Nicox Ophthalmics, Inc.

777 Main Street, Suite 1292, Fort Worth, Texas 76102 USA

Compound

NCX 470

Study Number

NCX-470-17001

Study Title

A Phase 2, Randomized, Multicenter, Masked, Parallel-Group, Dose Response Study Evaluating the Safety and Efficacy of NCX 470 (3 doses: 0.021%, 0.042%, and 0.065%) vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension

PROTOCOL

Version # 2.0

Released on 23 OCT 2018

Clinical Development Phase: 2

Sponsor: **Nicox Ophthalmics, Inc.**
777 Main Street, Suite 1292
Fort Worth, Texas 76102 – USA

NCT 03657797

PROTOCOL SIGNATURE PAGE

Study No.: NCX-470-17001

Title: A Phase 2, Randomized, Multicenter, Masked, Parallel-Group, Dose Response Study Evaluating the Safety and Efficacy of NCX 470 (3 doses: 0.021%, 0.042%, and 0.065%) vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension

APPROVAL OF STUDY PROTOCOL

Version: Version 2.0
Release Date: 23 OCT 2018

Site Details (Address and Telephone Number):

_____

_____

The undersigned confirms that:

- This protocol has been read in its entirety and agreed to all aspects.
- This study will be implemented and conducted diligently and in strict compliance with the protocol, Good Clinical Practices, and all applicable laws and regulations.
- All information supplied by Nicox or its legal representatives will be maintained in confidence and, when this information is submitted to an Institutional Review Board (IRB) it will be submitted with a designation that the material is confidential.

Principal Investigator:

(Printed Name)	Date	Signature

Sponsor: Nicox Ophthalmics, Inc.
777 Main Street, Suite 1292, Fort Worth, Texas 76102 USA

[redacted]

CONTACT INFORMATION

Protocol Identification
A Phase 2, Randomized, Multicenter, Masked, Parallel-Group, Dose Response Study Evaluating the Safety and Efficacy of NCX 470 (3 doses: 0.021%, 0.042%, and 0.065%) vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension.

Version #2.0 released on 23 OCT 2018

Sponsor
Nicox Ophthalmics, Inc.
777 Main Street, Suite 1292
Fort Worth, Texas 76102
USA

Sponsor Contact
[redacted]

Company Representing the Sponsor:
[redacted]

Primary Contact for Study Related Matters and SAEs:
[redacted]

Medical Monitor:
[redacted]

PROTOCOL HISTORY TABLE

VERSION #	VERSION DATE	REASONS FOR CHANGES	DETAILS OF CHANGES
1.0	18 JUN 2018	Original version	Not Applicable
2.0	23 OCT 2018	Amendment 1	
		To broaden eligible patient population	Increased age limit from [redacted]
		To allow greater flexibility for patient screening	Revised Screening Visit IOP measurement time to allow [redacted] Accordingly, revised inclusion criteria 5 to include subjects who had previously used a PGA or NO-donating PGA therapy to have a time-matched IOP [redacted].
		To identify an additional procedure that is not allowed	Revised exclusion criteria 11 [redacted]
		To exclude the use of prescription or OTC medications which interfere with the evaluation of safety and efficacy of the study medication	Added an exclusion criteria for patients who currently require treatment or are expected to require treatment with any ocular medications, including those applied to the eyelids or eyelashes, during the study period (over-the-counter artificial tears are allowed). Revised list of prohibited medications in accordance with updated exclusion criteria
		To allow greater flexibility for scheduling Week 4 Visit	Expanded Week 4 Visit window from [redacted]
		To allow greater flexibility for sequencing of assessments	Clarified that assessments at each visit should be performed in accordance with the site's standard clinical practice, and in accordance with instructions in Appendix 2
		To allow greater flexibility for scheduling visits	Clarified that the washout period between the Screening and Eligibility 1 Visit [redacted], and that the period between the Screening and Eligibility 2 Visit [redacted]

VERSION #	VERSION DATE	REASONS FOR CHANGES	DETAILS OF CHANGES
2.0	23 OCT 2018	Amendment 1 (continued)	
		Clarification	Appendix 1 -- Clarified the timing of the Exit Visit
			Section 7.1 and Appendix 2 -- Clarified that visual fields, [redacted]
			Section 6.5 -- Removed reference to [redacted]
			Section 7.8 – Clarified that an Unscheduled Visit form is not required for [redacted]
			Appendix 2 – Clarified time at which [redacted]
			Appendix 2 -- Corrected visit at which iris [redacted]
			Appendix 2 – Adding rounding guidelines for [redacted]
			Appendix 2 – Added guidelines as to when [redacted] collected in the order of assessments

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS	
ACE	Angiotensin-converting Enzyme
AE	Adverse Event
AEs	Adverse Events
ALT	Argon Laser Trabeculoplasty
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BCVA	Best Corrected Visual Acuity
BP	Blood Pressure
CI	Confidence Interval
COV	Close Out Visit
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
DBP	Diastolic Blood Pressure
DMP	Data Management Plan
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
[redacted]	[redacted]
[redacted]	[redacted]
logMAR	Logarithm of Minimum Angle Resolution
LS	Least Square
MI	Multiple Imputations
MIG	Minimally Invasive Glaucoma

MMP	Monitoring Management Plan
mmHg	Millimeters of Mercury
ND	Not Done
NO	Nitric Oxide
OAG	Open-Angle Glaucoma
OHT	Ocular Hypertension
PGA	Prostaglandin Analog
PGF2α	Prostaglandin F2α
PI	Principal Investigator
PP	Per Protocol
QD	*Quaque Die* (once daily)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDV	Source Data Verification
SLT	Selective Laser Trabeculoplasty
SMP	Safety Management Plan
TM	Trabecular Meshwork
TEAE	Treatment Emergent Adverse Event
US	United States
VA	Visual Acuity
vs.	Versus
WHO	World Health Organization

Note: the first occurrence of some abbreviations is not spelled out in the document (e.g., units of measure).

STUDY OUTLINE / PROTOCOL SYNOPSIS

Title	A Phase 2, Randomized, Multicenter, Masked, Parallel-Group, Dose Response Study Evaluating the Safety and Efficacy of NCX 470 (3 doses: 0.021%, 0.042%, and 0.065%) vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension
Study No.	NCX-470-17001
Sponsor	Nicox Ophthalmics, Inc.
Background and Rationale	Glaucoma is a leading cause of blindness worldwide (Jonas, 2017). Intraocular pressure (IOP) is the primary risk factor for glaucoma (Jonas, 2017), and lowering IOP to prevent optic nerve injury is currently the only proven effective treatment (Jonas, 2017). Topical prostaglandin analogs (PGAs), such as latanoprost, bimatoprost, and travoprost, are the most common first-line therapies used to lower IOP in glaucoma patients (Daka, 2014). Nicox is developing NCX 470, a nitric oxide (NO)-donating bimatoprost prostaglandin analog, as a new therapy for lowering of IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). When exposed to esterases in the eye, NCX 470 is cleaved into the prostamide bimatoprost, which in turn is converted to bimatoprost acid, a prostaglandin F2α receptor agonist, and into 6-(nitrooxy)-hexanoic acid, a NO-donating moiety. Nitric oxide relaxes the trabecular meshwork (TM) and increases outflow of the aqueous humor through the primary outflow mechanism from the anterior chamber (Gabelt, 2011; Heyne, 2013; Cavet, 2014). In an additive manner, bimatoprost acts by increasing the outflow of aqueous humor primarily through the uveoscleral pathway (Krauss, 2004). The additive effect of a NO-donor and a prostaglandin F2α receptor agonist has been established in clinical trials with latanoprostene bunod, a dual-acting single molecular entity with NO-donating moiety linked to latanoprost. Latanoprostene bunod ophthalmic solution, 0.024% (VYZULTA™) was developed for the reduction of IOP in patients with OAG or OHT (Meideiros, 2016; Weinreb, 2016). In addition to the clinical validation of this approach, extensive nonclinical studies for both NCX 470 and latanoprostene bunod support this dual mechanism of action of NO-donating PGAs for increased outflow via TM and uveoscleral pathways.
Study Period	Second half 2018-second half 2019
Study Phase	Phase 2
Study Design	Randomized, multicenter, masked, parallel groups, active comparator-controlled, dose-response study
Number of Subjects	This study will be conducted in approximately 20 sites in the United States. [redacted] and 420 will be randomized.

Study Objectives	The primary objective is to demonstrate that the mean diurnal IOP reduction at the Week 4 Visit with NCX 470 QD is non-inferior to latanoprost 0.005% QD for one of the tested concentrations of NCX 470. A secondary objective is to demonstrate that the mean diurnal IOP reduction at the Week 4 Visit with NCX 470 QD is superior to latanoprost 0.005% QD for one of the tested concentrations of NCX 470. Another secondary objective is to demonstrate that one of the tested concentrations of NCX 470 is safe and well tolerated.
Selection of Target Subject Population	The target population in this study will be adult men and women with a diagnosis of OAG or OHT in both eyes.
Study Medication, Comparator, Dosage and Mode of Administration	There will be 4 treatment groups, including 3 different concentrations of NCX 470 ophthalmic solution and an active comparator latanoprost ophthalmic solution 0.005%. Subjects will be randomized in a 1:1:1:1 ratio to receive NCX 470 or latanoprost QD in the evening, one drop in both eyes, in the following manner: • NCX 470 ophthalmic solution, 0.021% • NCX 470 ophthalmic solution, 0.042% • NCX 470 ophthalmic solution, 0.065% • Latanoprost ophthalmic solution, 0.005%
Study Conduct and Duration of Treatment	Subjects will be evaluated over 7 clinical visits. Eligible subjects will be withdrawn from their pre-study IOP-lowering medications after the Screening Visit (minimum washout duration: [redacted] Study medication will be administered QD for approximately 27 days from the evening of the Eligibility 2 Visit (Day 1) to the evening of the day before the Week 4 Visit (Day 28 [-2 days to + 1 day]).

