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I confirm that I have reviewed this document and agree with the content.

APPROVALS	
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Table of Contents

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BID	Twice-daily
BMI	Body Mass index
CI	Confidence Interval
CPK	Creatine Phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Estimated Glomerular Filtration Rate
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
INR	International Normalized Ratio
ITT	Intent-to-Treat
LBBB	Left Bundle Branch Block
LCVA	Low Contrast Visual Acuity
LSmeans	Least squared means

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
MMRM	Mixed effect model repeat measurement
OHT	Ocular Hypertension
OU	Each Eye
POAG	Primary Open-Angle Glaucoma
PP	Per Protocol
PT	Preferred Term
PTT	Partial Thromboplastin Time
QD	Once Daily
QTcB	Bazett Corrected QT Interval
QTcF	Fridericia Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SLT	Selective Laser Trabeculoplasty
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
ULN	Upper Limit of Normal
WHO	World Health Organization
WF	Washout Failure
WPW	Wolff-Parkinson-White syndrome
YAG	Yttrium Aluminium Garnet

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. TIMING OF ANALYSES

The final analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study. At that time, the database will be locked, the study will be unmasked, and then final analyses will be performed.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this study is 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.

All subjects were dosed (in a masked manner) with AM active drug during Weeks 1 – 4, and with PM active drug during Weeks 5 - 8.

3.2. SECONDARY OBJECTIVES

The secondary objectives are 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.

3.3. SUB-STUDY

The analyses for protocol "Low Contrast Visual Acuity (LCVA) Sub-study for IPC-02-1015", run on a subset of subjects from IPC-02-2015, is included in this SAP.

3.4. BRIEF DESCRIPTION

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 Ocular Hypertension (OHT) or Primary Open-Angle Glaucoma (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.

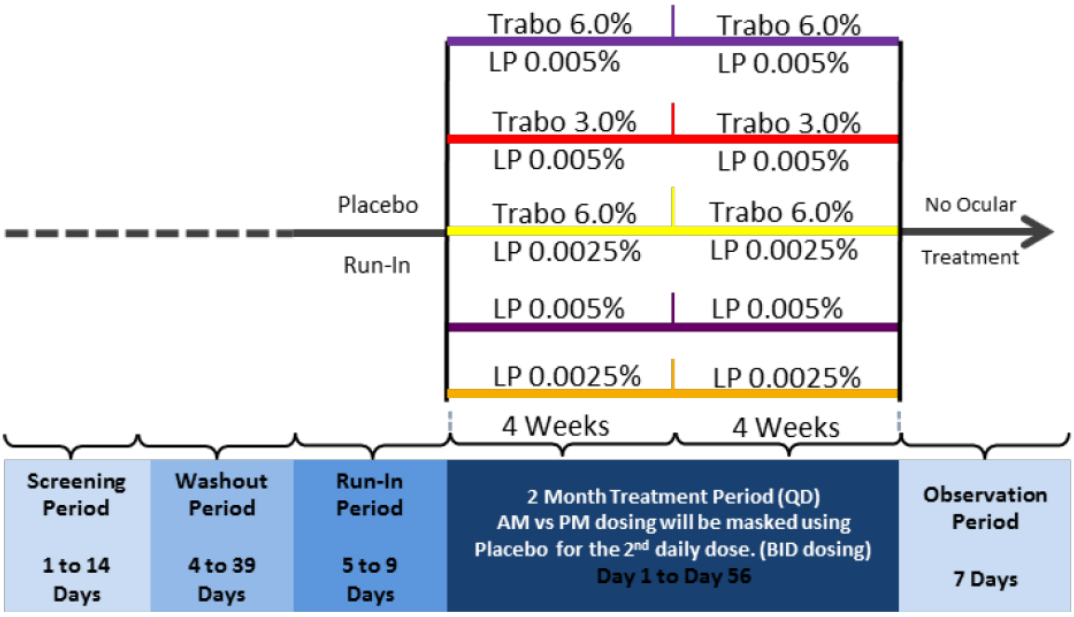
These periods are described in detail in the study protocol (Section 9.2).

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-Intraocular Pressures [IOPs]), local (ophthalmic) and systemic tolerability and safety assessments.

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

The following is a 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.



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

3.4.1. 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:

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 partner's oral/parenteral contraceptives) during the conduct of the study and for at least 1 month after last dose of study medication.

3.4.2. 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/M2, 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-glaucoma ophthalmologic disease that might exacerbate during the trial.

