. Subject has clinically significant abnormalities in their medical history or from the results of the physical examinations, vital signs, or clinical laboratory tests performed at Screening or during the Placebo Run-in period that may put the subject at risk in this trial or cause the subject not to complete the trial per protocol by the Investigator's judgment (Examples of clinically significant laboratory results include: both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2 times upper limit of normal (ULN) or either >3.0 times ULN, Total bilirubin > 2.0 times ULN, BMI > 40 kg/M^2, Hemoglobin A1C > 8.0%, or creatinine clearance <50 ml/min).
   Note: Subject with creatinine clearance <50 ml/min may still be eligible upon review and written approval by the Inotek Medical Monitor or his designee (a Board-certified physician) following review of the current medications, laboratory values, and medical history.
2. Subject has any new clinically significant field loss within the past year in either eye, or any non-glaucomatous ophthalmologic disease that might exacerbate during the trial.
3. Subject's ETDRS BCVA Snellen equivalent is worse than 20/80 in either eye.
4. Subject has a vertical cup-to-disc ratio >0.8 or an IOP in either eye above 34 mmHg at any examinations prior to Day 1 dosing in either eye.
5. Subject has a central corneal thickness <490 µm or >610 µm at Screening in <u>both</u> eyes. (If only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).
6. Subject is currently taking any drug that in the opinion of the Investigator might affect IOP including oral or ocular glucocorticoids. (Low to moderate stable doses [no change for 30 days] of nasal or dermatologic steroids are permitted).
7. Subject received oral/systemic beta-blocker within 28 days of screening.
8. Subject has history of clinically significant trauma to the globe of <u>both</u> eyes. (If only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).
9. Subject has had ocular or orbital surgery (conventional or laser, such as SLT or ALT) to <u>both</u> eyes (If only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).

   However, the following procedures are not exclusionary:

   a. At least 1 year prior to Screening: retinal laser, cataract extraction (no surgical complications such as capsular rupture or vitreous loss), peripheral iridotomy (with otherwise open angle per Exclusion Criteria # 25), and other extraocular (e.g., tear duct, pterygial, or palpebral) surgeries.
   b. At least 180 days prior to Screening: uncomplicated YAG laser capsulotomy.
10. Subject has any ocular abnormality that in the opinion of the Investigator might preclude reliable applanation tonometry in either eye.

11. Subject has a fundus in either eye that in the opinion of the Investigator cannot be well-visualized with pupillary dilation.
12. Subject has a history of or current retinal condition that, in opinion of the Investigator, could affect BCVA (i.e., diabetic retinopathy, central or branch retinal vein occlusion, cystoid macular edema, etc).
13. Subject cannot, or is unwilling to, function without contact lenses from Placebo Run-In Visit through the completion of the End-of-Study Visit.
14. Subject uses oral sympathomimetics (e.g., pseudoephedrine) within 14 days of start of Placebo Run-In Period, or the Investigator feels may be required during the study.
15. Subject used inhaled bronchodilators and/or inhaled steroids more than once per week on the average in the past 90 days, or the Investigator feels may be required during the study.
16. Subject uses dipyridamole, theophylline, or other adenosine antagonist medication within 4 days of the start of the Placebo Run-In Period, or the Investigator feels may be required during the study.
17. Subject used any of the following drugs (alone or in combination) for treatment of ophthalmologic illness:
    a. Parasympathomimetics or carbonic anhydrase inhibitors within 4 days of the start of the Placebo Run-In Period.
    b. Sympathomimetics or alpha adrenergic agonists within 14 days of the start of the Placebo Run-In Period.
    c. Topical ocular beta-blockers with 28 days of the start of the Placebo Run-In Period.
    d. Prostaglandins, prostamides or prostanoids within 35 days of the start of the Placebo Run-In Period.
18. Subject has any acute or chronic ophthalmologic illness requiring use of any non-IOP lowering ocular medication at screening and throughout study conduct (specific tear supplements are allowed as described in Section 9.3.9).
19. Subject has a history of significant cardiac rhythm disturbance or a complete left bundle branch block (LBBB). (Examples of significant rhythm disturbances include PR intervals above 220 msecs, history of 2nd or 3rd degree blocks, acquired or congenital long QT syndrome, atrial fibrillation or other atrial arrhythmia, ventricular arrhythmia, bradycardia (<50 bpm), or ventricular pre-excitation (WPW). Subjects with PR intervals between 221 msec and 240 msec (inclusive) may only be enrolled following receipt of the written approval of the Inotek Medical Monitor or his designee (a Board-certified physician) so as to ensure an opportunity to review, as necessary, the subject's ECG, medication and medical history with the study cardiologist.)
20. Subject has clinically significant corneal and/or conjunctival findings (including clinically significant hyperemia) related to any recurrent or chronic conditions including allergic conjunctivitis, blepharitis, pegueculae/pterygium, or keratoconjunctivitis sicca that might recur or worsen during the study and confound the ophthalmologic safety data.
21. Subject has a closed or occludable angle on gonioscopy (chamber angle less than 10 degrees), a history of angle-closure, or any non-POAG glaucoma (including neovascular

glaucoma) in both eyes at Screening (if only one eye is excluded based upon this criterion but the second eye does not meet this exclusion or any other exclusion criteria, the subject can be included).

22. Subject has a history of, or current, uveitis or any other inflammatory intraocular disease of either eye, unless the inflammatory process was caused by a topical ophthalmic medication that was stopped and has been in full remission for at least 1 year.
23. Subject received any investigational device or product within 30 days prior to the start of the Placebo Run-In Period or has ever been rejected on medical or psycho-social grounds from participation in a clinical trial.
24. Subject has a history of allergy to more than 3 structurally unrelated medications, unless approved in writing by the Sponsor Medical Monitor (or their designees, a Board-certified physician).
25. Subject has a history of significant sensitivity to latanoprost, trabodenoson, benzalkonium chloride, EDTA, or any of the other study drug excipients, or to local anesthetics or topical ophthalmic anesthetics such as lidocaine or to fluorescein.
26. Subject is unable to discontinue the use of prohibited medications delineated in Section 9.3.9 from the start of the Placebo Run-In Period through completion of the End-of-Study Visit.
27. Subject is unable to limit their daily consumption to ≤ 24 ounces of beer, ≤ 8 ounces of wine, or ≤ 4 ounces of liquor from the start of the Placebo Run-In Period through completion of the End-of-Study Visit.
28. Subject has any recent (acute) or chronic medical, psychiatric, drug or alcohol, or social problem that might in the opinion of the Investigator: (1) interfere with the subject's performance or completion of the trial; (2) obfuscate the subject's study data; or (3) render the subject unable to understand the nature, scope, and possible consequences of the study. Or subject is likely to be noncompliant with the protocol (e.g., uncooperative attitude; a history of significant mental depression, panic attacks, or manic episodes; inability to return for all planned visits, and/or unlikelihood of completing the study).
29. Subject is involved in any aspect of trial conduct including, Investigator, Sub-Investigator, other site staff, and/or immediate family members (first degree relative, spouse, adoptees, legal dependents) or employee of Inotek.

9. SCHEDULE OF ASSESSMENTS

Note: In the tables below, the number preceding a check denotes the number of times that a procedure is performed during that visit. For example, 3√ means that procedure is performed 3 times during that visit (specific timepoints are described in Section 9.2). If no number appears, then the procedure is performed only once.

The order of the assessments listed in Table 7, is random. However, throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any of the external eye assessments. Masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs, or blood sampling) so as not to affect the IOP results. Investigators and site personnel will perform study procedures in their appropriate order, as delineated in the clinical protocol.

Table 7: Schedule of Assessments

Study Period:	Screening Period Range	Washout and Placebo Run-in Period: Washout Range: 4 to 39 Days [f] Placebo Run-in Range: 5 to 9 Days			Treatment Period: Day 1 to Day 56 (± 2)			Observation Period: 7 Days (± 1) after EOT
Visit: **Procedure:**	**1 to 14 Days**	**Washout Visit [e]**	**Placebo Run-In Visit [a]**	**Day -1 [a]**	**Day 1 [a]**	**Day 28 [a] (± 2)**	**End-of- Treatment (EOT) Visit Day 56 [a] (± 2)**	**End-of-Study (EOS) Visit [g] 7 Days (± 1) after EOT**
Informed consent procedures	√							
Demographics and medical history	√							
Medication History / Concomitant medications	√	√	√	√	√	√	√	√
Enrollment criteria and/or safety data review	√	√	√	√	√			
Subject randomization					√			
Physical examination, complete (C) or directed (D)	√C				√D			√C
Height / weight	√							
Clinical laboratory tests (Central Lab)	√		√			√		√
Pregnancy test for females, central (C) or at the site (S)	√C Serum			√S Urine			√S Urine	
Adverse events review /reporting	√	√	√	√	√	√	√	√
Modified ETDRS-BCVA	√		√	√	√	√	√	√
External eye examination [h]	√		√ [h]	√ [h]	√	√ [h]	√ [h]	√
Slit Lamp examination	√		√	√	√	√	√	√
Masked-IOPs	√		√	4√	√	4√	4√	√
Dilated Fundus examination	√							√
Vital signs	√		√	√	√	√	√	√
12-Lead ECG	√		√					√
Gonioscopy [c]	√							

Study Period:	Screening Period Range	Washout and Placebo Run-in Period: Washout Range: 4 to 39 Days [f] Placebo Run-in Range: 5 to 9 Days			Treatment Period: Day 1 to Day 56 (± 2)			Observation Period: 7 Days (± 1) after EOT
Visit: / Procedure:	1 to 14 Days	Washout Visit [e]	Placebo Run-In Visit [a]	Day -1 [a]	Day 1 [a]	Day 28 [a] (± 2)	End-of- Treatment (EOT) Visit Day 56 [a] (± 2)	End-of-Study (EOS) Visit [g] 7 Days (± 1) after EOT
Central corneal thickness [d]	√							
Visual field test [b]	√							√
Drug/Dosing accountability				√	√	√	√	
Washout prohibited medication		√	√	√				
Study drug dosing					BID	BID	QAM	
Placebo Run-In dosing			BID	BID				

[a] On Placebo Run-In Visit and Days -1, 1, 28, and 56 all procedures will take place at the Investigational site.
[b] Measurements can be historical values within 90 days.
[c] Measurements can be historical values within 180 days.
[d] Measurements can be historical values within 1 year.
[e] Upon conclusion of all Screening Period activities, subjects who still meet the study enrollment criteria are invited to attend a Washout Period Visit (if washout is needed). This visit may be accomplished in person at the investigative site or by phone.
[f] Minimum length of washout required is described in Table 5.
[g] End-of-Study Visit is calculated as 7 Days (± 1) after the actual occurrence of the EOT Visit.
[h] Hyperemia assessments performed on Placebo Run-in Visit, Day -1, Day 28, and Day 56.

