Phase 3 Trial of NCX 470 vs Latanoprost in Subjects with Open-Angle Glauocma or Ocular Hypertension (Mont Blanc)

NCT#04445519

08-July-2020

Nicox Ophthalmics, Inc.

4721 Emperor Blvd., Suite 260, Durham, North Carolina 27703 - USA

Compound

NCX 470

Study Number

NCX-470-02

Study Title

A Phase 3, Randomized, Adaptive Dose-Selection, Multi-Regional, Double-Masked, Parallel-Group, 3–Month Trial Evaluating the Safety and Efficacy of NCX 470 vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension (Mont Blanc)

PROTOCOL

Version # 2.0

Released on 08-July-2020

Clinical Development Phase:	3
Sponsor:	**Nicox Ophthalmics, Inc.** **4721 Emperor Blvd., Suite 260,** **Durham, North Carolina 27703 - USA**

PROTOCOL SIGNATURE PAGE

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APPROVAL OF STUDY PROTOCOL

Version: Version 2.0
Release Date: 08-July-2020

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.
4721 Emperor Blvd., Suite 260, Durham, North Carolina 27703 - USA

On behalf of the Sponsor:

[redacted]

[redacted]

CONTACT INFORMATION

Protocol Identification
A Phase 3, Randomized, Adaptive Dose-Selection, Multi-Regional, Double-Masked, Parallel-Group, 3–Month Trial Evaluating the Safety and Efficacy of NCX 470 vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension (Mont Blanc)

Version #2.0 released on 08-July-2020

Sponsor
Nicox Ophthalmics, Inc.
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PROTOCOL HISTORY TABLE

REASONS FOR CHANGES	DETAILS OF CHANGES
Version 2.0, dated 08-July-2020; Amendment 1	
Limit the number of subjects randomized to treatment arm to be discontinued beyond the 30 randomized subjects target; describe handling of subjects and visits during Adaptive Dose Selection Period; describe study participation of discontinued subjects	• Added detail regarding the design of the dose-ranging phase of the trial, [redacted]
	• Clarified that the adaptive dose selection would be based on data from at least 30 subjects randomized into each of the three treatment arms [redacted]
	• Revised overall number of subjects [redacted] (Synopsis; Sections 1.2, 3.1, 4.1, 6.7)
	• Added guidance regarding handling of completed and new Eligibility 1 and Eligibility 2 Visit data based on Adaptive Dose Selection Period (new Section 3.3, Sections 7.2, 7.3)
	• Revised Section 3.2 [redacted]
	• Corrected the duration of treatment (6 weeks to 3 months) for subjects in the treatment arm to be discontinued [redacted]
	• Clarified the overall study duration of the trial, [redacted])
	• Specified that following the adaptive dose selection, ongoing subjects who were randomized to the discontinued arm should be discontinued at their next regularly scheduled visit [redacted]
Ensure adequate washout of investigational IOP-lowering medications	• Revised exclusion criteria #26 [redacted]

REASONS FOR CHANGES	DETAILS OF CHANGES
Consistency with exclusion criteria in Phase 2 trial NCX-470-17001	• Revised exclusion criteria #13 [redacted]
Ensure capture of all prior ophthalmic medications	• Added requirement to capture investigational ophthalmic products used in prior 12 months (Section 5.1)
Reduce burden on subjects and increase flexibility for sites	• Allowed prior visual field [redacted]
Support consistency of methodology within and across sites	• Added light meter (if required) to list of other study supplies provided to sites (Section 6.13)
	• Indicated that a replacement bulb with fenestrated sleeve (diffuser) was only required if applicable (Appendix 2)
Ensure earlier eligibility of screened subjects	• Removed allowance for pachymetry or gonioscopy [redacted]
Covid-19 precaution	• Specified that monitoring visits could include remote visits (Section 13.1)
Clarification	• Revised exclusion #16 [redacted]
	• Clarified that Exclusion Criteria #1, #4, #13 and #24 applied to either eye (Synopsis; Section 4.4)
	• Revised area of application for prohibited steroid medications for consistency with Exclusion Criterion #21 (Section 5.2)
	• Provided more detail regarding actual labeling of study medication (Section 6.4)
	• Revised terminology regarding packaging of study medication to “kit(s)” vs “box(es)” and include a description of kit (Sections 6.3, 6.4, 6.5, 6.6, 6.8, 7.3, 7.5, 7.6 and 13.1)
	• Clarified that the outer kit includes a storage temperature sticker (Section 6.4 and 6.5)
	• Specified that the unmasked site designee instructs subjects on proper storage and handling of study medication (Section 6.5)
	• Clarified that the maximum time of [redacted] days between Screening Visit and Eligibility 1 Visit [redacted]
	• Clarified that decision rules for selecting the NCX 470 dose would be detailed in the Adaptive Decision Committee charter, as well as in the SAP (Synopsis; Section 11.5.1)