3. Subject's Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (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 mm Hg 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 on 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 Selective Laser Trabeculoplasty [SLT] or Argon Laser Trabeculoplasty) 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.

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 Protocol 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, 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 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 Protocol 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.

3.5. DETERMINATION OF SAMPLE SIZE

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 approximately 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.

3.6. TREATMENT ASSIGNMENT & BLINDING

Treatment group assignment and randomization will occur on the Day 1 Visit utilizing a validated Interactive Response Technology. Subjects will be randomized in equally allocated groups (1:1:1:1:1) to 1 of the following 5 treatment arms:

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.

All site personnel and enrolled subjects will be 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. Subjects will receive 4 weeks of AM active drug dosing and 4 weeks of PM active drug dosing. AM and PM dosing will also be masked.

(Note that all subjects will be dosed, in a masked manner, with AM active drug during Weeks 1 – 4, and with PM active drug during Weeks 5-8). In the event of an emergency in which unmasking is required at an investigative site, the emergency procedures detailed in the clinical study protocol will be followed (Protocol Section 11.2).

3.7. ADMINISTRATION OF STUDY MEDICATION

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, as defined in Section 6.5.4 of the protocol, will be determined on Day 1.

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).

Table 1: Binocular Dosing Regimen of Each Treatment Group

		Study Period				
	Screening	**Washout Period**	**Placebo Run-In**	**Treatment Period**		**Observation Period**
Randomized Group:	Range: 1 to 14 days	Range: 4 to 39 days	Range: 5 to 9 days	28 ±2 days (Day 1 to Day 28)	28 ±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						

3.8. STUDY PROCEDURES AND FLOWCHART

A full description of the study visit schedule can be found in the study protocol. Table 2 below presents the schedule of assessments for the study.

Table 2: 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 test	√		√	√	√	√	√	√
Low Contrast Visual Acuity (LCVA) Test[i]				√		√	√	
External eye examination [h]	√		√[h]	√[h]	√	√[h]	√[h]	√
Slit Lamp examination	√		√	√	√	√	√	√
Masked-IOPs	√		√	4√	√	4√	4√	√
Dilated Fundus examination	√							√
Vital signs	√		√	√	√	√	√	√
12-Lead ECG	√		√					√

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
Gonioscopy [c]	√							
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.
[i] The Low Contrast Visual Acuity (LCVA) test is only to be conducted on POAG subjects enrolled in the IPC-02-2015 LCVA Sub-study.

4. ENDPOINTS

4.1. 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.

4.2. SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints include:

1. Daily IOP (average of the 4 serial IOPs taken during a dosing interval) calculated at the Week 4 visit and the Week 8 visit.

2. 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.

3. Mean IOP at 8AM, 10AM, 12PM, and 4PM for the subject's ‘study' eye calculated at the Week 4 and Week 8 visit for each of the doses/combinations tested.

4. 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 Week 4 and Week 8 visit each of the doses/combinations tested.

5. IOP change from study baseline [this calculates the change in IOP from the 8AM Day 1 baseline IOP] calculated at the end of the Week 4 and Week 8 visit for each of the doses/combinations tested.

4.3. SAFETY ENDPOINTS

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.

4.4. SUB-STUDY ENDPOINTS

The analysis of data from the Low Contrast Visual Acuity (LCVA) Sub-study (protocol IPC-02-2015-LCVA) is included under this statistical analysis plan:

Primary Sub-study Efficacy Endpoint:

Change from Day -1 baseline in monocular (study eye only) Letter Score using the SLOAN 2.5% visual acuity chart at Day 56.

Secondary Sub-study Efficacy Endpoint

1. Change from Day-1 baseline in binocular (both eyes together) Letter Score using the SLOAN 2.5% visual acuity chart at Days 28 and 56.

2. Comparison of LCVA between pooled latanoprost alone arms and pooled fixed-dose combination arms at Days -1, 28 and 56.

5. ANALYSIS POPULATION

The study populations include Intent-to-Treat (ITT), the Per-Protocol (PP), and the Safety population. The primary analysis will be performed using the Intent-to-Treat Population. All decision rules regarding any exclusion of a subject from Intent-to-Treat, Per-Protocol, and safety populations will be made and documented before locking the study database and unmasking this study.

5.1. 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.

5.2. 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 with all critical study criteria. Subjects with major protocol violations that could potentially impact efficacy results will be identified prior to unmasking/unblinding the study, and will be excluded from the PP population.