9.1. Study Duration per Subject

The maximum time that subjects may participate in this study following performance of the first Screening Period procedure is 128 days.

9.2. Study Periods, Visits, and Procedures

The procedures to be performed during the trial are discussed below and are listed in the Schedule of Assessments.

The clinical trial will include 5 study periods: Screening Period, Washout Period (if washout is needed), Placebo-Run-In Period, Treatment Period, and Observation Period. However, sites may pre-screen subjects before inviting them to review the Informed Consent Form (ICF) in order to increase the chances of a successful screening.

9.2.1. Pre-Screening

Sites will review medical records (utilizing inclusion/exclusion criteria) in order to identify potential subjects to be screened. Sites and subjects may also begin the informed consent procedures before the Screening Period begins. Doing so will provide adequate time for the site personnel, subjects, and the subjects' friends, families, and/or physicians to discuss the details of the study before subjects sign the ICF.

No study procedures (including Screening activities) may be performed before the ICF has been signed and dated, with a copy given to the subject and another copy placed in the subject's medical records. Only after the ICF has been signed may Screening activities be initiated.

9.2.2. Screening Period (1 to 14 Days)

Following completion of all the required informed consent procedures, subjects will enter the Screening Period and be assigned consecutive screening numbers. Screening may continue for a maximum of 14 days and may require more than 1 site visit. Subjects will remain in the Screening Period until the results (including central lab and ECG) obtained during Screening are reviewed and approved by an Investigator. Only subjects who continue to meet the study enrollment criteria at the conclusion of Screening may proceed into the Washout Period (if washout is needed) or Placebo Run-In Period.

Throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any external eye assessment. In addition, masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, electrocardiograms [ECGs], or blood sampling) so as not to affect the IOP results. Investigators and site personnel will perform study procedures in their appropriate order, as delineated in the clinical protocol.

The following procedures are performed during the Screening Period:

Prior to Masked-IOPs:

- Demographics.
- Medical history.

- Medications used in the past 45 days. These will herein be called Medication History.
- BCVA assessed.
- External eye and slit lamp examinations.

Masked-IOPs:

- Masked-IOPs performed (Following application of topical anesthetic and fluorescein or combined product [e.g. Fluress®]).

After Masked-IOPs:

- Gonioscopy performed (this is the only time this procedure is performed in this trial in order to confirm that the angle is not occludable). If this procedure was performed and documented in the subject's medical record within the past 180 days, this procedure need not be repeated (unless the Investigator suspects a change). The results are recorded. Note, must be performed prior to pupillary dilation.
- Fundus examination with pupillary dilation.
- Vital signs (supine position).
- 12-lead ECG performed.
- Complete physical examination (excluding eye, breast, rectal, or pelvic examinations).
- Height and weight determined.
- Collection of blood and urine samples for central clinical laboratory safety assessments.
- Pregnancy testing (serum), for females only.

The following procedures may be performed at any time during the Screening Period:

- Central corneal thickness measurements. If this procedure was performed and documented in the subject's medical record within the past year, this procedure need not be repeated and the data may be recorded.
- Visual field test. If this procedure was performed and documented in the subject's medical record within the past 90 days, this procedure need not be repeated and those data may be recorded.
- AEs occurring during the screening period will be documented.

At the conclusion of the final Screening visit, the following will be performed:

- Exclusion and inclusion (enrollment) criteria reviewed.
- Visit Closure Procedures for subjects who meet the enrollment criteria. These procedures include:
  - Providing subjects with relevant study instructions.

- Obtaining emergency contact information.
- Scheduling clinic appointments for the next scheduled site visit.

Only subjects who continue to meet the study enrollment criteria at the conclusion of the Screening Period may proceed to the following period. Note that subjects with equivocal or questionable findings obtained during the Screening Period may proceed into the next Period, but clarification of those findings is required. Subjects with clinically significant abnormal findings may **not** proceed into the next Period.

Subjects who fail screening may be re-screened at any time, without a 30-day waiting period, since the subjects never stopped their routine medications.

As soon as Screening has been satisfactorily completed, Washout Period activities (if washout is needed or Placebo Run-in Period activities may be initiated.

9.2.3. Washout Period (4 to 39 Days)

Upon conclusion of all Screening activities, subjects who still meet the study enrollment criteria are invited to attend a Washout Period Visit If washout is needed). This visit (if washout is needed) may be accomplished in person at the investigative site or by phone. The Washout Period begins with the initiation of the Washout Period Visit activities. The maximum time subjects may remain in this period is 39 days; the minimum is 4 days.

Subjects requiring no washout cannot continue to Placebo Run-In Period until all the Screening safety results have been reviewed by the Investigator. Once Screening results have been received and approved by the Investigator, subjects are notified that they have passed Screening and may proceed directly into the Placebo Run-In Period.

9.2.3.1. Washout Period Visit (if washout is needed)

The main goal of this visit is to begin washout of all IOP-lowering medications and other prohibited medications. At the discretion of the Investigator, this visit may be accomplished in person at the site or via a carefully documented telephone conversation.

The following activities are performed:

- Medication History (and prohibited medications identified).
- Washout of prohibited medication begins.
- AEs documented.
- Exclusion and inclusion (enrollment) criteria reviewed.
- Visit Closure Procedures will commence after the above activities have been completed:
  - Provide emergency telephone numbers.
  - Schedule the Placebo Run-In Visit.
  - Instruct subjects to begin washing out prohibited medications, including any prohibited anti-glaucoma medications.

9.2.3.2. Washout Period (if washout is needed)

During this interval, the following procedures are followed:

- Subjects will wash out prohibited medications for the period of time listed in the enrollment criteria and/or listed in Table 5.
- On the last day of the Washout Period, the site personnel will contact each subject and remind them to:
  - Arrive at the investigative site the next morning for their Placebo Run-In Visit.
  - Refrain from ingesting any caffeinated products on the Placebo Run-In Visit, and on all other site visit days, between 5 AM and 10:15 AM.

9.2.4. Placebo Run-In Period (5 to 9 Days)

Following completion of the Washout Period or screening period (if no washout is needed), subjects will enter the Placebo Run-In Period. During this period subjects will instill one drop of placebo into both eyes each morning and each evening.

This period includes 2 required visits to the investigative site, on the first day of Placebo Run-In (Placebo Run-In Visit) and the last day of Placebo Run-In (Day -1 Visit). The maximum time a subject will remain in the Placebo Run-In Period is 9 days; the minimum is 5 days.

9.2.4.1. Placebo Run-In Visit

Subjects will return to the site on the morning of the Placebo Run-In Visit, having refrained from ingesting any caffeine-containing foods or drinks between 5 AM and 10:15 AM.

Throughout the study, activities that could impact the findings on the biomicroscopy examination (e.g., topical ophthalmic eye drop application) are performed after all the anterior segment ophthalmic assessments. In addition, masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs, or blood sampling) so as not to affect the IOP results.

The following procedures are performed during the Placebo Run-In Visit:

Prior to Masked-IOPs:

- BCVA assessed.
- External eye* and slit lamp examinations.

  *Including baseline hyperemia assessment (utilizing grading scale).

Masked-IOPs:

- Masked-IOPs performed between 7:00 AM and 8:40 AM (Following application of topical anesthetic and fluorescein or combined product [e.g. Fluress®]).

After Masked-IOPs:

- Vital signs (supine position).
- 12-lead ECG performed.

- Collection of blood and urine samples for central clinical laboratory safety assessments.

The following procedures may be performed at any time during this visit:

- Medication history/Concomitant medications recorded.
- AEs documented.

At this visit, a subject with mean morning (7:00 AM through 8:40 AM) IOP values <25 mmHg in both eyes are ineligible to continue in the trial. However, if only 1 eye fails to meet the enrollment criteria and the contralateral eye qualifies, the subject can continue to participate.

After the initial activities are completed, the following procedures are performed at the site on subjects who continue to meet the enrollment criteria:

- Instillation of the first dose of matched placebo eye drops OU, between 7:40 AM and 9:00 AM.

Site Investigators must approve subjects for self-dosing. Subjects (or their caregivers) must demonstrate their eye drop dosing technique on Placebo Run-In Visit AM.

- Following completion of the above activities visit closure procedures are performed including:
  - Enrollment criteria reviewed.
  - Provide emergency telephone numbers and trial instructions.
  - Schedule the Day -1 site visit.
  - Distribute study drug (placebo) and dosing instructions.
  - Subjects are discharged from the site (subjects with continuing AEs are to remain under close observation until the Investigator determines that it is safe to discharge the subject from the site).

Subjects in the Placebo Run-In Period will continue to apply placebo to **both** eyes each morning between 7:00 AM and 9:00 AM and each evening between 7:00 PM and 9:00 PM.

NOTE: Whether 1 eye or both eyes qualify for the study, both eyes will receive matched placebo BID during the Placebo Run-In Period.