Inclusion Criteria	1) Subjects will be of legal age (at least 18 years of age) on the date the informed consent form (ICF) is signed and must be able to provide a written informed consent to participate in the study, in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local regulations, before initiating any study-related procedures. 2) Subjects will have a diagnosis of OAG or OHT in both eyes (OHT must have been documented for at least the past 6 months). 3) If treated for OAG or OHT, treatment nature and dose regimen must have been stable for both eyes for the 30 days prior to the Screening Visit. 4) Subjects will meet the following IOP requirements at the Eligibility 1 (Days -3 to -7) **and** Eligibility 2 (Day 1) Visits: • [redacted] [redacted] [redacted] 5) [redacted]. 6) Subjects with best-corrected visual acuity (BCVA), using Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, of +0.7 logMAR units (Snellen equivalent ~20/100) or better in each eye. 7) If female, subjects must either be incapable of pregnancy because of bilateral oophorectomy, hysterectomy, bilateral tubal ligation, or be post-menopausal (have been amenorrheic for at least 2 years) or must use an effective (e.g., double barrier) method of birth control for the duration of the study. Female subjects of childbearing potential must have a negative pregnancy test and not be nursing. 8) Subjects who are able and willing to comply with all study procedures.
Exclusion Criteria	1) Subjects < 18 or > 85 years old. 2) [redacted]. 3) Subjects with advanced glaucoma, pigmentary, or pseudo-exfoliative glaucoma, and subjects with a cup/disc ratio greater than 0.8, or a history of split fixation, or a field loss threatening fixation in either eye. 4) Subjects with narrow angles (3 quadrants with less than Grade 2 according to Shaffer anterior chamber angle grading system) and subjects with angle closure, peripheral anterior synechiae, congenital, and/or secondary glaucoma, or a history of angle closure in either eye. 5) [redacted]

	6) Subjects with any condition that prevents reliable applanation tonometry in either eye (e.g., significant corneal surface abnormalities, scars, keratoconus). 7) [redacted] 10) [redacted] 12) [redacted] 15) Subjects unwilling or unable to discontinue pre-study IOP-lowering medication(s) (see protocol Section 3.2). 16) Subjects with a known hypersensitivity or contraindications to PGA(s) or any of the ingredients in the study medications. 17) [redacted] 18) Subjects who currently require treatment or are expected to require treatment with ocular, topical, or systemic corticosteroids during the study period (inhaled, intra-articular, or intranasal steroids are allowed). 19) [redacted] 21) Subjects who currently require treatment or are expected to require treatment with any ocular medications, including those applied to the eyelids or eyelashes, during the study period (see protocol Section 5.2) (over-the-counter

	artificial tears are allowed – see protocol Section 5.1). 22) Subjects with a history or presence of uncontrolled systemic disease that, in the opinion of the Investigator, might increase the risk to the subject or confound the results of the study. 23) Subjects unwilling or unable to discontinue the use of hard contact lenses 1 week, or soft contact lenses 2 days prior to the Eligibility 2 Visit and Week 4 Visit. Subjects unwilling or unable to discontinue the use of contact lenses on study visit days. 24) Subjects participating in any drug or device clinical investigation within 30 days prior to the Screening Visit and/or during the period of study participation.
Study Endpoints	**Efficacy Measures** Primary Endpoint: The primary efficacy endpoint for this study is the reduction from baseline (based on Eligibility 1 and Eligibility 2 Visits) in mean diurnal IOP at the Week 4 Visit in the study eye. The primary efficacy analysis is the non-inferiority comparison of the treatment effect between each of the NCX 470 doses and latanoprost 0.005% at the Week 4 Visit for the study eye. A secondary efficacy analysis is the superiority comparison of the treatment effect between each of the NCX 470 doses and latanoprost 0.005% at the Week 4 Visit for the study eye. [redacted]
	Safety Measures Assessed by evaluating changes in the following: • Intraocular pressure • Slit-lamp biomicroscopy • Conjunctival hyperemia • Dilated ophthalmoscopy • Pachymetry • Best-corrected visual acuity (BCVA) • Vital signs • Non-fasting clinical laboratory tests • Urine pregnancy tests for females of childbearing potential • Rate of discontinuation from the study • AEs

Statistical Methods	**Sample size determination and efficacy analyses:** The primary objective of this study is to identify one NCX 470 concentration that is non-inferior to latanoprost ophthalmic solution, 0.005% in reduction of IOP. The secondary objective of this study is to identify one NCX 470 concentration that is superior to latanoprost in reduction of IOP. Additional secondary objective is to demonstrate that one NCX 470 concentration is safe and well tolerated. [redacted] [redacted]. Each subject's IOP will be measured at 8 AM, 10 AM, and 4 PM at the Eligibility 1 Visit, Eligibility 2 Visit, Week 1 Visit, Week 2 Visit, Week 4 Visit, and the Study Exit Visit. Mean diurnal IOP, defined as the mean IOP over the day based on values obtained at 8 AM, 10 AM, and 4 PM, will be calculated at the Eligibility 1 Visit, Eligibility 2 Visit, Week 1, Week 2, and at the Week 4 Visit. Mean diurnal IOP reduction from baseline is calculated as the average of the mean diurnal IOP values at the Eligibility 1 and Eligibility 2 Visits minus the mean diurnal IOP value at Week 4 Visit. [redacted] [redacted] The least squares (LS) mean of each of the NCX 470 treatment groups and latanoprost will be obtained from the ANCOVA or ANOVA model. Each of the NCX 470 treatment groups will be compared with the latanoprost group by computing a two-sided 95% confidence interval (CI) around the differences between the LS mean of each of the NCX 470 treatment groups and the LS mean of the latanoprost group. The differences among treatment groups will be calculated as NCX 470 minus latanoprost. The corresponding two-sided p-values for each comparison will be presented. [redacted]

	[redacted] [redacted] The primary efficacy assessment is the non-inferiority analysis of the difference in the treatment effect between each NCX 470 dose and latanoprost 0.005% at the Week 4 Visit. **Safety analyses:** Safety analyses are based on the safety dataset. The safety dataset will include all subjects who received at least one dose of study medication. Subject disposition, demographics, and baseline characteristics will be summarized and presented in data listings. A treatment-emergent AE (TEAE) is defined as an AE that occurs on or after treatment is initiated. Ocular TEAEs by treatment group: NCX 470 0.021%, 0.042%, and 0.065%, and latanoprost 0.005%, will be summarized, by relationship to study drug, and by severity. Non-ocular TEAEs will be summarized by treatment group, by relationship to study drug, and by severity. Serious AEs (SAEs), AEs resulting in study drug discontinuation, and deaths will be presented in data listings. Vital sign measurements (systolic and diastolic blood pressure, and heart rate) and clinical laboratory assessments (serum chemistry, hematology, and urinalysis) will be summarized by visit using descriptive statistics and presented in a data listing. Safety data (described above) will be summarized for treated study eyes and fellow eyes separately, with the exception of ocular adverse events, which will be summarized at the subject level accounting for all treated eyes.

1. INTRODUCTION

1.1 Background and Rationale

Glaucoma is a leading cause of blindness worldwide (Jonas, 2017). Globally it has been estimated that 57.5 million people were affected by primary open-angle glaucoma (POAG) in 2015, with this number projected to rise to 65.5 million by 2020 (Kapetanakis, 2016). Intraocular pressure (IOP) is the primary risk factor for glaucoma, and lowering IOP to prevent optic nerve injury is currently the only proven effective treatment (Jonas, 2017). Topical PGAs, such as bimatoprost, are considered as the mainstay of treatment due to their efficacy and safety in lowering IOP (Daka, 2014). Clinical trials reported greater reduction in IOP in subjects with OAG or OHT with bimatoprost 0.03% compared with either travoprost 0.004% or latanoprost 0.005% in some instances, and equivalence among the three treatments in others (Parrish, 2003; Gandolfi, 2001). All treatments presented an acceptable safety profile although lower incidences of conjunctival hyperemia have been reported with latanoprost 0.005% than with the other PGAs (Canadian Agency for Drugs and Technologies in Health, 2015; Daka, 2014).

Nicox is developing NCX 470, a nitric oxide (NO)-donating bimatoprost prostaglandin analog, as a new therapy for lowering IOP in patients with OAG or OHT. When exposed to esterases in the eye, NCX 470 is cleaved into its active metabolites, the prostamide bimatoprost, which in turn is converted to bimatoprost acid, a prostaglandin F2α receptor agonist, and into 6-(nitrooxy)-hexanoic acid, a NO-donating moiety. The active metabolites of NCX 470 include bimatoprost, the active ingredient in LUMIGAN®, (NDAs 021275 and 022184), and 6-(nitrooxy)-hexanoic acid which leads to the release of NO. Another NO-donating PGA (VYZULTA™, latanoprostene bunod ophthalmic solution, 0.024%), also discovered and invented by Nicox, received US FDA (Food and Drug Administration) approval in November 2017 for the reduction of IOP in patients with OAG or OHT (NDA 207795).

Bimatoprost and NO provide robust IOP-lowering activity by concomitantly activating two independent mechanisms: uveoscleral outflow and trabecular/Schlemm's canal conventional outflow facilities (Woodward, 2010; Cavet, 2014). Nitric oxide donors relax the TM and increase aqueous humor outflow (Gabelt, 2011; Heyne, 2013; Cavet, 2014). As a result, NO modulates IOP through the conventional pathway. In contrast, bimatoprost acts by increasing the outflow of aqueous humor primarily through the uveoscleral pathway (Krauss, 2004).