In regards to study dosing, a compliant subject is defined as one who after randomization missed no more than 2 study doses during the week preceding a scheduled site visit or any of the 3 doses immediately preceding a scheduled site visit.

Selected efficacy analyses will be performed on the PP population.

5.3. SAFETY POPULATION

Safety 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

5.4. PROTOCOL VIOLATION OR DEVIATIONS

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.

If protocol violations do occur as outlined in the criteria below, then the data from complete individual subjects, individual visits or individual evaluations may be excluded from selected analyses. The finalization of protocol violations and excluded data will be made prior to the randomization code being revealed.

All protocol violations will be presented in a data listing.

Violation Criteria

Subjects who meet any of the following violation criteria may be listed and presented in the study report:

- Non-compliance with inclusion criteria
- Non-compliance with exclusion criteria
- Non-compliance with randomization
- Non-compliance with study drug treatment - A compliant subject is defined as one who after randomization missed no more than 2 study doses during the week preceding a scheduled site visit or any of the 3 doses immediately preceding a scheduled site visit.
- Non-compliance with Informed Consent
- Non-compliance with handling of the investigation Product
- Prohibited Concomitant Treatment
- Non-compliance with the Visit Window
- Non-compliance with Study Procedure for the Washout period.
- Receipt of incorrect randomized study drug

Other reasons for violation may be added to this list, but will be done so prior to unmasking of the study.

Deviations from the procedures listed in the protocol that do not fit the definition of a violation are called protocol deviations. Deviations from the protocol will be documented on an ongoing basis by the study monitors, project manager, and other study personnel.

Prior to the time of database lock, prior to unmasking and while the protocol violations are being reviewed, the project manager will forward all relevant documentation highlighting protocol deviations to the appropriate members of the project team. These deviations will be included in the protocol violation document for agreement and will be listed with the protocol violations in the clinical study report (CSR).

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All analyses will be presented by treatment group and dosing regimen (AM dosing, Week 1 – Week 4; PM dosing, Week 5 – Week 8). Summary statistics for continuous variables will be described by number of subjects (n), mean, median, standard deviation (SD) and minimum and maximum. For continuous efficacy variables, the standard error of the mean (SE) may also be reported. Categorical variables will be summarized using counts and percentages. All data collected will be included in the data listings.

Statistical analysis and data descriptions will be carried out using SAS statistical analysis software (SAS Institute, Inc., Cary, North Carolina, USA) version 9.3 or higher.

Summary statistics and analyses will be displayed for the following treatment groups:

- trabodenoson 6.0% / latanoprost 0.005% QD
- trabodenoson 3.0% / latanoprost 0.005% QD
- trabodenoson 6.0% / latanoprost .0025% QD
- latanoprost 0.005% QD
- latanoprost 0.0025% QD

Unless otherwise noted, the baseline value will be considered to be the most recent non-missing value (or mean value in the case of IOP) obtained prior to the first dose of study drug.

6.2. KEY DEFINITIONS

Mean IOP: "Mean IOP" is the average of the 2 or 3 IOP measurements per eye performed at each time point.

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) ≥ 5 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.

First Dose Date: The first dose date is defined as the date on which the first drop of study drug in treatment period is taken.

Last Dose Date: The last dose date is defined as the date on which the last drop of study drug in treatment period is taken.

Baseline:

- The study baseline is the last valid mean IOP prior to the first drop of the study drug (8AM on Day 1) .
- The diurnal baseline is defined the mean IOP at the respective time point (8AM, 10AM, 12PM and 4PM) on Day -1 for analyzing time-matched change.

Study Day: The study day is the current event date relative to the first dose date in the treatment period. That is, the study day = the current event date – first dose date +1 if the current event date is on or after the first dose date. Otherwise, the study day = the current event date – first dose date. That is, the first dose date is Study Day 1, the day preceding the first dose date is Study Day –1.

6.3. 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.

Complete missing or partial date will be presented in the listings as reported on CRFs. Missing or incomplete onset dates for adverse events and concomitant medications will be imputed as needed in order to determine treatment emergence or determine the prior and concomitant medications.

If an AE has a completely missing onset date, then the AE will be considered a TEAE unless a non-missing stop date indicates otherwise. In cases where severity is missing for TEAEs, the AE will be considered to be the highest degree of severity: Severe. In cases where relationship information is missing for TEAEs, the AE will be considered to be related. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an adverse event or a medication has a partial start or stop date, the following rules will be used to determine whether it is an AE or a TEAE, or a prior or concomitant medication.