9.2.4.2. Placebo Run-In Period

During this interval, the following procedures are performed:

- Washout of prohibited medications continues (if washout was required).
- Apply matched placebo to both eyes each morning; apply matched placebo to both eyes each evening.
- On Day -2, site personnel will contact each subject and remind them to:
  - Not apply the Day -1 eye drops as dosing on that day must occur at the investigative site;

- Refrain from ingesting any caffeinated products in the morning of Day -1 from 5 AM to 10:15 AM;
- Bring the study medications to the site on Day -1 (the next day); and
- Apply matched placebo between 7:00 PM and 9:00 PM.

Subjects who fail to meet enrollment criteria (i.e. central lab or ECG) during this period may be re-screened 30 days later. **However, subjects who failed the IOP criteria in both eyes may never be re-screened for this trial.**

9.2.4.3. Day -1 Visit

Day -1 is defined as the day before Day 1 randomization. On Day -1, all subjects are required to visit the investigative site. Subjects will have refrained from applying any eye drops that morning and from ingesting caffeinated products between 5 AM and 10:15 AM.

Throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any of the external eye assessments. In addition, masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs, or blood sampling) so as not to affect the IOP results.

The following procedures are performed during the Day -1 Visit:

Prior to Masked-IOPs:

- Drug/Dosing (i.e., placebo) accountability reviewed (including time of last dose).
- BCVA assessed.
- External eye* and slit lamp examinations.

  *Including hyperemia assessment (utilizing grading scale).

Masked-IOPs:

- Masked-IOPs performed between 7:00 AM and 8:40 AM (Following application of topical anesthetic and fluorescein or combined product [e.g. Fluress®]).

After Masked-IOPs:

- Vital signs (supine position).
- Urine pregnancy test.

The following procedures may be performed at any time during this visit:

- AEs documented.
- Concomitant medications recorded.

At this visit, a subject with mean IOP values <25 mmHg in both eyes are ineligible to continue in the trial. However, if only 1 eye fails to meet the enrollment criteria and the contralateral eye qualifies, then the subject can continue to participate.

- The Investigator will review the enrollment criteria. Only eligible subjects may proceed to the morning dosing.

After the initial activities are completed, the following dosing procedures are performed at the site by qualified and experienced personnel:

- Apply Placebo eye drops to both eyes between 7:40 AM and 9:00 AM.

Following application of the Day -1 AM eye drops to both eyes, the following procedures are performed over the ensuing 8 hours post-dose:

- Masked-IOPs are performed at 2, 4, and 8 hours (each ±30 minutes) after the morning dose. (Reminder: the 8 hour IOP qualification is ≥21 mmHg for the study eye).
- Hyperemia assessment (utilizing grading scale) within 30 minutes prior to 4 hour IOP Measurement.

Note: Subjects may leave the site between the 4 hour and 8 hour post-dose IOP measurements. However, care should be taken to restrict subjects' sodium and liquid intake so as not to impact their IOPs. In addition, subjects should return at least 15 minutes prior to the 8 hour IOP reading so as to allow the subjects to rest and re-acclimate to the office conditions.

- Enrollment criteria are reviewed following completion of the above activities. Only subjects who complete the Placebo Run-In Period and meet the study enrollment criteria at the conclusion of Day -1 (including the minimum IOP measurement of at least 21 mm Hg at the 8 hour post dose time point) may proceed to Day 1 activities.
- Following completion of all the Day -1 activities, the following Visit Closure Procedures are performed:
  - Emergency telephone numbers and trial instructions reviewed.
  - Schedule the Day 1 Visit.
  - Site personnel will make arrangements for telephone contact between 7-9 PM with self-dosing subjects to assure proper dosing; and remind subjects to refrain from ingesting any caffeinated products in the morning of Day 1 between 5:00 AM and 10:15 AM.
  - Placebo is redistributed to subjects for self-dosing the Day -1 pm dose between 7:00-9:00 PM.
  - Subjects are discharged from the site.

Note: Subjects who withdraw from the trial prior to randomization or who fail to meet the Enrollment Criteria (for reasons other than failing the IOP criteria) after successfully screening but prior to randomization, may be re-screened 30 days after their exit. **However, subjects who were excluded because they failed to meet the IOP Enrollment Criterion may never be re-screened for this trial.**

9.2.5. Treatment Period

9.2.5.1. Day 1 Visit

All subjects are required to visit the investigative site on Day 1. Subjects will have refrained from applying any eye drops that morning or from ingesting caffeinated products from 5 AM to 10:15 AM.

Throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any of the external eye assessments. Masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs, or blood sampling) so as not to affect the IOP results.

The following procedures are performed during the Day 1 Visit:

Prior to Masked-IOPs:

- Drug/Dosing (i.e. Placebo Run-In) accountability reviewed (including time of last dose).
- BCVA assessed.
- External eye and slit lamp examinations.

Masked-IOPs:

- Masked-IOPs between 7:00 AM and 08:40 AM (Following application of topical anesthetic and fluorescein or combined product [e.g. Fluress®]). **Note:** This IOP measurement will be performed the same time (±30 minutes) as the IOP was measured on Day -1 AM.

After Masked-IOPs:

- Vital signs (supine position).
- Directed physical examination performed.

The following procedures may be performed at any time during this visit:

- AEs documented.
- Concomitant medications recorded.

At this visit, the Placebo Run-In Visit, or the Day -1 Visit, a subject with mean IOP values <25 mmHg in both eyes is ineligible to continue in the trial. However, if only 1 eye fails to meet the enrollment criteria and the contralateral eye qualifies, then the subject can continue to participate.

- The Investigator will review the enrollment criteria. Results of all data from beginning of Placebo Run-In Period through Day 1 AM, including pregnancy tests (females of childbearing potential), must be reviewed by the Investigator prior to randomization.

- Subjects who continue to meet the study enrollment criteria are randomized for masked assignment to 1 of 5 treatment cohorts.
- The study eye (see Section 6.5.4) is determined for randomized subjects and documented in source documentation for each subject.

After the safety assessments have been completed and results approved by the site Investigator, the following Day 1 AM dosing procedures may proceed.

- Site personnel to apply 1 drop of study drug between 7:40 AM and 9:00 AM to each eye. **Note:** Study drug dosing on the morning of Day 1 will be performed at the same time (±30 minutes) as the study drug dosing occurred on Day -1 AM.

Following application of the Day 1 eye drops, the following safety assessments are performed:

- The following Visit Closure Procedures are performed prior to discharge:
  - Provide emergency numbers and trial instructions.
  - Schedule the Day 28 Visit.
  - Distribute study drug and dosing instructions.
  - Discharge subjects from site (subjects with continuing AEs are to remain under close observation until the Investigator determines that it is safe to discharge the subject from the site).

9.2.5.2. Day 1 PM to Day 28

- During the Treatment Period, all subjects will apply study drug twice daily to both eyes (the 1 study eye and the contralateral eye), every morning between 7:00 AM and 9:00 AM and between 7:00 PM and 9:00 PM each evening.
- Site personnel will make arrangements for telephone contact on the day before the planned Day 28 Visit to remind subjects not dose prior to arriving in the clinic on the Day 28 Visit; remind subjects to bring the study medications to the clinic on the Day 28 Visit (the next day); and remind subjects to refrain from ingesting any caffeinated products in the morning of the Day 28 Visit from 5:00 AM to 10:15 AM.

9.2.5.3. Day 28 Visit

On Day 28 (±2 days), subjects will return to the investigative site for safety and efficacy assessments having refrained from applying any eye drops that morning or from ingesting caffeinated products from 5 AM to 10:15 AM.

Throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any of the external eye assessments. Masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs, or blood sampling) so as not to affect the IOP results.

The following procedures are performed during the Day 28 Visit:

Prior to Masked-IOPs:

- Drug/dosing accountability reviewed (including time of last dose and general compliance).
- BCVA assessed.
- External eye* and slit lamp examinations.

  *Including hyperemia assessment (utilizing grading scale).

Masked-IOPs:

- Masked-IOPs between 7:00 AM and 8:40 AM (Following application of topical anesthetic and fluorescein or combined product [e.g. Fluress®]). **Note:** This IOP measurement (as well as the other IOP measurements on this day) will be performed at the same time (±30 minutes) they were performed on Day -1.

After Masked-IOPs:

- Vital signs (supine position).

The following procedures may be performed at any time during this visit:

- AEs documented.
- Concomitant medications reported.

After completion of the initial assessments, the following Day 28 AM dosing-related procedures may proceed.

- Site personnel to apply 1 drop of study drug between 7:40 AM and 9:00 AM to both eyes. **Note:** Study drug dosing on the morning of the Day 28 Visit will be performed at the same time (±30 minutes) as the study drug dosing occurred on Day -1 AM.
  - **This is the last dose that will be applied with the study drug kit that was assigned at Randomization.** This kit will be collected from the subject and not re-distributed following this AM dose.

Following application of the Day 28 eye drops, the following procedures are performed over the ensuing 8 hours post-dose:

- Masked-IOPs are performed at 2, 4, and 8 hours (each ±30 minutes) after the morning dose.
- Hyperemia assessment (utilizing grading scale) within 30 minutes prior to 4 hour IOP Measurement.

Note: Subjects may leave the site between the 4 hour and 8 hour post-dose IOP measurements. However, care should be taken to restrict subjects' sodium and liquid intake so as not to impact their IOPs. In addition, subjects should return at least 15 minutes prior to the 8 hour IOP reading so as to allow the subjects to rest and re-acclimate to the office conditions.

Following completion of all the Day 28 Visit activities, the following Visit Closure Procedures are performed:

- Provide emergency numbers and trial instructions reviewed.

- Schedule the Day 56 Visit.
- Distribute new study drug kit (Assigned by Interactive Response Technology) and dosing instructions.
- Discharge subjects from site (subjects with continuing AEs are to remain under close observation until the Investigator determines that it is safe to discharge the subject from the site).