The additive effect of a NO donor and a prostaglandin F2α receptor agonist has been confirmed with latanoprostene bunod, a dual-acting NO-donating latanoprost developed for the reduction of IOP in patients with OAG or OHT (Meideiros, 2016; Weinreb, 2016). This approach is supported by the nonclinical data package compiled for NCX 470, as well as the publicly available data for bimatoprost.

NCX 470 exhibited potent and effective IOP-lowering activity in three ocular hypertensive animal models (Impagnatiello, 2015). Nonclinical pharmacology studies in well-established animal models of glaucoma and OHT have demonstrated that the IOP-lowering efficacy of NCX 470 is greater than that of equimolar doses of bimatoprost. In particular, in transient ocular hypertensive rabbits, known to respond poorly to PGF2α analogs and prostamides, NCX 470 lowers IOP likely via NO release. Additionally, an equimolar dose of NCX 470 at 0.042% lowers IOP more effectively than bimatoprost at 0.03% in ocular normotensive dogs at 12 hours post dose, as well as in laser-induced ocular hypertensive non-human

primates. Based on these data, Nicox intends to conduct a phase 2 study of NCX 470 ophthalmic solution.

1.2 Study Background

Nonclinical and Clinical Studies of NCX 470
A summary of all nonclinical studies already performed can be found in the Investigator's Brochure. No clinical data exist for NCX 470 as the current study, NCX-470-17001, is the first-in-human study of NCX 470.

Description of the Study Medication
[redacted] For further detail see Section 6.1.

Description of Active Comparator
[redacted] For further detail see Section 6.2.

Justification of the Study Design
The proposed phase 2 dose-response study will be the first-in-human study of NCX 470. This is a randomized, multicenter, masked, parallel-group, dose-response clinical study wherein subjects will be randomized in 1:1:1:1 ratio to receive one of the three concentrations of NCX 470 (0.021%, 0.042%, or 0.065%) or the active comparator latanoprost 0.005%. [redacted]

[redacted]

[redacted].

[redacted]

The once-daily (in the evening) dosing regimen for NCX 470 is consistent with that of other PGAs.

Justification of the Active Comparator Selection

Topical PGAs, such as latanoprost, bimatoprost and travoprost, are considered the mainstay of treatment for patients with OAG or OHT due to their efficacy and safety in lowering IOP (Li, 2016; Daka, 2014). Latanoprost accounted for 71% of all PGA prescriptions in the US in 2017, and more than one third of all prescribed IOP-lowering medications (IMS Data). As latanoprost was the first approved and remains the most widely prescribed PGA, latanoprost has a well-established safety and efficacy profile. Therefore, it is a reasonable choice for an active comparator in this study.

Selection of the Study Population

A total of approximately 420 male and female adults with OAG or OHT in both eyes will be randomized in this clinical study at approximately 20 investigative sites in the US. Up to 10 additional sites may be added based on enrollment rates.

1.3 Potential Risks and Benefits to Human Subjects

The potential risks to subjects that may occur in this study, are likely to be similar to those reported during the clinical development and marketing experience of bimatoprost, latanoprost, and latanoprostene bunod ophthalmic solutions.

[redacted]

The potential benefit to subjects is lowering of IOP. Elevated IOP represents a major risk factor for glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary Objective

The primary objective is to demonstrate that the mean diurnal IOP reduction at the Week 4 Visit with NCX 470 QD is non-inferior to latanoprost 0.005% QD for one of the tested concentrations of NCX 470.

[redacted]

Another secondary objective is to demonstrate that one of the tested concentrations of NCX 470 is safe and well tolerated.

2.2 Study Endpoints

The following endpoints will be collected in the course of the study:

- IOP collected at 8 AM, 10 AM, and 4 PM
- Slit-lamp biomicroscopy
- Conjunctival hyperemia
- Dilated ophthalmoscopy
- Pachymetry
- BCVA
- Vital signs
- Non-fasting clinical laboratory tests
- Urine pregnancy tests for females of childbearing potential
- Rate of discontinuation from the study
- AEs

2.3 Efficacy Evaluations

The primary efficacy endpoint for this study is the reduction from baseline (based on Eligibility 1 and Eligibility 2 Visits) in mean diurnal IOP at the Week 4 Visit in the study eye.

[redacted]

2.4 Safety Evaluations

Evaluations of safety include but are not limited to AEs, IOP, pachymetry, slit lamp biomicroscopy, conjunctival hyperemia, dilated ophthalmoscopy, BCVA, clinical labs, vital signs, and rate of discontinuation from the study.

Review of Safety Data by Medical Monitor

A review of masked ocular and systemic safety data from each subject will be performed on an ongoing basis by the Medical Monitor. [redacted]

3. STUDY DESIGN

3.1 Overall Study Design

This is a randomized, multicenter, masked, parallel-group, dose-response phase 2 clinical study. This study will be conducted in approximately 20 sites in the United States. Up to additional 10 sites may be added based on enrollment rates. [redacted]

Subjects will be assessed for initial eligibility at the Screening Visit (Figure 1). Subjects currently being treated with an IOP-lowering medication (pretreated) will be required to discontinue their IOP-lowering medication during a washout period which will occur between the Screening Visit and the Eligibility 1 Visit. [redacted]

Successful washout and IOP-based eligibility for all subjects will be determined at the Eligibility 1 Visit (Day -7 to -3) and the Eligibility 2 Visit (Day 1) with diurnal IOP measurements at 8 AM, 10 AM, and 4 PM at both visits. The baseline IOP for all study analyses will be based on the study eye mean diurnal IOP from the Eligibility 1 and Eligibility 2 Visits. Subjects meeting eligibility requirements will be randomized and study medication dispensed at the end of the Eligibility 2 Visit.

Subjects will be randomized in a 1:1:1:1 ratio to receive NCX 470 or latanoprost one drop in both eyes, QD in the evening:

- NCX 470 ophthalmic solution, 0.021%
- NCX 470 ophthalmic solution, 0.042%
- NCX 470 ophthalmic solution, 0.065%
- Latanoprost ophthalmic solution, 0.005%

Both eyes will be treated for the duration of the study. The study eye will be the eye with the highest baseline IOP value or the right eye (OD) if both eyes of a subject have the same IOP value at baseline. The contralateral eye will be considered as the fellow eye.

All doses will be self-administered or administered by a caregiver topically as eye drops in the evening.

[redacted]

[redacted]

[redacted]

[redacted] **Washout Period**

Subjects currently using IOP-lowering medication(s) must undergo a minimum washout period as specified in Table 1 below according to the pharmacological class of their IOP-lowering therapy.

The minimum washout period will begin at the Screening Visit and will be completed at the Eligibility 1 Visit (day -7 to -3) (Figure 1). The time between the Screening Visit and the Eligibility 1 Visit should [redacted] for any subject.

After the Eligibility 1 Visit there will be an additional 3 to 7 days without any IOP-lowering treatment before eligibility confirmation and randomization at the Eligibility 2 Visit. The time between the Screening Visit and the Eligibility 2 Visit [redacted]

For treatment-naïve subjects the Eligibility 1 Visit will be scheduled a minimum [redacted] after the Screening Visit to allow review of clinical laboratory results.

[redacted]

Table 1: Duration of Washout Period for IOP-Lowering Medications

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

Note: The longest washout should be used when taking medications from more than one class.

4. SUBJECT SELECTION

4.1 Number of Subjects and Sites

This study will be conducted at approximately 20 sites in the US. Up to 10 additional sites may be added based on enrollment rates. Overall, approximately [redacted] 420 subjects will be randomized into the study.

4.2 Subject Population Characteristics

The target population in this study will be adult men and women with a diagnosis of OAG or OHT in both eyes.

Subjects must meet the following IOP requirements at the Eligibility 1 Visit (Day -7 to -3) **and** the Eligibility 2 Visit (Day 1):

- [redacted]

4.3 Inclusion Criteria

Prior to inclusion in the study, each subject must fulfill all of the following criteria:

1) Subjects will be of legal age (at least 18 years of age) on the date the informed consent form (ICF) is signed and must be able to provide a written informed consent to participate in the study, in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local regulations, before initiating any study-related procedures.
2) Subjects will have a diagnosis of OAG or OHT in both eyes (OHT must have been documented for at least the past 6 months).
3) If treated for OAG or OHT, treatment nature and dose regimen must have been stable for both eyes for the 30 days prior to the Screening Visit.
4) Subjects will meet the following IOP requirements at the Eligibility 1 (Days -3 to -7) **and** Eligibility 2 (Day 1) Visits:
   - [redacted]
5) [redacted]
6) Subjects with best-corrected visual acuity (BCVA), using Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, of +0.7 logMAR units (Snellen equivalent ~20/100) or better in each eye.

7) If female, subjects must either be incapable of pregnancy because of bilateral oophorectomy, hysterectomy, bilateral tubal ligation, or be post-menopausal (have been amenorrheic for at least 2 years) or must use an effective (e.g., double barrier) method of birth control for the duration of the study. Female subjects of childbearing potential must have a negative pregnancy test and not be nursing.
8) Subjects who are able and willing to comply with all study procedures.

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1) Subjects < 18 or > 85 years old.

[redacted]

3) Subjects with advanced glaucoma, pigmentary, or pseudo-exfoliative glaucoma, and subjects with a cup/disc ratio greater than 0.8, or a history of split fixation, or a field loss threatening fixation in either eye.
4) Subjects with narrow angles (3 quadrants with less than Grade 2 according to Shaffer anterior chamber angle grading system) and subjects with angle closure, peripheral anterior synechiae, congenital, and/or secondary glaucoma, or a history of angle closure in either eye.