Table 3: Partial Date Imputation for TEAE Determination

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month imputed as January	Missing month imputed as December

The imputed date is only used for determining TEAEs, prior and concomitant medications. The collected partial dates will be reported in the listings.

6.4. VISIT WINDOWS

The analyses will be based on visit designation. Visit dates are required within specified time windows relative to Day 1 Visit (see Table 2: Schedule of Assessments). The visits out of the visit window are considered protocol deviations, but the measurements at these visits are also included in the analyses. If there is more than one measurement within the same visit designation, then the observation recorded at the time closest to the target day will be used. When there is more than one measurement on the same day, the latest observation will be used in the analyses.

For subjects withdrawing early, the end of study data collected (Early Termination visit) will be mapped to the next planned visit for summarization and analysis.

6.5. SUBGROUPS

Subgroup analyses will include:

- Primary diagnosis – POAG versus OHT.
- Day 1 pre-dose baseline IOP – Baseline >26 mmHg versus Baseline ≤26 mmHg.
- Washout vs. No Washout.
- Race: African Americans versus non-African Americans.
- Baseline corneal thickness: ≥490 microns and ≤555 microns, >555 microns and ≤610 microns.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

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 (also see Protocol 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 number of subjects receiving study treatment, including the washout and placebo run-in failures and the number of subjects who completed or discontinued the study and the reasons for any premature discontinuation from the study will be summarized by randomized treatment group. A by-subject listing of early withdrawal and study population will also be provided.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All baseline and demographic characteristics will be summarized by treatment group. This will include age, sex, race, ethnicity, primary ophthalmic diagnosis, height, weight, body mass index (BMI), Study baseline IOP (mean IOP at 8AM on Day 1) and Diurnal Baseline (average of the diurnal IOP measurement on Day -1).

Age will be calculated as of the screening visit date using SAS functions as floor((intck('month',date_of_birth,visit_date) - (day(visit_date) < day(date_of_birth))) / 12) ; BMI will be calculated as BMI (kg/m2) = Weight(kg)/[Height(m)^2].

All information collected at baseline and for demographics will be provided in data listings.

7.3. 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.

All medical and ophthalmologic history will be documented in the eCRF and will be summarized by treatment group.

All information collected at screening for medical and ophthalmologic history will be provided in data listings.

7.4. MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

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.

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.

Concomitant medications will be summarized by treatment group, and presented by WHO Drug Dictionary Anatomic-Therapeutic-Chemical Code (ATC) level 3 with the highest occurrence in the overall column. Within each ATC level 3 group, prior and concomitant medications will be displayed by Preferred Term (standard medication name) in decreasing order in the overall column.

All medications (prior and concomitant medications) will be listed by subject.

8. EFFICACY

All efficacy data will be presented by randomized treatment group and dosing regimen (AM dosing, Week 1 – Week 4 when randomized treatment is used during AM; PM dosing, Week 5 – Week 8 when randomized treatment is used during PM).

The confidence interval and the adjusted means will be computed for the study eye. IOP measurements will be summarized separately for the study eye and non-study eye using descriptive statistics.

For the study eye, all the efficacy end points (both primary and secondary) will be evaluated by presenting descriptive statistics (n, mean, median, standard deviation and range) by treatment group, and visit. Empirical SE of the means and 90% and 95% CI's (assume standard normal distribution) will also be computed. In addition adjusted means (adjusts for differences in baseline values) and 90% and 95% CI's, will be computed based on an Mixed effect Model Repeated Measure (MMRM) model with treatment, visit, and the interaction of treatment and visit as the independent variables and baseline IOP as the covariate. All efficacy analyses will be performed on the ITT population and PP population.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint is the daily IOP-change from diurnal baseline (average of the 4 diurnal changes from baseline calculated during a dosing interval) calculated at the Week 4 (after 4 weeks of AM dosing regimen) visit and the Week 8 visit (after 4 weeks of PM dosing regimen). The four IOP measurements from Day -1 are used as the diurnal baseline for the analyses at both Week 4 and Week 8.