9.2.5.4. Day 28 PM to Day 56

- During the Treatment Period, all subjects will apply study drug twice daily to both eyes (the 1 study eye and the contralateral eye), every morning between 7:00 AM and 9:00 AM and between 7:00 PM and 9:00 PM each evening.
- Site personnel will make arrangements for telephone contact on the day before the planned End-of-Treatment Visit to remind subjects not dose prior to arriving in the clinic on the End-of-Treatment Visit; remind subjects to bring the study medications to the clinic on the End-of-Treatment Visit (the next day); and remind subjects to refrain from ingesting any caffeinated products in the morning of the End-of-Treatment Visit from 5:00 AM to 10:15 AM.

9.2.5.5. End-of-Treatment (Day 56) Visit

On Day 56 (±2 days), subjects return to the investigative site for safety and efficacy assessments having refrained from applying any eye drops that morning or from ingesting caffeinated products from 5 AM to10:15 AM.

Throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any of the external eye assessments. Masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs, or blood sampling) so as not to affect the IOP results.

The following procedures are performed during the Day 56 Visit:

Prior to Masked-IOPs:

- Drug/dosing accountability reviewed (including time of last dose and general compliance).
- BCVA assessed.
- External eye* and slit lamp examinations.

  *Including hyperemia assessment (utilizing grading scale).

Masked-IOPs:

- Masked-IOPs between 7:00 AM and 8:40 AM (Following application of topical anesthetic and fluorescein or combined product [e.g. Fluress®]). **Note:** This IOP measurement (as well as the other IOP measurements on this day) will be performed at the same time (±30 minutes) they were performed on Day -1.

After Masked-IOPs:

- Vital signs (supine position).
- Urine pregnancy test.

The following procedures may be performed at any time during this visit:

- AEs documented.
- Concomitant medications reported.

After completion of the initial assessments, the following Day 56 AM dosing-related procedures may proceed.

- Site personnel to apply 1 drop of study drug between 7:40 AM and 9:00 AM to both eyes. **Note:** Study drug dosing on the morning of Day 56 will be performed at the same time (±30 minutes) as the study drug dosing occurred on Day -1 AM.

Following application of the Day 56 AM eye drops, the following procedures are performed over the ensuing 8 hours post-dose:

- Masked-IOPs are performed at 2, 4, and 8 hours (each ±30 minutes) after the morning dose.
- Hyperemia assessment (utilizing grading scale) within 30 minutes prior to 4 hour IOP Measurement.

  Note: Subjects may leave the site between the 4 hour and 8 hour post-dose IOP measurements. However, care should be taken to restrict subjects' sodium and liquid intake so as not to impact their IOPs. In addition, subjects should return at least 15 minutes prior to the 8 hour IOP reading so as to allow the subjects to rest and re-acclimate to the office conditions.

Following completion of all the Day 56 activities, the following Visit Closure Procedures are performed:

- Schedule the End-of-Study Visit.
- Discharge subjects from site (subjects with continuing AEs are to remain under close observation until the Investigator determines that it is safe to discharge the subject from the site).

As part of the rescue plan in Section 9.5, any subject whose mean IOP in either eye exceeds 34 mmHg, at any timepoint or who an investigator judges there being significant clinical risk will complete collection of the 4 serial IOP measurements and be withdrawn from the study. Please refer to Section 9.4 for complete instructions on withdrawal of subjects from the trial.

9.2.6. Observation Period (7 ±1 days)

9.2.6.1. Observation Period

- During the Observation Period, no ocular medications are applied.

- Site personnel will make arrangements for telephone contact on the day before the End-of-Study Visit to remind subjects of their site visit the next day and to refrain from ingesting any caffeinated products in the morning of End-of-Study Visit between 5:00 AM to 10:15 AM.

9.2.6.2. End-of-Study Visit (7 ±1 days) after EOT

Seven (±1) days after the End-of-Treatment all subjects are required to return to the investigative site for End-of-Study activities.

Throughout the study, activities that could impact the findings on the external eye examination (e.g., topical ophthalmic eye drop application) are performed after any of the external eye assessments. Masked-IOP measurements are performed prior to any assessment that might make the subject anxious or uncomfortable (e.g., vital signs, ECGs or blood sampling) so as not to affect the IOP results. Investigators and site personnel will perform study procedures in the appropriate order, as delineated in the clinical protocol.

The following procedures are performed during the End-of-Study Visit:

Prior to Masked-IOPs:

- BCVA assessed.
- External eye and slit lamp examinations.

Masked-IOPs:

- Masked-IOPs performed between 7:00 AM and 9:00 AM (Following application of topical anesthetic and fluorescein or combined product [e.g. Fluress®]).

After Masked IOPs:

- Visual field test (Must occur prior to dilation).
- Fundus examination with pupillary dilation.
- Vital signs (supine position).
- 12-lead ECG performed.
- Complete physical examination (excluding eye, breast, rectal, or pelvic examinations).
- Collection of blood and urine samples for central clinical laboratory safety assessments.

The following procedures may be performed at any time during this visit:

- AEs documented.
- Concomitant medications recorded.

Visit Closure Procedures are performed after completion of the above procedures including:

- Advise subjects to restart their routine (pre-trial) medication(s) per the discretion of the treating physicians.

- Provide appropriate medical follow-up to subjects with continuing AEs.
- Subjects are discharged from the site.

9.3. Study Procedure Details

9.3.1. Subject Information and Consent Form

Subject informed consent is obtained by the Investigator or his designee prior to study enrollment in accordance with the FDA Code of Federal Regulations (CFR) on GCP and ICH guidelines (see Title 21 CFR, Part 50, ICH [E6] for description of Informed Consent Procedures). The Investigator's responsibilities relating to informed consent are discussed in Section 15.3.

9.3.2. Enrollment and Randomization

This is a double-masked, multi-center clinical study. All subjects who have signed the ICF and meet the entry criteria through Day 1 (AM) are eligible for enrollment, randomization, and treatment with the study drug.

Treatment group assignment and randomization will occur on the Day 1 Visit utilizing a validated Interactive Response Technology.

To mimic what is generally seen in clinical trials, the number of subjects with ocular hypertension as their diagnosis will be limited to approximately 30% of the total subjects enrolled. Additionally, so the trial mirrors the general population demographics (so as to improve generalizability of the results) the proportion of African American subjects will be approximately 25% or less but not less than 12% of the total subjects enrolled.

Any subject who completes 39 days in the Washout Period must either proceed the following day to the Placebo Run-In Period or be terminated from the trial.

Any subject who completes the Placebo Run-In Period must either proceed to Day 1 or return to the Washout Period. However, the days the subject was in Placebo Run-In must be applied to the Washout Period and such subjects still may not exceed the maximum of 39 days permitted for the Washout Period.

Subjects who were terminated from the study solely because they had reached the maximum number of days permitted in the Washout Period or the Placebo Run-In Period but could not proceed into the next study period, may re-enter Screening after a 30-day waiting period for possible re-enrollment. At the time of termination, such subjects are instructed to contact their primary ophthalmologist for treatment instructions.

9.3.3. Masking Procedures

All site personnel, and enrolled subjects are masked to the study drug assignments until the last subject has completed all study-related activities and the database has been locked. All Sponsor personnel directly involved in the conduct of the study will also remain masked until after data lock.

In the event of an emergency in which unmasking is required at an investigative site, the emergency procedures found in Section 11.2 will be followed.

9.3.4. Study Drug Administration

Only subjects currently enrolled in the study with appropriately signed, dated, and witnessed informed consent and meeting the eligibility criteria may receive the study drug.

Subjects who continue to meet the study enrollment criteria during the Day 1 Visit will receive the study drug. Study drug is applied by trained site personnel, the subject, and/or the subject's caregiver who was certified by the site Investigator. The person administering the dose will allow the drop formed at the tip of the eyedropper to fall freely into the conjunctival sac (fornix). The drop should not be allowed to touch any part of the eye or its surrounding tissues before it is (they are) released from the eyedropper's tip. During the Treatment Period, study drug will be applied to both eyes.

During administration of study drug, any solution that falls on the skin surrounding the eye is blotted away immediately and the skin cleansed with a cool wet wipe. If the entire administered dose of study drug falls on the skin surrounding the eye (i.e., none of the liquid enters the eye), a new dose of study drug is applied to the conjunctival sac (fornix).

Once the appropriate dose has been applied to the lower conjunctival sac (fornix) of the study eye, the Investigator or designee will allow the lower eyelid to gently return to its natural position. The subject is instructed to gently close both eyes for a minimum of sixty (60) seconds. The person who applied the dose will then remove all excess liquid from the eyelids and surrounding skin of the dosed eye using an absorbent material (e.g., gauze or tissue).

All used and unused study drugs must be returned to the site for drug accountability after each subject completes their participation in the trial (End-of-Study Visit).

The post-dose time points of this protocol refer to the time when the study drug dosing has been completed.

On days when AM pre-dose IOPs are measured, subjects will be asked not to ingest any caffeinated products from 5:00 AM through 10:15 AM that day.

9.3.5. Demographics

The birth date, gender, race and ethnicity of each subject will be documented in the Case Report Form (CRF).

9.3.6. Medical and Ophthalmologic History

Medical history, including any diseases, past surgeries, psychiatric illnesses and relevant medical history will be documented in the CRF, with particular attention given to cardiovascular conditions including hypertension, cardiac arrhythmias, and heart conduction disturbances. Ophthalmologic history will include ocular trauma and surgery, eye infections and inflammation, retinal vein occlusion, and acute or chronic vision disturbances.

POAG is generally defined as a condition in which subjects have: (1) elevated IOPs and (2) abnormal findings on examination of the optic disc and/or a visual field defect that correlates

with the optic disc abnormalities and is consistent with POAG. OHT is defined as a condition in which subjects have consistently elevated IOPs but fail to fulfill the above POAG definition. However, for the purposes of this study, the Investigator's clinical diagnosis of POAG or OHT is adequate to meet this entry criterion.