[redacted]

6) Subjects with any condition that prevents reliable applanation tonometry in either eye (e.g., significant corneal surface abnormalities, scars, keratoconus).

[redacted]

[redacted]

15) Subjects unwilling or unable to discontinue pre-study IOP-lowering medication(s) (see protocol Section 3.2).

16) Subjects with a known hypersensitivity or contraindications to PGA(s) or any of the ingredients in the study medications.

[redacted]

18) Subjects who currently require treatment or are expected to require treatment with ocular, topical, or systemic corticosteroids during the study period (inhaled, intra-articular, or intranasal steroids are allowed).

[redacted]

21) Subjects who currently require treatment or are expected to require treatment with any ocular medications, including those applied to the eyelids or eyelashes, during the study period (see protocol Section 5.2) (over-the-counter artificial tears are allowed – see protocol Section 5.1).

22) Subjects with a history or presence of uncontrolled systemic disease that, in the opinion of the Investigator, might increase the risk to the subject or confound the results of the study.

23) Subjects unwilling or unable to discontinue the use of hard contact lenses 1 week, or soft contact lenses 2 days prior to the Eligibility 2 Visit and Week 4 Visit. Subjects unwilling or unable to discontinue the use of contact lenses on study visit days.

24) Subjects participating in any drug or device clinical investigation within 30 days prior to the Screening Visit and/or during the period of study participation.

5. CONCOMITANT MEDICATION(S)

5.1 Previous and Concomitant Medication(s)

All non-ophthalmic medications used in the 3 months prior to the Screening Visit and all ophthalmic medications used in the 12 months prior to the Screening Visit must be recorded. Additionally, all medications used between the Screening Visit and the Exit Visit must be recorded.

Eligible subjects will discontinue all previous IOP-lowering medication(s), if applicable, on the day of the Screening Visit. However, the initiation of treatment with an IOP-lowering medication with a shorter washout period than the subject's IOP-lowering medication at screening is permitted between the Screening Visit and Eligibility 1 Visit.

The use of over-the-counter artificial tears is allowed provided they are administered a minimum of 15 minutes before or after the instillation of the study medication.

Diagnostic ophthalmic agents administered throughout the study will not be captured in the concomitant medication log.

5.2 Prohibited Medication(s)

All the prohibited drugs mentioned below are also listed in Section 4.4 ("Exclusion Criteria").

From the Screening Visit through the Exit Visit subjects must not receive:

- Any other ocular medications, including those applied to the eyelids or eyelashes (artificial tears are allowed – see protocol Section 5.1)
- [redacted]

Medication which is considered necessary for the subject's safety may be given at the discretion of the Investigator and/or their health care provider during the study. If possible, the Medical Monitor should be consulted prior to the administration of the disallowed medication (if not possible, the Medical Monitor should be notified as soon as possible thereafter) to determine whether the subject may continue in the study.

6. STUDY SUPPLIES

6.1 Description of Study Medication

[redacted]

6.2 Description of Active Comparator

The active comparator is a sterile, isotonic, buffered ophthalmic aqueous solution containing 0.005% latanoprost. [redacted]

6.3 Packaging of the Study Medication

[redacted]

[redacted]

All study medication will be packaged, labeled, and supplied to the site by the study medication supplier under the direction of Nicox. Each kit contains sufficient study medication for the duration of the study treatment period.

6.4 Labeling of the Study Medication

All labeling will be in English and will comply with US federal regulations for investigational drug product.

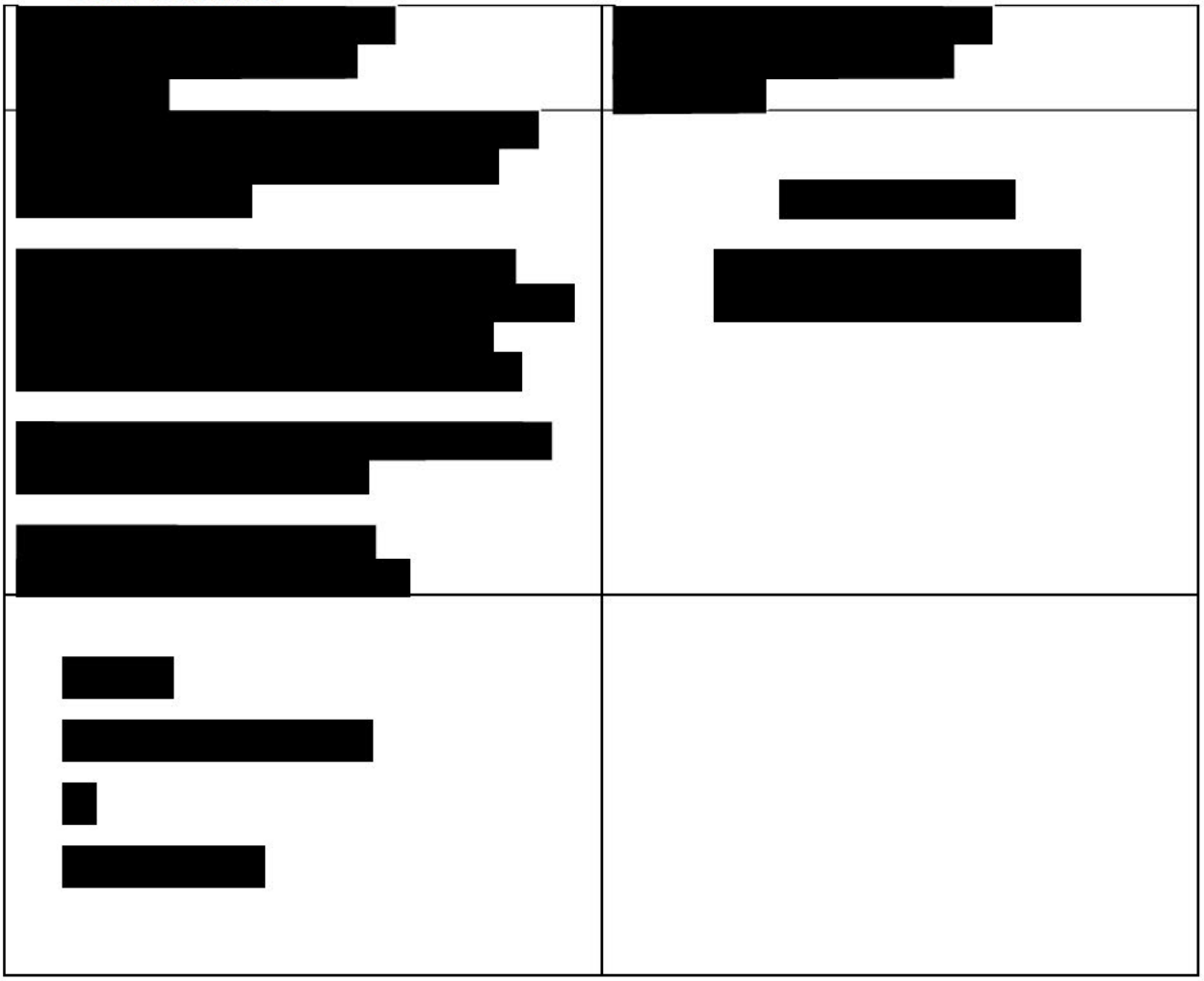
The outer box of each kit will have a label consisting of 2 parts:

- A permanent portion affixed to the kit, and
- A tear-off portion attached to the permanent portion by a perforated joint.

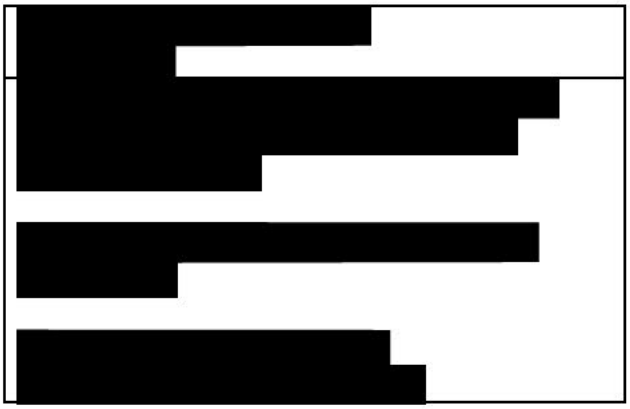
The tear-off portion of the masked label will be removed from the kit (one tear-off label per kit) and placed on the subject's source documentation where it will remain available to the Investigator throughout the subject's participation in the study (date of dispensing must be reported in the subject's source documentation).

The outer box, inner box and the two bottles will be labeled as described below:

Outer Box Label



Inner Box Label



Bottle Label

Each subject will be given a copy of the study medication dosing and storage instructions.

6.5 Storage of the Study Medication

It is the Principal Investigator's responsibility to ensure that all study medication is stored in a secure area and administered only to randomized subjects and in accordance with conditions specified in this protocol. **Only the unmasked site designee authorized by the Principal Investigator** may have access to the study medication and will be responsible for delivering/collecting the study medication to/from the subjects.

6.6 Accountability of Study Medication

The study medication will be shipped by the study medication supplier to each study site. The receipt of study medication by the unmasked site designee should be documented. The dispensed and returned study medication will be recorded by the unmasked site designee on an inventory.

It is the responsibility of the unmasked site designee to maintain detailed study medication accountability records. The importance of returning the box with the two bottles must be emphasized to the subjects. Study medication deliberately and/or accidentally destroyed must be accounted for and the reason must be documented. Any discrepancy between dispensed and returned study medication must be explained and documented by the unmasked site designee.