The daily IOP-change at Day 28 (AM dosing regimen) from diurnal baseline is calculated as average of the following diurnal changes:

Day 28 8AM IOP Change = Day 28 8AM IOP minus Day -1 8AM IOP

Day 28 10AM IOP Change =Day 28 10AM IOP minus Day -1 10AM IOP

Day 28 12PM IOP Change =Day 28 12PM IOP minus Day -1 12PM IOP

Day 28 4PM IOP Change=Day 28 4PM IOP minus Day -1 4PM IOP

The daily IOP-change at Day 56 from diurnal baseline will be defined similarly.
The daily IOP-change at Day 28 and Day 56 from diurnal baseline will be analyzed using Mixed effect Model Repeated Measure (MMRM) model with Daily IOP-change from diurnal baseline as the dependent variable, and treatment, visit, and the interaction of treatment and visit as factors, and Daily IOP at Day -1(average IOP of the four serial time points on Day -1) as a covariate. Taking into consideration the correlation of these visits, as well as intra-visit, the covariance structure will be assumed to be unstructured. In the event convergence cannot be attained, alternative structures will be attempted in the following order: Toeplitz, compound symmetry, and then autoregressive. Least squared means (LS means) will be estimated from the model by time point and treatment. LS means for each treatment group at Day 28 and Day 56 will be estimated using LS means from the MMRM model. The comparison of the

treatments are exploratory by nature, therefore multiplicity will not be controlled for. The following pair-wise treatment comparisons will be made between treatment groups:

- Trabodenoson 6.0%/ Latanoprost 0.005% vs Latanoprost 0.005% only;
- Trabodenoson 6.0%/ Latanoprost 0.0025% vs Latanoprost 0.0025% only;
- Trabodenoson 3.0%/ Latanoprost 0.005% vs Latanoprost 0.005% only.
- All three groups of Trabodenoson / Latanoprost vs. Latanoprost 0.005%
- Trabodenoson 6.0%/ Latanoprost 0.005% AND Trabodenoson 3.0%/ Latanoprost 0.005% vs. Latanoprost 0.005%.

The distribution of the data will be visually examined, and the residuals from the MMRM model will be investigated for normality using the univariate Shapiro-Wilk W-test. The primary endpoint, as well as parameters that do not meet the assumptions of a normal distribution will also be analyzed using a non-parametric version of the MMRM model above, utilizing ranked IOP post-baseline data. The Median, Q1, and Q3 will be summarized for each treatment group and combined treatment group and the p-values will be presented for the pairwise treatment differences of LS mean differences of rank at each visit.

The effect of AM dosing vs PM dosing will be analyzed by examining the within subject difference between the AM dosing (or Day 28) and PM dosing (or Day 56) within each treatment. The LS mean will be estimated from the model by the visit and treatment interaction. The within subject correlation will be adjusted by the covariance matrix used in the model.

The daily IOP change from diurnal baseline will be descriptively summarized for the following subgroups:

- Primary diagnosis – POAG versus OHT.
- Day 1 pre-dose baseline IOP – Baseline >26 mmHg versus Baseline ≤26 mmHg.
- Washout vs. No Washout.
- Race: African Americans versus non-African Americans.
- Baseline corneal thickness: ≥490 microns and ≤555 microns, >555 microns and ≤610 microns.

8.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

The following secondary analyses will be performed.

8.2.1. Daily IOP

Daily IOP, the average of the 4 serial IOPs taken during a dosing interval, will be calculated at the Week 4 visit (Day 28 – after 4 weeks of AM dosing regimen) and the Week 8 visit (Day 56 – after 4 weeks of PM dosing regimen).

Daily IOP=average of IOP at 8AM, 10AM, 12PM, and 4PM.

Daily IOP at Day 28 (AM dosing) and Day 56 (PM dosing) will be analyzed using a similar MMRM model as section 8.1, with Daily IOP as the dependent variable, treatment, visit, and the interaction of treatment and visit as factors, and Daily IOP at Day -1 (average IOP of the four serial time points on Day -1) as a covariate.

The mean daily IOP vs visit day will be plotted by treatment group.

8.2.2. Daily IOP –change from Study Baseline

A change from study baseline (8AM Day 1 predose IOP) analysis will be performed.

The endpoint at Day 28 (after 4 weeks of AM dosing) is calculated as the average of the following:

Day 28 8AM IOP Change from study baseline =Day 28 8AM IOP minus Day 1 8AM PRE-DOSE IOP

Day 28 10AM IOP Change from study baseline = Day 28 10AM IOP minus Day 1 8AM PRE-DOSE IOP

Day 28 12PM IOP Change from study baseline = Day 28 12PM IOP minus Day 1 8AM PRE-DOSE IOP

Day 28 4PM IOP Change from study baseline =Day 28 4PM IOP minus Day 1 8AM PRE-DOSE IOP

The endpoint at Day 56 will be calculated similarly.