Each subject will be questioned regarding all anticipated elective medical procedures that may occur during the subject's planned participation in the study and these must be documented in the subject's medical record and the medical history section of the CRF.

9.3.7. Medication History

Medication history (past 45 days) will be documented during Screening. Any medication received by the subject prior to their signing the ICF and through completion of the washout period will be captured as Medication History. Any medication received by the subject following the start of the Placebo Run-In Period will be captured as Concomitant Medications.

Any medication taken consistently by the subject for 30 days prior to Screening and is not a prohibited medication may be continued during the trial if appropriately documented and captured in the CRF.

9.3.8. Concomitant Medications and Treatments

All concomitant medications taken by subjects from the start of the Placebo Run-In Period through completion of the End-of-Study Visit, including all additions, subtractions, or adjustments of medications, vitamins, and/or herbal supplements, must be documented in the CRF.

The Investigators and their designees are obligated to ensure the well-being of all subjects during this study. Consequently, no medication or treatment will be withheld from a subject requiring medical intervention. This may include treatments received by the subject prior to enrollment as well as in response to new medical conditions developed during the study. The Investigator or designee must inform a subject when concomitant medical intervention or treatment is indicated and report this in the appropriate section of the CRF.

9.3.9. Prohibited Medications

Tobacco products, electronic cigarettes, cannabis (medical or recreational) over-the-counter or herbal medications, alternative medicines, or analgesics are all prohibited from start of Placebo Run-In Period through completion of the End-of-Study Visit, with the exception of:

- ≤5 cigarettes daily,
- Oral vitamin D calcium supplementation, multivitamins, and/or AREDS vitamins for ocular health taken consistently for at least 30 days prior to Screening,
- Aspirin, acetaminophen, or ibuprofen taken consistently for approximately 30 days prior to Screening, with no anticipated dosing changes to take place during study conduct,

- Preservative free artificial tears, if taken consistently for at least 30 days prior to Screening and not administered within one hour of study medication AM or PM dosing. Of note, cyclosporine containing agents such as Restasis® are NOT allowed.
- Other vitamins, herbal supplements, or alternative medications taken consistently for at least 30 days prior to Screening AND approved by one of the medical monitors for each subject.

9.3.10. Prohibited Activities

Heavy exercise (e.g., running, heavy lifting, bicycling, power walking, kickboxing, rowing, and sit ups) and physical labor are prohibited from the start of the Placebo Run-In Period through the completion of the End-of-Study Visit, so as not to cause exercise-induced increases in serum creatinine phosphokinase (CPK) levels. Moderate exercise (e.g., swimming and walking outside or on a treadmill) is permitted.

Contact lenses may not be worn from the start of the Placebo Run-In Period through the completion of the End-of-Study Visit.

9.3.11. Prohibited Foods

More than 24 ounces of beer, 8 ounces of wine, or 4 ounces of liquor per day are prohibited from the start of the Placebo Run-In Period through completion of the End-of-Study Visit.

Caffeinated products are prohibited (e.g., chocolate, coffee, tea, or cola) from 5 AM through 10:15 AM on Placebo Run-In Day and Days -1, 1, 28, 56, and EOS Visit.

9.3.12. Vital Signs, Height, and Weight

Throughout the study, vital signs (resting blood pressure, pulse rate, temperature, and respiratory rate) will be obtained with the subject in a supine position after the subject has rested for 5 minutes.

Oral temperatures should not be obtained within 5 minutes of the ingestion of any food or drink in order to avoid their influencing the results.

Respiratory rate and manually-obtained pulse/heart rates will be recorded following a minimum of 30 seconds of observation. Pulse/heart rates may be measured electronically (for example, via an electronic blood pressure reader, monitor, or ECG). However, the heart rate data from a scheduled ECG may not be used to obtain these vital sign data.

The subject's height and weight will be documented in the CRF during the Screening Visit.

9.3.13. Physical Examination

Two types of physical examinations will be performed during the trial:

1. Complete physical examination includes skin, ears, nose, throat, lymph nodes, chest, heart, lungs, abdomen, as well as the neurological and musculoskeletal systems.
2. Directed physical examination includes skin, throat, chest, heart, lung, and abdomen.

Neither type of physical examination includes an eye, breast, rectal, or pelvic examination. Eye examinations are performed independent of the physical examinations.

All abnormal findings must be recorded whether they are new or were recorded previously in the CRF. For example, a surgical scar must be noted each time a physical examination is recorded.

9.3.14. Laboratory Tests

All Central Laboratory blood samples will be collected, processed and shipped as per the Central Laboratory's Instruction Manual on the same day as sampling. Samples will be obtained as per the time points listed in the Schedule of Assessments.

9.3.14.1. Hematology, Coagulation Parameters, and Clinical Chemistry Profile

Blood will be collected for hematology analysis including:

- White blood cell count
- White blood cell differential in absolute numbers, not percentages
- Hemoglobin
- Hematocrit
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration
- Red blood cell count
- Platelet count

Blood for coagulation analysis including:

- International normalized ratio
- Partial thromboplastic time

Blood for a clinical chemistry including:

- ALT
- AST
- Albumin
- Alkaline phosphatase
- Direct bilirubin
- Total bilirubin
- Blood urea nitrogen or urea
- Calcium and corrected calcium
- Total cholesterol
- Chloride
- Creatinine*
- Glucose
- Lactate dehydrogenase
- Inorganic phosphorus
- Potassium
- Total protein
- Sodium
- Triglycerides
- Uric acid
- Total CPK

*estimated glomerular filtration rate (GFR) will be estimated using the formula used by the central laboratory.

9.3.14.2. Urinalysis

Urine samples will be collected and analysis will include:

- Glucose
- Protein
- Erythrocytes
- Leukocytes

- pH
- Ketones
- Nitrites

9.3.14.3. Pregnancy Testing

Samples for pregnancy testing will be obtained from females of childbearing potential (as defined in Inclusion Criteria # 4) and will be performed on blood (during screening) and urine (at Day -1 and End-of-Treatment) samples.

9.3.14.4. Determination of Clinical Significance

The Investigators will use medical judgment when determining the clinical significance of any findings.

Subjects with clinically significant abnormal findings at Screening, Washout, Placebo Run-In Day, Day -1, or Day 1 pre-dose are excluded from this clinical study.

9.3.15. Electrocardiogram (12-Lead ECG)

A standard, surface 12-lead ECG for RR, PR, QRS, and QT intervals, heart rate, and rhythm will be obtained. ECGs in a digital format will be interpreted by a Board-Certified cardiologist at a central laboratory. The QT interval results will be adjusted for rate using the Bazett (QTcB) and Fridericia (QTcF) corrections.

Cardiac dysrhythmias will be documented by occurrence (date and time), severity, type, and duration. Isolated premature ventricular contractions and supraventricular extrasystolic waveforms will not be recorded.

Should an ECG recorded at any time after Screening demonstrate either a clinically significant change from the ECG obtained at screening or any new objective abnormality, the Investigator will immediately obtain an unscheduled ECG.

9.3.16. Ophthalmologic Examinations and Measurements

9.3.16.1. Ophthalmologic Procedures

The following ophthalmologic procedures will be performed as part of this trial. Only the personnel listed below may perform these activities.

1. External eye and slit lamp examinations: This will include a pen light examination of the peri-orbital area (i.e., eyelids, eyelashes and conjunctivae) and a slit lamp examination of the eyelids, eyelashes, conjunctivae, sclerae, cornea, anterior chamber, anterior vitreous, iris, and lens. This examination may be performed only by an optometrist or ophthalmologist.
    a. Hyperemia assessments are to be conducted on Day -1, Day 28, and Day 56 by a trained optometrist or ophthalmologist using a pen light and the sponsor provided hyperemia grading scale. Whenever possible, the same individual should perform hyperemia assessments for a subject throughout the trial.

2. Fundus examination (ophthalmoscopy/ funduscopy). This will consist of optic nerve examination including (vertical) cup to disc ratio, retinal vasculature, macula assessment, and peripheral retinal assessment. This examination may only be performed by an optometrist or ophthalmologist. If possible, the same person must perform this activity throughout the study on any one particular subject.
3. Gonioscopy: Careful examination of the angle via gonioscopy will only be performed once at Screening as part of the internal eye examination to confirm that the subject's angle is open (>10 degrees) and non-occludable. **Schaeffer grading is required.** If this procedure was performed within the past 180 days and documented in the subject's medical record, this procedure need not be repeated (unless the Principal Investigator [PI] suspects a change). This examination may be performed only by an optometrist or ophthalmologist.
4. Masked IOPs: Instructions for the masked reading of IOPs are described below. The slit lamp portion of the IOP measurement may be performed by a masked optometrist or ophthalmologist. If possible, the same operator (ophthalmologist or optometrist) must perform these activities on the same Goldmann tonometer throughout the study on any one particular subject. However, the person responsible for the pressure gauge IOP reader (see Section 9.3.16.2) may be a trained certified ophthalmic assistant (COA), certified ophthalmic technician (COT), nurse, or research coordinator.
5. Modified ETDRS Best-corrected visual acuity (BCVA) will be performed based on the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. This activity may be performed by an optometrist, ophthalmologist, or COT. A well-trained and experienced nurse or research coordinator may also perform this activity.
6. Visual Fields: The recommend visual fields include Humphrey (24-2 full threshold, 24-2 SITA standard, 30-2 central threshold, [Note: 24-2 SITA fast not allowed]) and Octopus (GI dynamic strategy, GI normal strategy, 24-2 dynamic strategy, 24-2 normal strategy). If this procedure was performed within the past 90 days, and documented in the subject's medical record, this procedure need not be repeated (unless the Principal Investigator [PI] suspects a change). This may be performed by a trained certified ophthalmic assistant (COA), certified ophthalmic technician (COT), nurse, or research coordinator.
7. Central Corneal Thickness will be performed utilizing an ultrasound pachymeter. If this procedure was performed within the past 365 days, and documented in the subject's medical record, this procedure need not be repeated (unless the Principal Investigator [PI] suspects a change). This examination may be performed only by an optometrist, ophthalmologist, or a trained certified ophthalmic technician (COT)
8. Eye drop application: This activity must be performed by an ophthalmologist, optometrist, COA, COT, or a research coordinator experienced in eye drop administration. Qualified subjects (or their caregivers) may apply the eye drops.