6.7 Assigning Subjects to Treatment and Study Masking

Each site will be assigned a [redacted] ID by the Sponsor or its representative. At the Screening Visit, the site will assign a [redacted] to each subject and record it in the screening log. The site will then register the subject in the EDC system [redacted]

At the Eligibility 2 Visit (Day 1), utilizing the IRT/EDC system, approximately 420 subjects will be randomly assigned to one of the three concentrations of NCX 470 or the active comparator latanoprost 0.005% solution in a masked fashion in a 1:1:1:1 ratio.

The subjects, investigators, site staff measuring IOP or evaluating safety parameters, the Sponsor, the Medical Monitor, and [redacted] interacting with the clinical sites (or handling study data) will be masked to the treatment assignment. **The unmasked site designee will not perform any other study activities except handling study medication.**

IRT assignment is based on a randomization schedule created by an unmasked statistician. Please refer to the Investigator Instruction Manual for the IRT for further details.

6.8 Study Medication Dispensing and Collection

For each subject fulfilling eligibility criteria, the clinical site staff will access the IRT to randomize study subject(s) at the Eligibility 2 Visit (Day 1). A randomization number will be allocated to each subject and study medication kit number will be issued. [redacted] The randomization and the medication kit number must be allocated only on the day of the first treatment administration during the Eligibility 2 Visit (Day 1).

Once all Eligibility 2 Visit study procedures have been completed, [redacted].

In the event the subjects need a replacement kit, utilize the IRT. Please refer to the Investigator Instruction Manual for the IRT for further details.

Subjects will be instructed to return their study medication [redacted] only to the site's unmasked study medication designee at Week 4 Visit. An inventory will be conducted by the unmasked site designee.

6.9 Instructions for Use and Administration

The study medication must be administered one drop in each eye by the subject or caregiver, **at 8 PM [redacted] from the evening of the Eligibility 2 Visit (Day 1) to the evening prior to the Week 4 (Day 28 [redacted] No study medication will be administered by the investigational site staff.**

6.10 Emergency Subject Unmasking

If unmasking of a subject becomes critical to the subject's safety, the Principal Investigator must authorize such decision. If possible, such decision should be first consulted with both

the study Sponsor and the Medical Monitor. The study treatment assignment of a subject should be unmasked via the IRT. In a situation when the IRT system is not accessible, the unmasking can be achieved via scratch-off portion of the study kit label located in the source documentation. The Sponsor and the Medical Monitor must be notified within 24 hours following an emergency unmasking of any subject.

6.11 Study Medication Compliance

It is important to encourage the subject to be compliant with the study treatment. Compliance will be captured in a subject diary, and collected at the Week 1, Week 2, and Week 4 Visits. The subject will be instructed on diary completion.

6.12 Return of Study Medication by the Clinical Sites

Return of used and unused study medication by the clinical site to the study medication supplier should be performed following the completion of the last subject last visit at the site, and only after database lock and following onsite verification by the CRA.

6.13 Other Study Supply

Sites will also be provided with:

- [redacted]

Additional supplies may be provided once discussed and approved by the Sponsor.

7. STUDY PROCEDURES BY VISIT

The following sections provide a list of procedures and assessments for each study visit as outlined in the Times and Events Schedule (Appendix 1).

Ocular examination procedures will be performed bilaterally beginning with the right eye and in accordance with the site's standard clinical practice. Refer to Appendix 2 for information on the methods of clinical evaluation.

7.1 Screening Visit

Prior to any study assessments, potential subjects will be identified and the Investigator (or designee) will conduct the informed consent process. The purpose of the study, the study methods (visits and assessments), risks/benefits, and subject responsibilities will be discussed. The subject's willingness and ability to participate in the study will be assessed. If the subject chooses to proceed with study participation, written informed consent and subject authorization will be obtained as appropriate for local privacy regulations. The original signed document will be retained in the subject records and a copy will be provided to the subject.

Perform the following procedures and/or collect the following information:

- Assign the screening number and record in the screening log
- Record any AEs from the time the subject signs the ICF
- Record demographic data
- Record past and current relevant medical and ophthalmic history (history of OAG or OHT must be documented), including previous ocular surgery(ies)/procedure(s)
- Record concomitant medication(s), including any ongoing IOP-lowering treatment(s) at Screening and in the past 3 months for non-ophthalmic and 12 months for ophthalmic medications
- [redacted]

- [redacted]

[redacted]

Washout Period

At the Screening Visit, eligible subjects will be instructed to discontinue their current IOP-lowering medication(s), if applicable. The duration of the washout period will be based on their previous IOP-lowering medication(s). Refer to Washout period (Section 3.2) to determine the duration of the washout period for each subject.

Subjects who are not required to undergo a washout period may proceed to the Eligibility 1 Visit [redacted]

7.2 Eligibility 1 Visit ([redacted])

- Record any AEs which occurred since the Screening Visit
- Record any changes in concomitant medication(s)
- [redacted]

[redacted]

- Review inclusion/exclusion criteria and determine eligibility

If subject meets all criteria assessed, schedule Eligibility 2 Visit, and instruct subject to not resume IOP-lowering medication. Remind contact lens wearers to discontinue use prior to Eligibility 2 (1 week prior for hard contact lenses and 2 days prior for soft contact lenses).

7.3 Eligibility 2 Visit (Day 1)

Eligibility 2 Visit will occur 3 to 7 days after the Eligibility 1 visit [redacted]

- Record any AEs which occurred since the last visit and during this visit
- Record any changes in concomitant medication(s)
- [redacted]

[redacted]

- [redacted]

Subject may resume normal contact lens wear, if applicable, but must discontinue use on study visit days.

7.4 Week 1 Visit ([redacted])

- Record any AEs which occurred since the last visit and during this visit
- Record any changes in concomitant medication(s)
- [redacted]

7.5 Week 2 Visit [redacted]

- Record any AEs which occurred since the last visit and during this visit
- Record any changes in concomitant medication(s)
- [redacted]

Remind contact lens wearers to discontinue use prior to Week 4 Visit (1 week prior for hard contact lenses and 2 days prior for soft contact lenses).

7.6 Week 4 Visit (Day 28 [redacted]

- Record any AEs which occurred since the last visit and during this visit
- Record any changes in concomitant medication(s)
- [redacted]
- Review subject diary for compliance and collect it

7.7 Exit Visit (Day 29 [redacted]

The Exit Visit will occur the day after the Week 4 Visit [redacted]

- Record any AEs which may have occurred since the last visit and during this visit
- Record any changes in concomitant medication(s)
- [redacted]
- Utilize IRT/EDC to exit the subject

7.8 Unscheduled Visits

Additional examinations or analyses may be performed as necessary to ensure the safety of subjects during the study period. An electronic Case Report Form (eCRF) must be

completed for each unscheduled visit with documentation of the following mandatory assessments:

- Adverse event(s) (if applicable)
- Concomitant medications
- BCVA (*Note: Refraction is repeated only if a decrease in BCVA of 10 or more letters per EDTRS occurs from the Screening Visit)*
- Slit lamp biomicroscopy
- IOP

The Investigator may perform any other examination that is regarded as appropriate. Please refer to the eCRF Completion Guidelines for detailed instructions.

[redacted]

8. SCREEN FAILURES, COMPLETION AND DISCONTINUATION

8.1 Subject Screen or Eligibility Failures

Subjects who are screen or eligibility failures should not be randomized into the study. The reason for screen/eligibility failure must be documented in the source document and in the eCRF.

8.2 Subject Completion

A subject is considered to have completed the study at the end of the Exit Visit (Day 29).

8.3 Subject Early Discontinuation

A subject may be discontinued from the study prior to the final study visit at the discretion of the Investigator, Sponsor, and/or IRB. Subjects may also discontinue their participation in the study at any time per their own decision.

A subject may be discontinued from the study for the following reasons, including but not limited to:

- Serious adverse event: If it is determined by the Investigator that **only** removal from the study could reduce subject's risk or that the occurred SAE prevents the subject from further participation in the study treatment or follow-up, the subject may be withdrawn.
- Violation of eligibility criteria: In case a subject has been randomized into the study despite not meeting study inclusion/exclusion criteria, or non-compliance with inclusion or exclusion criteria has occurred during the course of the study, the subject may be discontinued.
- Lack of compliance with the study procedures or loss to follow-up.
- [redacted]

A subject must be discontinued from the study for the following reasons, including but not limited to:

- [redacted]
- Withdrawal of consent
- Subject becoming pregnant in the course of the study

Procedures for Discontinuation

If a subject is discontinued or withdraws consent during the washout period, no procedures other than those which may be related to the follow-up of AEs will be required. The Investigator will document the reason for the subject withdrawal.

If a subject is discontinued for reasons other than withdrawal of consent during the 28 day Treatment Period – before the Exit Visit - the Week 4 Visit assessments should be performed and documented. [redacted]

If a subject withdraws their consent during the 28 day Treatment Period, all efforts should be taken to complete both Week 4 and Exit Visit procedures prior to subject's exit.

If a subject is discontinued due to an AE, the status of the AE at the time of discontinuation will be recorded in the eCRF.

Any SAE, occurring within one month (30 days) following the last treatment day should be collected and reported. This refers both to early discontinuation and normal study termination. [redacted]

8.4 Subject Lost to Follow-up

Subjects who fail to present for a study visit should be contacted in an attempt to have the subject comply with the protocol and to return the diary and study medication, if applicable. If a subject cannot be contacted with a minimum of three documented telephone calls followed by a certified letter and there is no known reason for withdrawal (e.g., withdrawn consent), the reason for withdrawal from the study will be recorded as "lost to follow-up". The date of withdrawal will be considered as seven days after the certified letter was mailed.

8.5 Study Termination

Investigators and subjects should understand that the study may be discontinued by the Sponsor (Nicox) at any time, without their consent.