REASONS FOR CHANGES	DETAILS OF CHANGES
Clarification	• Clarified that in Study NCX-470-17001, NCX 470 resulted in up to 1.4 mmHg greater IOP-lowering efficacy than latanoprost based on reduction from baseline in time-matched IOP over the Week 1, 2 and 4 Visits (Section 1.2)
	• Clarified that pachymetry [redacted]
	• Clarified that baseline IOP analyses will be based [redacted]
	• [redacted]
	• Other minor clerical corrections or clarification of terminology (Synopsis; Section 2.3, 3.1, 4.3, 4.4, 6.3, 6.4, 6.6, 6.7, 6.8, 6.12, 8.6, 11.5.1, 11.5.3; 13.3, Appendix 2; Appendix 3)
Administrative	• Added a section to identify the Coordinating Investigator for the trial (Section 14.7)
	• Updated List of Abbreviations; added change history for Amendment 1
Version 1.0, dated 20-Feb-2020; Original Protocol	
Original version	Not Applicable

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS	
ACE	Angiotensin-converting Enzyme
ADC	Adaptive Decision Committee
AE	Adverse Event
ALT	Argon Laser Trabeculoplasty
AM	*Ante Meridiem* (before midday)
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASA	Advanced Surface Ablation
BCVA	Best Corrected Visual Acuity
CFR	Code of Federal Regulations
CI	Confidence Interval
COV	Close Out Visit
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
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
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
[redacted]	[redacted]
LASIK	Laser-Assisted in situ Keratomileusis
LDPE	Low Density Polyethylene
[redacted]	[redacted]
logMAR	Logarithm of Minimum Angle Resolution

LS	Least Square
MCMC	Monte Carlo Markov Chain
MI	Multiple Imputations
MIGS	Minimally Invasive Glaucoma Surgery
MP	Monitoring Plan
mmHg	Millimeters of Mercury
NCS	Not Clinically Significant
NDA	New Drug Application
NO	Nitric Oxide
OAG	Open-Angle Glaucoma
OHT	Ocular Hypertension
PGA	Prostaglandin Analog
PGF2α	Prostaglandin F2α
PI	Principal Investigator
PM	*Post Meridiem* (after midday)
POAG	Primary Open-Angle Glaucoma
PP	Per Protocol
PRK	Photorefractive Keratectomy
QD	*Quaque Die* (once daily)
R&D	Research and Development
SAE	Serious Adverse Event
SD	Standard Deviation
SAP	Statistical Analysis Plan
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
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 3, Randomized, Adaptive Dose-Selection, Multi-Regional, Double-Masked, Parallel-Group, 3–Month Trial Evaluating the Safety and Efficacy of NCX 470 vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension (Mont Blanc)
Study No.	NCX-470-02
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, 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 (Medeiros, 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. The results of the Phase 2 trial “Dolomites”, NCX-470-17001 demonstrated that all tested concentrations of NCX 470 (0.021%, 0.042%, and 0.065%) once daily (QD) met the primary efficacy endpoint of non-inferiority to latanoprost 0.005% QD for reduction from baseline in mean diurnal IOP at Day 28. In pre-specified secondary efficacy analyses, NCX 470 0.065% was superior to latanoprost for mean IOP reduction from baseline at all 3 time points (8AM, 10AM and 4PM) on Day 28, with the difference reaching up to 1.4 mmHg. Mean IOP reduction from baseline at the 3 time points across Days 7, 14 and 28 ranged from 7.6 to 9.8 mmHg for NCX 470 0.065% compared with 6.3 to 8.8 mmHg for latanoprost. Additionally, all three concentrations of NCX 470 were well tolerated. The most frequent adverse event was conjunctival hyperemia. There were no treatment-related serious adverse events, and no evidence of treatment-related systemic side effects. NCX 470 showed increased IOP-lowering efficacy with each incremental concentration of NCX 470, with a conjunctival hyperemia dose-response which plateaued at the middle dose (0.042%). The separation of the dose-response