Note: Whenever an external eye examination and/or BCVA are scheduled with IOP measurements, the external eye examination and BCVA will be performed before application of the topical anesthetic for the IOP measurements.

Subjects will be instructed to avoid rubbing their eyes at any time during the study.

9.3.16.2. Instructions for Masked-IOP Readings via Goldmann Applanation Tonometry

Topical anesthetic and fluorescein will be applied prior to performing the masked-IOP assessment described below. This can be a combined topical anesthetic and fluorescein product (such as Fluress®, Flurox™, etc) or administration of a topical anesthetic and fluorescein separately.

Performance of the masked-IOP readings requires 2 trained personnel working together: (1) the tonometer operator responsible for positioning the subject and adjusting the tonometer; and (2) the IOP reader who reads the pressure gauge setting and records the IOP results.

The masked-IOP measurements will be performed as follows:

1. The tonometer operator must be an ophthalmologist or optometrist and will prepare the subject and the instrumentation. The subject should be comfortably seated at the tonometer. The subject should not be leaning, straining, stretching or stooping. The temperature and lighting in the tonometry room should be as consistent as possible from visit to visit.
2. The tonometer operator should not be able to read the IOP gauge from his position behind the tonometer. If necessary, the gauge will be shielded.
3. The IOP reader (any trained and experienced site personnel) sets the tonometer gauge to a setting between 10-20 mmHg.
4. The tonometer operator adjusts the pressure in a masked fashion and instructs the IOP reader to record the pressure without removing his eyes from the slit lamp.
5. The IOP reader records the measurement and resets the tonometer to a setting between10-20 mmHg, avoiding the setting used above. The tonometer operator will not be informed of the result obtained from the first pressure reading.
6. The tonometer operator adjusts the pressure again in a masked fashion and instructs the IOP reader to record the second pressure without removing his eyes from the slit lamp.
7. The IOP reader records the measurement. The tonometer operator will not be informed yet of the result obtained from the pressure readings.
8. The IOP reader calculates the difference between the 2 IOP measurements obtained.
9. If the 2 IOP readings differ by ≤2 mmHg, the IOP reader informs the tonometer operator that the readings are complete. The tonometer operator may then remove his eyes from the instrument and be told the results. However, if the first 2 IOP results differ by more than 2 mmHg, the IOP reader will again reset the tonometer to 10-20 mm Hg. The tonometer operator then adjusts the pressure again in a masked fashion and instructs the IOP reader to record the third IOP measurement.

Note: Goldmann Applanation Tonometer calibration will be checked monthly and recorded in a calibration log.

9.4. Withdrawal of Subjects

Subjects will be informed that they are free to withdraw from the study at any time.

The reason for any premature withdrawal must be explained in detail in the source document.

A subject may be withdrawn from the study under the following conditions:

- Subject withdraws consent.
- Subject's compliance to the protocol is poor, per discretion of the Investigator.
- Any condition that, in the Investigator's opinion, may cause risk to the subject (see also Section 9.5). In this case, the Investigator will specify the reason for the subject's withdrawal.

  Note: All effort will be made to capture the complete set of serial IOP measurements for the subject on the day of withdrawal.

- Occurrence of a concomitant disease that violates the study protocol due to its severity or duration or due to changes in treatment being required.

Any subject who withdraws or is withdrawn from the study should undergo the End-of-Study Visit procedures, preferably 7 (±1) days later, in order to assure the safety of the subject.

The data handling of subjects who fail to complete all scheduled visits is described in the Section 12.3.

9.5. Rescue Plan

In order to ensure subject safety, careful attention should be paid at each visit to the subject's IOP and general ophthalmologic condition. If any of the following occur, the subject should be withdrawn and begun on therapy per the Investigator's judgement:

- If subject's IOP in either eye exceeds 34 mmHg at any timepoint during the trial.
- At any time during the study the Investigator assesses there is a clinically significant risk to the subject's safety.

Due to each subject's clinical condition being unique, this rescue plan does not recommend a specific recue therapy for subjects. If a subject meets one of the conditions specified in this rescue plan, the Investigator should use their clinical judgment and knowledge of the subject's specific condition to institute the best treatment for that subject. For instance, if subject was on more than one drug or a fixed dose combination therapy prior to entry in the study, it may be determined that it is in the best interest of the prior subject to restart this therapy immediately to ensure a rapid return of the IOP into the target range for that subject.

10. TOLERABILITY AND SAFETY

10.1. Adverse Events

An AE is any unfavorable medical occurrence in a study subject that develops or worsens during the period of observation in the clinical study. No causal relationship with the study medication or with the clinical study procedure is implied by the use of the term "adverse event." AEs fall into the categories "non-serious" and "serious." Seriousness is not the same as severity (see Section 10.2).

Treatment-emergent Adverse Events (TEAEs) are AEs that occur following the first dose of study drug on Day 1 AM.

Surgical procedures themselves are not AEs; they are therapeutic measures taken for the AE, and will be documented as such. Planned hospital admissions and study-related procedures are also not AEs.

10.2. Clarification of the Difference between "Severe" and "Serious"

Severity describes the intensity of an event, irrespective of its medical significance (such as severe headache). This is not the same as seriousness, which is based on ICH guidelines. Seriousness (not severity) defines SAE reporting obligations. The severity of all AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in detail on the CRF.

- Mild: Discomfort noticed but no disruption of normal daily activity.
- Moderate: Discomfort sufficient to reduce or affect daily activity.
- Severe: Inability to work or perform normal daily activity.

10.2.1. Laboratory Test and Diagnostic Procedure Abnormalities

An abnormal result will not be recorded as an AE unless one or more of the below occurs:

- The abnormal test is accompanied by symptoms.
- The test result leads to an alteration or interruption in study medication.
- The test result requires medical or surgical intervention (e.g., significant hyponatremia).
- The test result is considered clinically significant by an Investigator.

If such an event occurs, the test should be repeated and appropriately monitored (Section 10.2.2).

10.2.2. Follow-up of Adverse Events

All AE related symptoms and/or signs will be followed until there is a return to the baseline status, all associated parameters have returned to normal (or are no longer considered clinically significant), or no further improvement is anticipated. Follow-up is mandatory, irrespective of causal relationship to the study drug(s). SAEs will be monitored until resolution, as medically indicated.

10.2.3. Documentation and Reporting of Adverse Events by Investigator

Instructions for the completion of AE reports in a clinical study are provided by the Sponsor. The following approach should be taken for documentation:

- All AEs (whether serious or non-serious, or considered an alert term) must be documented on the AE page of the CRF.
- Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually, as separate events.
- An AE should only be recorded once, irrespective of the study period, with the event stop date being the date of resolution, resolution with sequelae, or otherwise. If the same AE re-emerges after resolution, or the severity and/or the relatedness to study drug changes after the AE has been recorded in the CRF, a new event should be reported with the new description.
- Relationship of the AE to each study drug must always be assessed by the Investigator, as indicated in the CRF and SAE Report form.
- When appropriate, relevant supportive documents (e.g., medical reports, photographs) may be submitted to the Sponsor.
- The period of observation for the collection of AEs extends from the time the subject signs ICF until the conclusion of the End-of-Study Visit.
- If the Investigator is made aware of a drug-related SAE in a study subject after completion of the End-of-Study Visit, an SAE Report form should be completed. If the study site has been closed, the Sponsor Medical Monitor or his designee should be contacted.

10.3. Serious Adverse Events

An SAE is any AE that, at any dose, results in at least one of the following outcomes:

- Death. Death is an outcome, not an event. Where the cause of death is uncertain, the reported SAE should be the same as the term on the subject's death certificate.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an AE or SAE that hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization.
- Persistent or significant disability or incapacity. "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
- A congenital anomaly or birth defect.

- A medically serious event based upon appropriate medical judgment. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.4. Special Interest Adverse Events and Overdoses

There are no AEs of special interest in this clinical trial.

Any overdose of the study drug is to be reported to the Sponsor in an expedited detailed manner. For example, if 2 drops of study drug are applied to an eye instead of 1 drop, this should be reported as an overdose. In contrast, repeating an eye drop application due to uncertainty regarding the proper application of the first dose will not be considered an overdose.

Any AEs or SAEs, as defined in Section 10.1 and Section 10.3, associated with an overdose will be reported as such.

10.5. Reporting of Adverse Events

10.5.1. Reporting of Serious Adverse Events by Investigators

If the AE is serious, the Investigator must complete an SAE Report form, in addition to the AE page in the CRF.

The SAE Report Form must be completed in accordance with instructions provided by the Sponsor or designee. The completed form must be faxed or emailed to the Sponsor Pharmacovigilance designee within 24 hours of discovery of the SAE.

If, for any reason, the Investigator cannot notify the Sponsor Pharmacovigilance designee via the appropriate form or if the Investigator suspects that using this method will delay the notification (e.g., during a holiday period), the Investigator may verbally notify the Sponsor Medical Monitor or Designee via telephone. The SAE Report form must still be relayed at the earliest possible opportunity. SAEs must be reported to the IRB according to IRB guidelines.

The initial report must be as complete as possible, including details of the current illness and the SAE, and an assessment of the causal relationship between the event and the investigational product(s) or the study procedures.

Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented as a follow-up on the SAE Report form.

In addition, when a non-serious event becomes serious, details must be forwarded, within 24 hours of Investigator awareness that an AE has become serious, to the Sponsor or designee on an SAE Report form, with the date of the seriousness upgrade as the SAE start date.

All ancillary documentation (e.g., discharge letters, laboratory reports and consultations) must be sent to the Sponsor or designee. In the event of an SAE resulting in death, post-mortem reports should be routinely sent to the Sponsor or designee.

Any SAEs including death due to any cause, which occurs in any subject entered into treatment in this study or within 30 days following (self-reported by patient) cessation of treatment,

whether or not related to the investigation product, must be reported to the Sponsor within 24 hours. All subjects with SAEs must be followed-up for outcome.

10.5.2. Reporting of Serious Adverse Events by Sponsor

It is the Sponsor's responsibility to ensure that all legal reporting requirements are met. The Sponsor shall notify all applicable regulatory bodies and Investigators, while sites will notify IRBs, of any AE associated with the use of the drug that is both serious and unexpected as required by IRB regulations, and this will be done within applicable timelines.

10.5.3. Periodic Reporting of Adverse Events by Sponsor

The Sponsor will send a periodic safety summary to the Investigator and/or the local regulatory agencies as required by law and local regulations.

11. EMERGENCY PROCEDURES

11.1. Emergency Sponsor Contacts

In emergency situations, the Investigator must contact the Sponsor Medical Monitor or designee.

11.2. Emergency Unmasking

Should a serious safety concern arise and the Investigator feels it necessary to immediately obtain the code assignment of a specific subject, the Investigator may request the code assignment of only that specific subject from the electronic randomization system without obtaining prior permission from the Sponsor Medical Monitor or Designee. The Investigator must contact the Sponsor Medical Monitor (or designee) by telephone within 12 hours of such circumstances.

In all other cases, the Investigator must contact the Sponsor Medical Monitor (or designee) for unmasking approval. A decision to unmask the assignment code of a study subject must be made jointly by the Investigator, and the Sponsor Medical Monitor or designee. The decision to unmask a study subject will be documented in writing by the Sponsor Medical Monitor (or designee) before a subject's treatment group assignment is unmasked.

The time, date, reason(s) for the unmasking, and the actual treatment assignment must be documented in the subject's source documents at the time of the unmasking.

11.3. Emergency Treatment

During a subject's participation in the study, the Investigator or institution will ensure that emergency medical care is provided to a subject for all AEs as required. The Investigator or designee will inform a subject without delay whenever an emergent medical issue arises or if emergency medical intervention is required.

Local ocular conditions that may be emergent are included in Section 9.5, Rescue Plan.

12. STATISTICAL PLAN

12.1. Sample Size Determination

To address the primary objective of this trial, based on an assumed SD of 3.3 mmHg, a sample size of 30 subjects in each group will provide an estimate of the effect on IOP with a 95% Confidence Interval with a ½ width (precision) of no greater than 1.2 mmHg.

In order to compensate for an anticipated drop-out rate of 10%, approximately 33 subjects will be enrolled in each of the 5 treatment groups in order to complete the trial with approximately 165 enrolled subjects and a total of 150 evaluable subjects.

12.2. Analysis Populations

12.2.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all subjects who are randomized and who receive at least 1 dose of study drug (a modified ITT).

All efficacy analyses will be performed on the ITT population. For efficacy analysis, subjects will be analyzed in the treatment group to which they were randomized.

12.2.2. Per-Protocol Population

The Per-Protocol (PP) population is defined as all subjects who are included in the ITT population, who have at least 1 post dose IOP determination, and who were compliant. Subjects with major protocol violations, identified prior to unmasking/unblinding the study, will be excluded from the PP population.

Subjects who meet these criteria are “evaluable subjects”. In regards to study dosing, a compliant subject is defined as one who after randomization missed no more than 3 non-consecutive doses during the week preceding a scheduled site visit or 2 consecutive doses during the week preceding a scheduled site visit.

Selected efficacy analyses will be performed on the PP population.

12.2.3. Treated Population

Treated population is defined as all subjects who receive at least one dose of study drug. For safety analysis, all subjects will be analyzed according to the treatment actually received.

12.2.4. Washout Failure Population

The Washout Failure Population will include all subjects who had a Washout Visit or Placebo Run-In Visit and did not receive study drug.

All data collected in the electronic CRF (eCRF) for this population will be presented in the data listings.

12.3. Handling of Dropouts or Missing Data

Subjects who withdraw or are withdrawn from the study after the study drug has been applied will not be replaced.

The reason(s) for any premature withdrawal must be explained in detail in the CRF and source documents.

12.4. Statistical Analyses

All analyses will be presented by treatment group. Continuous variables will be described as the mean, median, standard deviation and range of n observations. Where applicable standard error of the means (SE) will be presented. Categorical data will be described with contingency tables including frequency and percent. A detailed statistical analysis plan will be developed prior to unmasking study data. Statistical analysis and data descriptions will be carried out using SAS statistical analysis software (SAS Institute, Inc., Cary, NC).

12.5. Demographic and Baseline Characteristics

The comparability of the dose groups will be summarized by the evaluation of the demographic information, including age, gender, race and ethnicity, and primary diagnosis for all subjects.

12.6. Efficacy

12.6.1. Efficacy Endpoints

- Mean Daily IOP-change from diurnal baseline (average of the 4 diurnal changes from baseline calculated during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.
- Mean Daily IOP (average of the 4 serial IOPs taken during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.
- Mean Daily IOP-change from study baseline (average of the 4 changes from study baseline calculated during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.
- Mean IOP at 8AM, 10AM, 12PM, and 4PM for the subject's ‘study' eye calculated at the end of each of the 4 weeks of treatment for each of the doses/combinations tested.
- IOP change from diurnal baseline [this is the time-matched subtraction of each of the 4 IOP timepoints of the circadian curve post randomization from the pre-randomization circadian curve] calculated at the end of the 4 weeks of treatment for each of the doses/combinations tested.
- IOP change from study baseline [this calculates the change in IOP from the 8AM Day 1 baseline IOP] calculated at the end of the 4 weeks of treatment for each of the doses/combinations tested.

12.6.2. Efficacy Analyses

The primary analysis will be performed on the ITT population. These analyses will be repeated based on the per-protocol population. The primary efficacy analysis will be based on the study eye. All the efficacy analyses will be assessed for each of the different treatment groups:

- Trabo 6.0% + LP 0.005%
- Trabo 6.0% + LP 0.0025%
- Trabo 3.0% + LP 0.05%
- LP 0.005%
- LP 0.0025%

IOP measurements will be evaluated by presenting descriptive statistics by treatment group, visit, and time point. For the efficacy endpoints means and 95% CI will be computed. In addition, adjusted means (adjusts for differences in baseline values) and 95% CI, will be computed based on an Analysis of Covariance (ANCOVA) model with treatment as the independent variable and baseline IOP as the covariate.

The effect of AM dosing vs PM dosing will be assessed using within subject comparisons.

12.7. Safety

12.7.1. Safety Analyses

The tolerability and safety of trabodenoson will be assessed based on AEs, findings of physical examinations, vital signs, clinical laboratory test results, 12-lead ECG tracings, BCVA, bilateral complete external and internal eye examinations with a standardized masked grading of conjunctival hyperemia, IOPs, drug exposure, concomitant medications, and withdrawals/terminations. These findings will be summarized by treatment group. AEs will be categorized by System Organ Class (SOC) and Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs as well as the severity and relationship to study drug will be summarized by treatment group.

12.7.2. Pharmacodynamic Assessments

In order to provide a robust assessment of potential systemic effects of therapy, vital signs (resting blood pressure, pulse rate, temperature, and respiratory rate) and laboratory measurements (e.g., ECGs) will be descriptively analyzed as pharmacodynamic markers.

13. CLINICAL SUPPLIES

13.1. Storage and Handling of Ophthalmic Study Drug and Matched Placebo Product

All Study Drug and Placebo will be sent to the clinical study site where it will be stored at 2-8 °C. Subjects will store the study drug in the refrigerator and shake it vigorously prior to dosing (instructions located in the Pharmacy Manual). Storage, labeling, handling, returns and accountability are described in detail in the study's Pharmacy Manual.

13.2. Dose Verification and Drug Accountability

All details of the drug receipt, storage, preparation, randomization, dispensation and returns (or destruction) will be contained within the Pharmacy Binder. This includes inventory and dispensing logs, temperature monitoring and drug storage locations, etc. maintained by the Pharmacist (or a trained designee).

14. STUDY DOCUMENTATION AND RECORDS RETENTION

14.1. Data Collection Methods

Electronic Data Capture (EDC) will be utilized in this trial. The EDC system is fully validated and conforms to Title 21 Code of Federal Regulations (CFR) Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements.

The trained Investigational site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture forms as needed) into the EDC system. All information on the eCRFs must be traceable to these source documents. Instances of missing or uninterpretable data will be discussed with the study site for resolution. The study site is responsible for providing missing data and resolutions to the data queries and for correcting the eCRFs as appropriate. Electronic CRFs must be reviewed, signed, and dated by the Investigator. Training for each site on the use of the EDC will be conducted and documented. All original laboratory, and ECG reports will be kept with the subject source documentation and a copy will be transmitted to the Sponsor (or designee), if required.

General compliance will be assessed at each study visit.

14.2. Monitoring

Inotek (or designee) will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

Before an investigational site can enter a subject into the study, a representative of Inotek will visit the investigational study site to:

- Determine the adequacy of the facilities;
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Inotek or its representatives. This will be documented in a Clinical Study Agreement between Inotek and the Investigator.

During the study, a monitor from Inotek or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the case report forms, and investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).

- Record and report any protocol deviations not previously identified.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Inotek (or designee) and those SAEs that met criteria for reporting have been forwarded to the IRB.