Daily IOP –change from study baseline on Day 28 and Day 56 will be analyzed using the same MMRM model, with Daily IOP as the dependent variable, treatment, visit, and the interaction of treatment and visit as factors, and study baseline (Day 1 8AM pre-dose IOP) as a covariate.

8.2.3. Mean IOP at 8AM, 10AM, 12PM and 4PM

A mean IOP at each time point will be calculated for the subject's study eye at the end of week 4 and week 8 for each treatment group.

Mean IOP at each time point on Day 28 and Day 56 will be analyzed using the same MMRM model, with the IOP from the diurnal baseline as the dependent variable, treatment, visit, and the interaction of treatment and visit as a factor, and diurnal baseline of the corresponding time point as a covariate.

The mean IOP at 8AM, 10AM, 12PM and 4PM vs visit day will be plotted by treatment, for Day 28 and Day 56.

8.2.4. IOP Change from Diurnal Baseline

IOP change from diurnal baseline analysis, the time-matched subtraction of each of the 4 IOP time points of the circadian curve post randomization from the pre-randomization circadian curve, will be calculated at the end of the 4 weeks of treatment (Day 28 AM dosing, and Day

56, PM dosing) for each of the doses/combinations tested.

IOP change from diurnal baseline will be analyzed using the same MMRM model as section 8.2.3, with diurnal baseline of the corresponding time point on Day -1 as a covariate.

8.2.5. IOP Change from Study Baseline

IOP change from study baseline, calculated as the change in IOP from 8AM Day 1 baseline IOP, is computed at the end of the 4 weeks of treatment (Day 28 AM dosing, and Day 56 PM dosing) for each of the doses/combinations tested.

IOP Change from study baseline at 8AM will be analyzed using the same MMRM model as section 8.2.3, with Day 1 pre-dose IOP at 8AM as a covariate.

8.3. EXPLORATORY ANALYSES

An analysis of the primary endpoint, daily IOP change from diurnal baseline, will be performed excluding subjects considered to be "non-responders" to latanoprost. "Non-responders" will be defined as subjects with a daily IOP improvement from diurnal baseline of < 2 mmHg at Day 28 and Day 56.

Summary statistics by treatment group will be presented, and pairwise treatment comparisons, as well as the analysis of the effect of AM dosing vs PM dosing will be performed as described in section 8.1.

8.4. LCVA SUB-STUDY ENDPOINTS AND ANALYSES

Analyses for LCVA 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.

Demographic data and baseline characteristics will be descriptively summarized by dose group for this sub-study population.

Primary LCVA Endpoint:

- Change from Day -1 baseline in monocular (study eye only) Total Letter Score using the SLOAN 2.5% visual acuity chart at Day 56.

Secondary LCVA Endpoints:

- Change from Day -1 baseline in binocular (both eyes together) Total Letter Score using the SLOAN 2.5% visual acuity chart at Days 28 and 56.
- Comparison of the LCVA Total Letter Score between pooled latanoprost alone arms and pooled fixed-dose combination arms at Days -1, 28 and 56.

All LCVA total letter score will be summarized for the ITT population, and by primary diagnosis. The LCVA analyses of change from baseline will be performed on the ITT

population, POAG subjects. The analysis for LCVA 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%

LCVA Letter Scores will be evaluated by presenting descriptive statistics for the change from baseline by treatment group and visit. Means and 90% and 95% Confidence Intervals (CI) will be computed.

Secondary analyses will be performed using the same methods as above for:

- the change from baseline in binocular LCVA Total Letter Score;
- the change from baseline in monocular LCVA Total Letter Score, pooling the latanoprost alone dose arms and pooling the fixed-dose combination arms (in addition, for the pooled dose groups, adjusted means and 95% CI will be computed based on an Analysis of Covariance (ANCOVA) model with treatment as the independent variable and baseline LCVA as the covariate).

Baseline is defined as the Day -1, pre-dose LCVA Letter Scores.

Listings and descriptive summaries will include all LCVA sub-study subjects. Analyses will include only POAG subjects.

8.5. SAFETY

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. The Safety population is used as the analysis population for all the safety analyses. AEs will be categorized by System Organ Class (SOC) and Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1). The incidence of AEs as well as the severity and relationship to study drug will be summarized by treatment group.