9. PROTOCOL COMPLIANCE

Subjects who experience major protocol deviations will have all their data excluded from the Per Protocol (PP) analysis. The list of major protocol deviations, as well as minor protocol deviations, will be finalized prior to database lock.

In order to correctly identify and document protocol deviations, protocol deviations will be categorized as follows:

- **Minor Deviation:** Deviation considered to not impact the primary efficacy outcome of the study (*i.e.,* does not affect the study results).
- **Major Deviation:** Deviation considered to impact the primary efficacy outcome of the study (*i.e.,* affects the study results).

All deviations will be recorded by the site and classified by the Sponsor.

10. ADVERSE EVENTS

10.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Lack of efficacy will be reported as a treatment failure, not as an AE.

10.2 Severity of Adverse Event

The severity of an AE should be categorized as mild, moderate or severe per Investigator's judgment with the following scale in consideration:

- **Mild**: Awareness of a sign or symptom that does not interfere with the subject's usual activities or is transient, resolved without treatment and with no sequelae.
- **Moderate**: interferes with the subject's usual activities, and or requires symptomatic treatment.
- **Severe**: symptom(s) causing severe discomfort and significant impact of the subject's usual activities and requires treatment.

10.3 Causal Relationship with Study Medication

A determination of the relationship between an AE and the study medication must be made by the Investigator for each AE. The following terms to evaluate the causality of the AE with the study drug should be used:

- **Unrelated:** a simultaneous disease, a simultaneous treatment or any other known cause is clearly responsible for the safety event and the AE is not related to the study medication.

- **Unlikely:** on the basis of the available knowledge regarding the subject's history, the disease process, the timing of the safety event in relation to the administration of the study medication and the mode of action of study medication, a relation between the study medication and the safety event is unlikely, but cannot be totally excluded.

- **Possible:** this relation exists when the safety event follows the reasonable chronological sequence from the moment of the study medication administration, but when the safety event could also have been caused by the clinical condition of the subject or by other treatment administered to the subject.

- **Probable:** this relation exists when the safety event follows a reasonable chronological sequence from the moment of the study medication administration, corresponds to a known effect of the study medication, is confirmed by the observation of an improvement upon discontinuation of the study medication

administration, and therefore the study medication is the most probable of all the causes.

- **Definite:** this relation exists when the safety event follows a reasonable chronological sequence from the moment of the study medication administration, corresponds to a known effect of the category of the studied medication, is confirmed by the observation of an improvement upon discontinuation of the study medication, and no other reasonable cause exists.

Early exit for lack of efficacy/worsening of the disease will not be considered as an adverse event but as a treatment failure.

10.4 Serious Adverse Events

SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Results in-subject hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Results in a congenital anomaly/birth defect (Section 12.2 - Procedure in Case of Pregnancy), or
- Results in life-threatening illness or injury (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe, or had continued untreated).
- Results in a significant and persistent loss or impairment of vision.

Additionally, medical events that may not meet these criteria, may be considered an SAE if, based on the medical judgment of the Investigator, such medical events may require an intervention to prevent any of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided: the term "severe" is often used to describe the intensity of a specific event. This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

Elective or planned procedures requiring hospitalization will not be considered SAE’s; however, other events may occur during this hospitalization that may be considered serious or non-serious adverse events and will need to be captured according to the protocol.

10.5 Adverse Event Reporting

In this study, subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (*e.g.*, “How has your health been since the last visit?”). If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the AE Form(s).

Additionally, subjects will be instructed to contact the Investigator, and/or study coordinator if any significant AEs occur between study visits.

From the signing of the ICF on the day of the Screening Visit and through the Exit Visit, all AEs must be recorded on the appropriate AE form. All AEs must be reported whether or not considered causally related to study medication. For every AE, the Principal Investigator will provide an assessment of the severity and causal relationship to study medication, document all actions taken with regard to study medication, and any other treatment measures for the AE.

10.6 Serious Adverse Event Reporting

Any SAE occurring from the signing of the ICF on the day of the Screening Visit, and up to 30 days following the most recent study drug administration (for a subject who exited the study early or after normal study termination) must immediately be reported to the company representing Nicox, and recorded on the appropriate forms. All subjects with an SAE must be followed up and the outcomes reported. Subjects must be followed until complete healing or stabilization or blood tests are back to normal or up to 30 days after the end of the study treatment, whichever occurs first. The Investigator must supply the company representing Nicox with any additional requested information (e.g., autopsy reports and final medical reports).

In the event of an SAE, the Investigator must:

1) Notify Sponsor's Primary Contact for Study Related Matters and SAEs immediately (see contact information on Page 2 and Section 12.1), at the latest within 24 hours of becoming aware of the initial SAE. Complete an SAE Form (see instructions for completion of SAE Form in Appendix 3) and send it to the Primary Contact for Study Related Matters and SAEs. Retain all submission confirmations with the items submitted.
2) Obtain and maintain in subject's files pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3) Complete and submit further follow-up reports for data collected until the SAE has resolved or a decision for no further follow up has been taken.
4) Promptly inform the local IRB and/or other applicable regulatory body as required by local regulations.

11. STATISTICAL CONSIDERATIONS AND METHODS OF ANALYSIS

An analysis plan containing detailed statistical methods, including accounting for multiplicity, will be generated and finalized prior to database lock.

11.1 Determination of Sample Size and Power Calculations

The primary objective of this study is to demonstrate that the diurnal mean IOP reduction at Day 28 with NCX 470 QD is non-inferior to latanoprost 0.005% QD for one of the tested concentrations of NCX 470.

[redacted]

11.2 Analysis Population

For the 28-day treatment evaluation period, three different populations will be used in the analysis: an intent-to-treat (ITT) population, a Per Protocol (PP) population, and a safety population.

The ITT population will include all randomized subjects. Demographics, baseline characteristics, and efficacy variables will be analyzed using the ITT population. These analyses will be performed on an as-randomized basis.

The PP population will include all randomized subjects who received study medication, who had at least one follow-up visit and who had no major protocol deviations (see Section 9) during the 28-day treatment period. The final PP population will be determined and approved by Nicox prior to database lock. Demographics, baseline characteristics, and efficacy variables will be analyzed using the PP population. These analyses will be performed on an as-treated basis.

The safety population will include all randomized subjects who received at least one dose of the study medication during the 28-day treatment period and will be used for the safety analyses. All safety variables will be analyzed on an as-treated basis using the safety population.

11.3 Data Display

Data will be analyzed separately using the following treatment groups wherever appropriate:

- NCX 470 ophthalmic solution, 0.021%
- NCX 470 ophthalmic solution, 0.042%
- NCX 470 ophthalmic solution, 0.065%
- Latanoprost ophthalmic solution, 0.005%

11.4 Collection and Derivation of Primary Efficacy Assessments

For both eyes, IOP will be measured at either 8 AM [redacted] or 10 AM [redacted] or 4 PM [redacted] at the Screening Visit, and at all three time points, 8 AM [redacted]., 10 AM [redacted] and 4 PM [redacted]., from the Eligibility 1 Visit to the Exit Visit.

Handling of missing values:

The primary efficacy analyses will be based on the ITT population with observed data only. To check for robustness of outcomes, missing data will be handled using multiple imputation (MI) methods as detailed in the formal statistical analysis plan.

11.5 Hypothesis and Methods of Analysis

11.5.1 Primary Efficacy Analysis

Efficacy will be assessed by the primary variable:

Mean change from baseline (average of Eligibility 1 and Eligibility 2 Visits) in mean diurnal IOP at the Week 4 (Day 28) Visit.

Each subject's IOP will be measured at 8 AM, 10 AM, and 4 PM at the Eligibility 1 Visit, Eligibility 2 Visit, Week 1 Visit, Week 2 Visit, Week 4 Visit and the Study Exit Visit. Mean diurnal IOP, defined as the mean IOP over the day based on values obtained at 8 AM, 10 AM, and 4 PM, will be calculated at the Eligibility 1 Visit, Eligibility 2 Visit, Week 1, Week 2, and at the Week 4 Visit. Mean diurnal IOP reduction from baseline is calculated as an average of the mean diurnal IOP values at the Eligibility 1 and Eligibility 2 Visits minus the mean diurnal IOP value at the Week 4 Visit. Descriptive statistics for the mean diurnal IOP values at the Eligibility 1 Visit, Eligibility 2 Visit, average of mean diurnal IOPs at the Eligibility 1 and Eligibility 2 Visits, and Week 4 Visit will be presented.

[redacted]

The least squares (LS) mean of each of the NCX 470 treatment groups and latanoprost will be obtained from the ANCOVA or ANOVA model. Each of the NCX 470 treatment groups will be compared with the latanoprost group by computing a two-sided 95% confidence interval (CI) around the differences between the LS mean of each of the NCX 470 treatment groups and the LS mean of the latanoprost group. The differences among treatment groups will be calculated as NCX 470 minus latanoprost. The corresponding two-sided p-values for each comparison will be presented.

[redacted]

[redacted]

The primary efficacy assessment is the non-inferiority analysis of the difference in the treatment effect between each NCX 470 dose and latanoprost 0.005% at the Week 4 Visit.

Detailed statistical methodology will be provided in the SAP.

[redacted]

11.5.3 Safety Analysis

Safety analyses are based on the safety dataset. The safety dataset will include all subjects who receive at least one dose of study medication.

Subject disposition, demographics, and baseline characteristics will be summarized and presented in data listings.

A treatment-emergent AE (TEAE) is defined as an AE that occurred on or after the treatment was initiated. Ocular TEAEs by treatment group: NCX 470 0.021%, 0.042%, and 0.065%, and latanoprost 0.005%, will be summarized, by relationship to study drug, and by severity. Non-ocular TEAEs will be summarized by treatment group as follows: non-ocular TEAEs, by relationship to study, and by severity. Serious AEs (SAEs), AEs resulting in study drug discontinuation, and deaths will be presented in data listings.