Prior to study start, the Investigator will be informed of the anticipated frequency of the monitoring visits. The Investigator will also receive a notification prior to each monitoring visit during the course of the study. It is expected that the Investigator and/or his/her sub Investigator(s) and other appropriate staff are available on the day of the visit in case any questions arise. The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.3. Data Retention

All relevant correspondence (e.g., with the Sponsor, CRO, IRB, etc.) relating to this clinical study conduct will be maintained in the appropriate file at the site.

The Investigator must retain all records, including the source documents, ICFs, central laboratory reports including ECGs, and all other study-related documentation at the study site for a period of at least 2 years following the date the last marketing application is approved for the study drug for the indication for which it is being investigated, or 2 years after the date that the FDA has been notified that all clinical investigation of the drug has been discontinued, whichever is greater, unless notified otherwise in writing by the Sponsor. These documents will, however, be retained for a longer period if required by the applicable regulations or if requested by the Sponsor. The Investigator must contact the Clinical Operations Department of the Sponsor and gain written approval prior to destroying any records. No study documents will be destroyed or moved to a new location without prior written approval of the Sponsor. If the Investigator relocates, retires, or withdraws from a clinical study for any reason, all records required for the study will be transferred to an agreed-upon designee, e.g., another Investigator.

15. CLINICAL STUDY ADMINISTRATION, ETHICS, AND CONDUCT

15.1. Good Clinical Practice

GCP is an important ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of study subjects are protected.

15.2. Confidentiality

15.2.1. Study Confidentiality

All information regarding the nature of the investigation provided by the Sponsor or its designee to the Investigator and his / her staff or designees (except for information required by law or regulations to be disclosed to the IRB, the subject, and/or the appropriate regulatory authorities) must be maintained in confidence by the Investigator and his / her staff or designees.

15.2.2. Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and subject number on eCRFs and other documents submitted to the Sponsor. Documents not submitted to the Sponsor include those that identify the subject (e.g., the signed ICF), and must be maintained in strict confidence by the Investigator, except as necessary to allow auditing by the IRB, Sponsor or its designee, FDA, and/or equivalent authorities.

15.2.3. Financial Disclosure

Prior to the start of the study, Investigators will release sufficient and accurate financial information that permits the CRO/Sponsor to demonstrate that an Investigator and all personnel listed on the FDA Form 1572 have no personal or professional financial incentive regarding the future approval or disapproval of the study medication such that his or her research might be biased by such incentive.

15.3. Subject Information and Informed Consent

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document that includes information about the study will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

All ICFs must contain the minimum elements as mandated by the FDA and ICH guidelines and will be subject to the Sponsor's (or designee's) approval as well as the IRB's approval. The

Sponsor (or designee) may submit ICFs to a central IRB for review and approval or favorable opinion contingent upon the prior Investigator permission and review.

The Investigator will not undertake any measures or procedures specifically required of a subject for the clinical study until valid consent has been obtained.

The Investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed, as per the site's standard operating procedures.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the ICF must be revised, submitted to the IRB for review and approval or favorable opinion. The revised ICF must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised ICF must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the amendment.

15.4. Study Closure

Completion or premature termination of the study will be reported by the Sponsor to the regulatory agency and by the Sponsor or by the Investigator to the IRB as required by local regulations or by the IRB. Once the database is locked, and all efforts are made to settle all outstanding queries, site closeout will occur. Study materials must be returned, disposed of or retained, as directed by the Sponsor.

15.5. Early Termination of the Clinical Trial

The Sponsor may at any time terminate this clinical trial. In the event of premature termination of the study, the Sponsor will notify the Investigators in writing. Notification will include instructions regarding subjects in the study at the time of termination. The Investigators or designee must immediately confirm receipt of this notification in writing. The Sponsor and the Investigators will then agree to a timely closure of the site by the Study Monitor(s) assigned by the Sponsor to the site. Drug accountability and data collection procedures discussed in Section 12.6 will be followed.

15.6. Termination of an Investigative Site

The Sponsor may at any time terminate a study site. Early termination of an investigative site should occur after verbal communication with the site.

Reasons for such actions include:

- Violations of GCP and/or regulatory guidelines.
- Investigator malfeasance, disbarment, or inappropriate behavior.
- Protocol or contract violation.
- Threat to the proper conduct, reliability, safety, or timely conclusion of the study.
- Failure to meet enrollment goals

16. INVESTIGATOR'S OBLIGATIONS

16.1. General

The Investigator agrees that the study will be conducted in accordance with the clinical protocol, FDA's GCP guidelines, ICH guidelines, and the Declaration of Helsinki (see Section 19.1). The Investigator will conduct all aspects of this study in accordance with all governmental, state and local laws.

The Investigator must sign and return the Investigator Signature Page of the protocol and/or amendments (if applicable) and provide to the Sponsor a current signed and dated curriculum vitae (CV). Each Sub-Investigator and study member must provide the Sponsor with a current CV, and license, if applicable. For studies conducted under an IND, the Investigator must sign and return a completed Form FDA 1572, "Statement of Investigator," to the Sponsor or its designee.

The Investigator must make study data accessible to the study monitors, Clinical Research Associate, IRB, FDA, and/or equivalent government regulatory authorities.

Prior to performing any study procedures on subjects, the Investigator will provide a copy of the most current, IRB-approved ICF to the potential participant to read. The Investigator will discuss the study protocol (explain the nature, purpose, procedures, possible risks, benefits, and duration) with the potential participant. The potential participant must be given ample time and opportunity to read the information and to enquire about details of the study. During and after the discussions, the Investigator will answer all protocol or procedural questions the potential participant may have. Once the Investigator is assured that the potential participant understands the implications of participating in the study, the potential participant or his/her legal authorized representative will be asked to give consent to participate in the study by signing and dating the ICF. Likewise, the person obtaining the consent is required to sign and date the ICF. A signed copy of the ICF must be provided to the subject.

The original ICF will be kept at the investigational site. The subject's medical record should include a statement that the subject has accepted to participate in this investigational study by signing the ICF.

16.2. Institutional Review Board

Before initiation of the study, the Investigator or designee must obtain approval of the clinical protocol and ICF from the IRB complying with the provisions specified in FDA CFR, Title 21, Part 56, ICH Guidelines, and all governmental, state and local laws.

A copy of the written IRB approval of the protocol, ICF and any other documentation (such as advertising) as appropriate must be provided to the Sponsor or its designee prior to initiation of the study. The approval letter must identify the IRB name and address, the clinical protocol by title and/or protocol number, and the date approval was granted. Furthermore, the approval letter must contain a statement that the IRB complies with the FDA CFR, Title 21, Part 56, and ICH Guidelines for a study conducted under an IND, or other applicable government regulations for studies not conducted under an IND.

The Investigator is responsible for supplying the IRB with the data required for continued review of this study at intervals not exceeding one year, or at intervals otherwise specified by the IRB. The Investigator shall supply the Sponsor with written documentation of this continued review. When necessary, an extension or renewal of the IRB approval must be obtained and this shall also be forwarded to the Sponsor.

A list of the IRB members will be forwarded to the Sponsor in accordance with local regulations.

The IRB and the regulatory authorities will be provided with any amendments for their review and/or approval. A yearly status report on the progress of the study will be submitted by the Investigator to the IRB per their regulations.

16.3. Protocol Adherence

The Investigator and his/her designees are required to adhere to the protocol. While deviations from the protocol are discouraged, they may be necessary in order to eliminate an immediate hazard to subjects or to facilitate adherence to protocol procedures.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a subject and that are deemed crucial for the safety and well-being of a particular subject may be instituted for that subject only. The Investigator or other attending physician will contact the Sponsor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB; however, the Sponsor and the IRB must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the subject's eCRF the reasons for protocol deviation and the ensuing events.

16.4. Protocol Amendments

Amendments may include the following: changes that affect the safety of subjects, or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject-selection criteria. Such changes will be prepared as a protocol amendment by the Sponsor. Protocol amendments must undergo IRB approval prior to implementation. Should the ICF require changes, the revised ICF must be approved also according to the same procedure.

16.5. Audits and Inspections

The Investigator will permit study-related monitoring, audits and inspections by the IRB, the Sponsor or its designee, government regulatory bodies, and quality assurance groups of all study-related documents. This includes direct access to source documents, regulatory documents, data collection instruments, study data, etc. The Investigator will ensure that all study-related facilities (e.g., pharmacy, laboratories, etc.) are maintained in accordance with GCP guidelines.

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable quality assurance offices.

17. USE OF DATA AND PUBLICATIONS

All information concerning the product as well as any matter concerning the activities and trade secrets of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and shall remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

In addition, the Sponsor has full ownership of the eCRFs that were completed as part of the study.

By signing the clinical study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international drug registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the Investigator's name, address, qualifications and extent of involvement. The Sponsor will ensure that a final report on the study is prepared.

As required by local regulations or by the IRB, a summary of the clinical study will be submitted by the Sponsor to the regulatory authorities and by the Sponsor or Investigator to the IRB.

The Investigator (or Sub-Investigator) may be required to sign a statement in the clinical study report confirming that, to the best of his or her knowledge, the above report accurately describes the conduct and results of the study.

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19. APPENDICES

19.1. Declaration of Helsinki

The World Medical Association
Declaration of Helsinki

World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and as revised by the World Medical Assembly in Tokyo, Japan in October 1975, 35th World Medical Assembly in Venice, Italy in October 1983, and in the 41st World Medical Assembly Hong Kong in September 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

10. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
11. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
12. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
13. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
14. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
15. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
16. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
17. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
18. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a

physician who is not engaged in the investigation and who is completely independent of this official relationship.

19. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
20. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

1. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
2. In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method.
3. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
4. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
5. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

1. The subjects should be volunteers — either healthy persons or patients for whom the experimental design is not related to the patient's illness.
2. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
3. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.