8.6. EXTENT OF EXPOSURE

Exposure to study treatment will be summarized by treatment group. Duration of treatment will be defined as:

Duration = (last dose date minus first dose date) plus 1.

If last dose date is missing, end-of-study date will be used.

The duration of treatment will be summarized using descriptive statistics.

8.7. TREATMENT COMPLIANCE

The compliance will be expressed as a percentage and calculated as the number of doses taken divided by the number expected to have been taken times 100. The compliance with study medication will be summarized using descriptive statistics.

8.8. ADVERSE EVENTS

AEs will be categorized by System Organ Class (SOC) and Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA version 19.1).

AE summary tables will focus on treatment emergent adverse events (TEAEs), defined as AEs that occur following the first dose of study drug on Day 1 AM. The data listings will include all AEs. Non-treatment emergent AEs will be flagged in the listings;

The following AE subsets will be summarized by SOC, PT, and treatment group:

- Treatment emergent AEs
- Treatment emergent serious adverse events (SAE)
- Adverse events leading to study withdrawal

Treatment emergent AEs will also be summarized by SOC, PT, maximum severity (mild, moderate, severe), and treatment group. A summary of treatment emergent AEs by SOC, PT, maximum relationship (not related, related) to study drug, and treatment group will also be provided. A separate listing of serious adverse events and listing of adverse events leading to study drug discontinuation will also be provided.

8.9. LABORATORY EVALUATIONS

The following laboratory tests will be performed for this study:

Hematology:

- White Blood Cell Count
- White Blood Cell Differential in absolute numbers, not percents
- Hemoglobin
- Hematocrit
- Mean Corpuscular Volume
- Mean Corpuscular Hemoglobin Concentration
- Red Blood Cell Count
- Platelet Count

Coagulation analysis:

- International Normalized Ratio (INR)

- Partial Thromboplastin Time (PTT)

Clinical chemistry:

- 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
- Glomerular filtration rate (GFR) will be estimated using the formula used by the central laboratory

Urinalysis:

- Glucose
- Erythrocytes
- Protein
- Leucocytes
- pH
- Nitrites
- Ketones

Findings from the central laboratory data will be summarized by lab parameter, study visit, and treatment group using descriptive statistics. Categorical and numeric variables will be presented separately.

Absolute parameter value will be summarized at Baseline. Baseline is defined as the last non-missing value before the first dose of study medication. Day 28 and EOS. Changes from Placebo-Run-in visit to Day 28 and EOS will also be summarized.

Shift tables presenting the change, relative to the normal range, from baseline to post Day 1 visits will be provided.

Only scheduled laboratory results will be summarized. All laboratory results (i.e., scheduled and unscheduled) will be listed. Results outside predefined normal ranges will be flagged in the data listing.

8.10. VITAL SIGNS

Vital signs will be assessed at Screening, Placebo Run-In Visit, Day -1, Day 1, Day 28, Day 56 and EOS. Results for resting systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be summarized by study visit and treatment group. Changes from baseline in blood pressure, pulse rates and respiratory rates will be summarized by visit and treatment. Height and weight will be assessed during the screening period. Summary statistics of height and weight will be presented together with the baseline parameters. Baseline is defined as the last non-missing value before the first dose of study medication.

Vital sign measurements will be presented for each subject in a data listing.

8.11. ECG

ECGs will be assessed at Screening, Placebo Run-In Visit, and EOS. 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.

The quantitative (interval measurements) along with changes from baseline will be summarized by visit and treatment group. Baseline is defined as the last non-missing value before the first dose of study medication. QT, QTcB, and QTcF in the categories below will be summarized using frequency and percentage:

1) > 450 for male and 470 for female;
2) >500;
3) Change > 60;
4) Change between 30-60 (inclusive);
5) Change <30.

The overall ECG interpretation (normal / abnormal, clinically significant / abnormal, not clinically significant) collected on the CRF will be summarized by treatment group.

All data obtained from the ECGs will be listed.

8.12. 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.

Complete physical examination occurs during screening and at the end of study visit.

Directed physical examination occurs on Day 1.

A separate listing of all abnormal findings for complete physical examination and directed physical examination will be provided.

8.13. EYE EXAMINATIONS, IOP ASSESSMENT, BCVA AND LCVA

Safety assessments of the eye include:

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. Hyperemia assessments are to be conducted at Placebo Run-In, Day -1, Day 28, and Day 56 at pre-dose and 8 hours post dose. A score of '0' means hyperemia and a non-zero value means hyperemia. The incidence of hyperemia will be tabulated at Day -1, Day 28 and Day 56 for both pre-dose and post-dose. Change in incidence of hyperemia from Day -1 to Day 28 and Day 56 will be presented in a shift table by comparing Day -1 time-matched incidences. Frequency of abnormal results from the examinations will be summarized by treatment, visit, timing relative to study drug dosing, and eye (study eye or non-study eye).