Vital signs measurements (systolic and diastolic blood pressure, and heart rate) and clinical laboratory assessments (serum chemistry, hematology, and urinalysis) will be summarized by visit using descriptive statistics and presented in a data listing.

Other ocular safety data will be summarized for treated study eyes and fellow eyes separately, with the exception of ocular adverse events, which will be summarized at the subject level accounting for all treated eyes.

Results from the clinical laboratory assessments (serum chemistry, hematology, and urinalysis) will also be summarized.

11.5.4 Dose Selection Process

Once this study's efficacy and safety results become available, the NCX 470 dose with the most favorable efficacy/safety ratio will be selected to be used in the phase 3 studies.

11.5.5 Interim Analysis

There is no interim analysis planned for this study.

12. EMERGENCY PROCEDURES

12.1 Emergency Contact Procedure

In case of any Safety Event including an SAE, the first person to contact is:

[redacted]

The secondary contact is the study Medical Monitor:

[redacted]

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. Each subject will receive the Investigator's emergency contact information (to call if needed).

12.2 Procedure in Case of Pregnancy

If a pregnancy occurs during the study, pregnancy itself is not regarded as an AE unless there is a suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication.

If a female subject becomes pregnant during the study, the subject will be withdrawn from the study immediately. However, any pregnancies must be followed up, and their outcomes must be reported to Nicox or to the company representing Nicox (i.e., mother and fetus(es) must be followed up at least until the birth of the infant and one month after the birth of the infant). Follow-up will include course, duration, outcome of the pregnancy and the health of the infant, as applicable.

If the outcome of pregnancy is:

- Elective abortion without complications: it must be documented and reported to Nicox or to the company representing Nicox, but it should not be handled as an AE.
- Any spontaneous miscarriage or abortion for medical reasons or congenital anomaly or birth defect: it must be documented and handled as a SAE and full details will be requested.

Any complications during pregnancy must be recorded as AEs and may constitute SAEs if they fulfill any of the specified criteria for a SAE.

13. STUDY MANAGEMENT

13.1 Monitoring

Site monitoring is conducted to assess that subject protection, study procedures, study drug administration, and data collection processes meet protocol, ICH, GCP, and regulatory guidelines/requirements.

Before the study starts, the company representing Nicox will visit/call the investigational sites to:

- Determine the adequacy of the facilities,
- Discuss with the Investigator(s), and other personnel involved in the study, about their responsibilities with regard to protocol adherence, and also about Sponsor's responsibilities.

During the study, a monitor from the company representing Nicox will monitor the study on a periodic basis by having regular contacts with the investigational sites, including on-site visits, to:

- Provide information and support to the Investigator(s),
- Confirm that facilities and investigational site staff remain acceptable,
- Ensure that the investigational site study team is adhering to the protocol, including verifying the accuracy of data recorded in the eCRF and that the study medication logs are being maintained.

Any detected non-compliance with the approved study protocol, GCP, or any applicable regulatory requirements will be fully documented by the monitor. During the monitoring visits, the Investigator and clinical study staff should be available for questions, verification of data from the source documentation, and possible correction to the eCRF.

Following each monitoring visit, the Investigator will be sent a follow up letter detailing any actions required by either the investigational site staff or the monitor. Any actions must, wherever possible, be addressed immediately, or by the next scheduled monitoring visit.

The monitor and the CRO's clinical operations team will be reachable between visits if the Investigator, or other study staff at the site, needs information and advice.

13.2 Source Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) GCP Section 4.9, and regulatory and institutional requirements for the protection of subject confidentiality.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source documents may include, but are not limited to, a subject's medical records, hospital charts if any, clinic charts if any, the Investigator's subject study files, pharmacy dispensing records, recorded data from automated instruments, as well as the results of diagnostic tests such laboratory tests.

13.3 Source Data Verification

To ensure that data in the eCRF is accurate and complete and in accordance with subject source documents and other source data, source data verification (SDV) will be performed by the monitor on eCRF's and SAE and pregnancy related documents as detailed in the Monitoring Management Plan (MMP). The SDV consists of a comparison of the source documentation and other relevant records to the eCRFs. This will require direct access to all original records for each subject.

It will be verified that documentation of the informed consent is on file for all subjects screened whether or not they were randomized into the study.

13.4 Completion of Electronic Case Report Forms

eCRFs must be completed for each subject enrolled in the trial, including screening failures. eCRFs should be completed as soon as possible after the subject visit. All eCRFs must be checked for consistency, accuracy, and completeness by the responsible Investigator and personally electronically signed and dated by them.

13.5 Data Management

The study Data Management Plan (DMP) will describe the methods used to collect, check and process clinical data, as well as the process for database locks. The DMP will be developed by the company representing Nicox and approved by Nicox. It will also list the roles and responsibilities of the various functions and personnel involved in the data management process.

[redacted]

13.6 Audits and Inspections

Authorized representatives of Nicox or the company representing Nicox, a regulatory authority, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of such audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the approved protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator must contact Nicox or the company representing Nicox immediately if contacted by a regulatory agency about an inspection at their site.

The presence of the CRA at the site is mandatory in case of an inspection or audit (at least for the SDV audit and the debriefing with the Principal Investigator). Nevertheless, when justified, the CRA may be represented by another CRO representative involved in the study (*e.g.,* lead CRA).

13.7 Access to Source Data

Nicox, authorized representatives of the company representing Nicox, or regulatory authority representatives will be allowed to have full and direct access to the various records relating to the trial (*i.e.,* Subject's data records, laboratory results reports, etc…) to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being reported.

13.8 Training of Staff

The Principal Investigator will maintain records of all individuals at their site involved in the study (medical, nursing, and other staff). The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the study staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved. The Principal Investigator must inform the monitor, in a timely manner, of any change in the study site staff.

13.9 Changes to the Protocol

Neither the Investigator nor the site staff may implement any changes to the protocol without approval by Nicox and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (*e.g.,* change in monitors, change of telephone numbers). If a protocol amendment requires a change to a particular site's Informed Consent Form, then Nicox or the company representing Nicox and the site's IRB must be notified. Approvals of the revised Informed Consent Form by Nicox or the company representing Nicox, and the IRB are required before the revised form is used.

Nicox or the company representing Nicox will distribute amendments and new versions of the protocol to each Principal Investigator(s) and site study staff for review and any applicable training.

14. ADMINISTRATIVE, LEGAL, AND ETHICAL ASPECTS

14.1 Conduct of the Trial

The trial will be conducted according to the protocol, the ICH Consolidated Guideline for Good Clinical Practice (ICH GCP E6 (R2) - March 2018), and the applicable regulatory requirements.

14.2 Ethical Principles

The study has to be conducted in accordance with the principles of the Declaration of Helsinki (1964), as amended or clarified by the General Assembly of the World Medical Association (World Medical Association Declaration of Helsinki, last amended October 2013).

14.3 Health Authorities and Institutional Review Board (IRB)

This study is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56).

The study protocol and subject informed consent form must be submitted to the appropriate properly constituted IRB. The approval from the IRB must refer to the exact protocol title and number, and identify all documents reviewed and their corresponding versions. A list of the IRB review board members as well as a statement of compliance with GCP and applicable laws and regulations should be also provided. Copies of all IRB correspondence with the Investigator should be given to the company representing Nicox.

The company representing Nicox is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun.

The Principal Investigator is also responsible for providing the IRB with safety reports of any unexpected SAEs from any clinical study conducted with the study medication, as dictated by the IRB requirements. These safety reports will be provided to the Principal Investigator by the company representing Nicox.

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol. In addition, the IRB must approve all materials used to recruit subjects for the study. Either the Principal Investigator, or the company representing Nicox, must submit progress reports to the IRB according to the IRB requirements and local regulations and guidelines. The Principal Investigator must also provide the IRB with any reports of Serious Adverse Events from the study site, as dictated by the IRB requirements.

14.4 Subject Information and Consent

It is the responsibility of the Investigator to obtain written and signed informed consent prior to enrollment into the study (*i.e.,* at the Screening Visit) and before any procedure related to the trial is performed.

The methods of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50 “Protection of Human Subjects”, the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements.

The Investigator or their designee must fully explain and adequately inform the subject of the purpose of the study prior to entering a subject into the clinical trial or performing any trial-specific procedures.

Once the subject fully agrees to participate in this study, written ICF must be documented by the subject's personally dated signature and the personally dated signature of the informing Investigator/designated person conducting the informed consent discussion. The subject will receive one copy and the original ICF will be filed in the subject study file on site.

The dates when the written informed consent was obtained for the subject and when the subject withdraws or exits the study, must be documented in the subject source documents so that it is known if the subject is currently participating in a clinical study.

In signing the ICF, a subject accepts direct access to their data by Nicox, the company representing Nicox, monitor, auditor, and Health Authority representatives.

14.5 Confidentiality Regarding Trial Subjects Data

In order to maintain subjects' privacy, all study materials will identify subjects in a fully anonymized manner. The Investigator will grant the company or its designated representatives, or regulatory authorities the right to access subject's original medical records for verification of the data gathered in the study. Subject's confidentiality will be maintained and will not be made publically available unless mandated by applicable laws and regulations.

14.6 Archiving at the End of the Study

After the close-out visit at each site, the study is considered completed. A copy of the final completed CRFs will be stored in the Investigator's archives for up 2 years following the final approval of the last marketing authorization, together with all the other site study-specific documents (including Investigator's site file). Neither of these is ever transferred to the Sponsor.

All study-related materials must be stored in a secure manner and must remain available upon request from Nicox or any Health Authority.

15. PUBLICATION POLICY

The institutions, investigators, and all study personnel shall regard all study data as confidential until analyses and review of the analyses are performed by Nicox.

The institutions and investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of Nicox.

16. REFERENCES

Canadian Agency for Drugs and Technologies in Health. Prostaglandin analogues for ophthalmic use: a review of the comparative clinical effectiveness and cost-effectiveness. 2015 July 30.

Cavet ME, Vittitow JL, Impagnatiello F, Ongini E, Bastia E. Nitric oxide (NO): An emerging target for the treatment of glaucoma. Invest Ophthalmol Vis Sci. 2014;55:5005-15.

Daka Q, Trkulja V. Efficacy and tolerability of mono-compound topical treatments for reduction of intraocular pressure in patients with primary open angle glaucoma or ocular hypertension: an overview of reviews. Croat Med J. 2014;55:468-80.

Gabelt BT, Kaufman PL, Rasmussen CA. Effect of nitric oxide compounds on monkey ciliary muscle in vitro. Exp Eye Res. 2011;93:321-7.

Gandolfi S, Simmons ST, Strum R, Chen K, VanDenburgh AM, Bimatoprost Study Group 3. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. Adv Ther. 2001 May-Jun;18(3):110-21.

Heyne GW, Kiland JA, Kaufman PL, Gabelt BT. Effect of nitric oxide on anterior segment physiology in monkeys. Invest Ophthalmol Vis Sci. 2013;54:5103-10.

Impagnatiello F, Toris CB, Batugo M, Prasanna G, Borghi V, Bastia E, et al. Intraocular pressure-lowering activity of NCX 470, a novel nitric oxide-donating bimatoprost in preclinical models. Invest Ophthalmol Vis Sci. 2015;56:6558-64.

Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-16.

Jonas JB, Aung T, Bourne, RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. Lancet 2017 Nov 11;309(10108):2183-93.

Kapetanakis VV, Chan MP, Foster PJ, Cook DG, Owen CG, Rudnicka AR. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. Br J Ophthalmol 2016;100:86-93.

Krauss AHP, Woodward DF. Update on the mechanism of action of bimatoprost: a review and discussion of new evidence. Surv Ophthalmol. 2004;49 (suppl 1):S5-11.

Li T, Lindsley K, Rouse B, Hong H, Shi Q, Friedman DS, et al. Comparative effectiveness of first-line medications for primary open-angle glaucoma: a systematic review and network meta-analysis. Ophthalmology. 2016 Jan;123(1):129-40.

Medeiros FA, Martin KR, Peace J, Scassellati SB, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR Study. Am J Ophthalmol. 2016;30223-9.

Parrish RK, Palmberg P, Sheu WP, for the XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol. 2003 May;135(5):688-703.

Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014 May 14;311:1901-11.

Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. Ophthalmology. 2016 May;123(5):965-73.

Woodward DF, Krauss AHP, Nilsson SFE. Bimatoprost effects on aqueous humor dynamics in monkeys. J Ophthalmol. 2010;23:926192.

APPENDIX 1: TIME AND EVENTS TABLE

Table 2: Times and Events Schedule	**Screening Visit**	**Eligibility 1 Visit** [redacted]			**Eligibility 2 Visit** Day 1			**Week 1 Visit** Day 7 [redacted]			**Week 2 Visit** Day 14 [redacted]			**Week 4 Visit** Day 28 [redacted]			**Exit Visit**[j] Day 29 [redacted]		
Time		**8 AM**	**10 AM**	**4 PM**	**8 AM**	**10 AM**	**4 PM**	**8 AM**	**10 AM**	**4 PM**	**8 AM**	**10 AM**	**4 PM**	**8 AM**	**10 AM**	**4 PM**	**8 AM**	**10 AM**	**4 PM**
Informed consent	X																		
Screening number (IRT/EDC)	X																		
Demographics	X																		
Medical/Ophthalmic history	X																		
Concomitant medications[a]	X		X			X			X			X			X			X	
[redacted]	X	X			X			X			X			X			X		
[redacted]	X																X		
[redacted]	X	X															X		
[redacted]																			
[redacted]	X	X			X			X			X			X			X		
[redacted]	X																		
[redacted]	X	X			X			X			X			X			X		
[redacted]	X	X			X			X			X			X			X		
[redacted]	X													X					
IOP[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X						X									X			
[redacted]	X																		
[redacted]	X																		X
[redacted]	X																		
Adverse events[f]	X		X			X			X			X			X			X	
Randomization (IRT/EDC)[g]							X												
Dispense study medication[h]							X												
Collect study medication														X					
Dispense/collect subject diary[i]							X		X			X			X				
Study exit (IRT/EDC)																			X

[redacted]

APPENDIX 2: METHODS OF CLINICAL EVALUATION

For all assessments, sites should use the same instrument(s) and the same examiner whenever possible throughout the study. All ophthalmic assessments will be performed **bilaterally**. The right eye will be assessed first, then the left eye.

[redacted]

2. CLINICAL LABORATORY COLLECTION

Blood and urine samples will be collected and processed per the instructions in the central laboratory manual.

Urine pregnancy test is to be conducted on site by study staff per the instructions on the pregnancy kit.

3. MANIFEST REFRACTION AND BEST CORRECTED VISUAL ACUITY (BCVA)

The manifest refraction and visual acuity (VA) measurements should be obtained by a physician, optometrist, or trained technician, and every effort should be made to have the same assessor complete the assessment for a given subject using the same equipment and method every time.

3.1. Manifest Refraction

Manifest refraction will be performed using the site's standard procedures. Refraction will be assessed at the Screening Visit and must be repeated only if a decrease in VA of 10 or more letters Screening Visit as assessed per ETDRS occurs during the study, or may be repeated at the discretion of the Investigator.

The correction obtained and recorded at Screening will be used (i.e., placed in trial frames, use of phoropter/optometer or equivalent) for each measurement of best corrected visual acuity (BCVA) at follow-up visits.

3.2. Best Corrected Visual Acuity (BCVA)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4. VISUAL FIELD

[redacted]

[redacted]

[redacted]

5. CONJUNCTIVAL HYPEREMIA ASSESSMENT

[redacted]

6. SLIT LAMP EXAMINATION

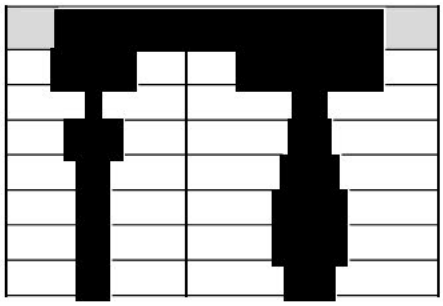
[redacted]

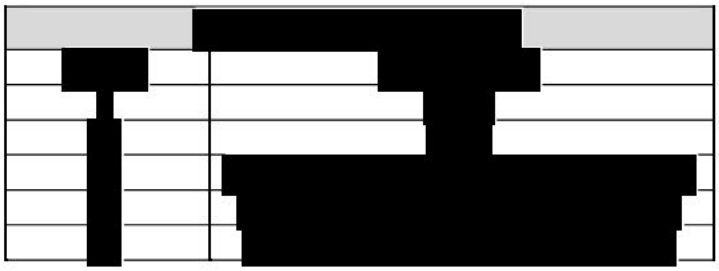
[redacted]

- Eyelid

- Conjunctiva (including conjunctival hyperemia grading, see above)
- Cornea
- Lens
- Iris/Pupil
- Anterior Chamber (including anterior chamber cell and flare, see below)

[redacted]





7. IRIS COLOR ASSESSMENT

[redacted]

8. INTRAOCULAR PRESSURE (IOP)

Intraocular pressure will be measured at **8 AM** [redacted] **10 AM** [redacted] **and 4 PM** [redacted] **at all visits *except* the Screening Visit, at which it will be measured at 8 AM** [redacted] **or 10 AM** [redacted] **or 4 PM** [redacted]

Intraocular pressure will be taken by two qualified study site personnel using a Goldmann applanation tonometer affixed to a slit lamp. The tonometer should be checked for calibration monthly. The measurement must be performed prior to any contact assessments and pupil dilation.

The subject and slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest. Both eyes will be tested, with the right eye preceding the left eye. One person will adjust the dial in a masked fashion (the "Measurer") and a second person will read and record the value (the "Reader"). The tension knob is pre-set at a low pressure value (4-6 mmHg) before and after each measurement.

One person, the "Measurer," will look through the binocular viewer of the slit lamp at low power. The Measurer follows the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the Measurer takes his/her fingers off the tension knob and the second person ("the Reader") records the IOP reading in the source document. The procedure will be repeated on the same eye twice consecutively.

If the measurements are within 2 mmHg or less of each other, the mean of the 2 readings will be calculated and recorded. If the 2 readings differ by more than 2 mmHg, a third (consecutive) reading will be taken and the median (middle) IOP will be recorded.

Rounding of the mean IOP result is not allowed (i.e., a mean of 25.5 mmHg does not qualify as 26 mmHg for meeting eligibility criteria, or a mean of 35.5 mmHg does not qualify as 36 mmHg).

[redacted]

[redacted]

11. DILATED OPHTHALMOSCOPY

Dilated ophthalmoscopy will be performed after the final IOP measurement of the day for the specified visits and at the discretion of the Investigator.

[redacted] The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve
- Cup-to-Disc

All findings should be recorded with appropriate medical terminology avoiding colloquialisms and abbreviations.

12. INTERACTIVE RESPONSE TECHNOLOGY (IRT)

Interactive response technology (IRT) activities will be performed as described in the IRT Site User Manual.

[redacted]

[redacted]