2. Dilated Fundus examination (ophthalmoscopy/ funduscopy) will be performed at the screening period and end of study visit. The examination consists of optic nerve examination including (vertical) cup to disc ratio, optic nerve head, retinal vasculature, macula assessment, and peripheral retinal assessment. Abnormal findings will be listed. Cup to disc ratio will also be summarized by descriptive statistics by treatment group, visit and eye (study and non-study). Frequency of visibility and abnormal results from the examinations will be summarized by treatment, visit, timing relative to study drug dosing, and eye (study eye or non-study eye).

3. Masked IOPs: The Masked IOPs will be measured at Screening, Placebo Run-In Visit, Day -1, Day 1, Day 28 and Day 56 and EOS.

4. Gonioscopy will be performed once at Screening in order to confirm that the subject's angle (>10 degrees) is open 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).Binary findings (open versus closed/narrow), Schaeffer grade, and other pathology findings will be listed and no statistical analyses will be performed.

5. Best corrected visual acuity test (BCVA) will be performed via a modified Early Treatment Diabetic Retinopathy Study (ETDRS) protocol at Screening, Placebo Run-In Visit, Day -1, Day 1, Day 28, Day 56 and EOS. Descriptive statistics will be provided for BCVA. Total letter scores will be tabulated by treatment group, visit, and eye (study and non-study eye).BCVA total letter score, Snellen equivalent, refraction left and right eye will be listed for each subject.

6. Low Contrast Visual Acuity (LCVA) will be performed in a subset of subjects enrolled in the LCVA sub-study, using 2.5% Contrast Sloan Letter Charts at Placebo Run-In Visit, Day -1, Day 28 and Day 56. Descriptive statistics will be provided for LCVA. Total letter scores will be tabulated by treatment group, visit, eye (study and non-study eye), and for both eyes together (binocular). LCVA total letter score will be listed for each subject.

7. 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). Visual fields will only be performed at Screening and the End of Study visit. Mean deviation (dBel) and p value will be summarized by treatment, visit and eye. For the end of study visit, the frequency of clinically significant progression will be tabulated by eye and treatment. A listing of visual field program used, mean deviation (dBel) and P value by subject will be provided.

8. 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). A listing of the findings will be provided.

For all summaries, non-study eye findings will also be summarized for comparison with the study eye.

8.14. OTHER SAFETY

Samples for pregnancy testing will only be obtained from enrolled females of childbearing potential (as defined in Inclusion Criteria #4) and will be performed on blood (during Screening) and urine (at Day -1 and Day 56(EOT)) samples.

9. INTERIM ANALYSES

There is no planned interim analysis.

10. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

- Washout failure population is defined in the protocol, but not used. It is thus removed from the SAP.
- 90% confidence intervals have been included, in addition to the 95% confidence intervals.
- An exploratory analysis on daily IOP change from diurnal baseline, excluding “non-responders” to latanoprost has been added.
- The LCVA analysis will only be performed on the ITT population due the small sample size in the Per-Protocol Population.

11. REFERENCE LIST

12. PROGRAMMING CONSIDERATIONS

The following conventions will be followed for this study.

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® 9.3 or later (SAS® Institute Inc., Cary, NC, USA) Computer-generated table, listing and figure output will adhere to the following specifications.

12.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs. / A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

12.2. TABLE, LISTING, AND FIGURE FORMAT

12.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:

<Sponsor Name> Protocol XXX (
Draft/Final Run <date>

- All output should have Page n of N at the bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date and time of table and listing creation should appear bottom. The source listing number for table will appear bottom left.
- The SAS program name should appear on each page.

12.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is in the top left portion of table and listing. A table or listing number followed by the title of table or listing will be presented. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

12.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

12.2.5.2. Table Conventions

- Units will be included where available
- All tables have their source listing referenced in a footnote
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, standard deviations and standard error should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Std Error	X.XX
Median	XXX.X
Minimum	XXX

Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available. The unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion.
- In the case that a subject's record has been continued to the next page, an appropriate identification (eg., subject ID number) must be presented at the beginning of that page.

12.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

13. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

INC Research SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.