	curves in IOP lowering vs. conjunctival hyperemia showed a favorable therapeutic index thereby allowing for a higher concentration of NCX 470 (i.e., 0.1%) to be evaluated in this trial alongside the highest dose tested (0.065% NCX 470) in the Phase 2 Dolomites trial. An adaptive design will be utilized wherein one of the NCX 470 doses will be discontinued during the adaptive evaluation, which will occur after at least 30 randomized subjects in each arm complete their Week 2 Visit.
Study Period	Q2 2020-Q2 2021
Study Phase	Phase 3
Study Design	Randomized, multi-regional, double-masked, parallel groups, active comparator-controlled clinical trial with adaptive dose selection.
Number of Subjects	This trial will be conducted at approximately 50 sites in the United States and [redacted] in China. [redacted] Approximately [redacted] 670 randomized. [redacted]
Objectives	The primary objective is to demonstrate that NCX 470 (0.065% or 0.1%) QD is non-inferior to latanoprost 0.005% QD based on mean IOP reduction from time-matched baseline at the 8AM and 4PM time points at the Week 2, Week 6 and Month 3 Visits. A secondary objective is to demonstrate that NCX 470 QD is superior to latanoprost 0.005% QD based on mean IOP reduction from time-matched baseline at the 8AM and 4PM time points at the Week 2, Week 6 and Month 3 Visits. Another secondary objective is to demonstrate that NCX 470 (0.065% or 0.1%) QD is safe and well tolerated when administered to subjects for 3 months.
Selection of Target Subject Population	Adult men and women with a diagnosis of OAG or OHT in both eyes.

Study Medication, Comparator, Dosage and Mode of Administration	During the initial adaptive design dose-ranging phase, at least 30 subjects will be randomized in each arm in a 1:1:1 ratio to receive NCX 470 ophthalmic solution (0.065% or 0.1%), or latanoprost ophthalmic solution, 0.005% QD in the evening, one drop in each eye. • NCX 470 ophthalmic solution, 0.065% (minimum 30 subjects randomized) • NCX 470 ophthalmic solution, 0.1% (minimum 30 subjects randomized) • Latanoprost ophthalmic solution, 0.005% (minimum 30 subjects randomized) 

<table>
<tr><td>Trial Conduct and Duration of Treatment</td><td>Subjects will be evaluated over 6 clinical visits. Subjects who meet inclusion/exclusion criteria at the Screening Visit will be withdrawn from their pre-study IOP-lowering medications, [redacted].
<table>
<tr><th>IOP-Lowering Medication</th><th>Minimum Washout Period</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td></td></tr>
<tr><td colspan="2">[redacted]</td></tr>
</table>
[redacted] After the adaptive dose selection of one dose of NCX 470 to be studied further and discontinuation of the other dose of NCX 470, subjects will be randomized in a 1:1 ratio to receive the selected dose of the NCX 470 ophthalmic solution or latanoprost ophthalmic solution, 0.005% QD in the evening, one drop in each eye for 3 months.</td></tr>
<tr><td>Inclusion Criteria</td><td>1) Subjects [redacted] years old. Subject must 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 [redacted]
3) If treated for OAG or OHT, treatment nature and dose regimen must have been stable for both eyes for [redacted] prior to the Screening Visit.
4) Subjects will meet the following IOP requirements at the Eligibility 1 (Days [redacted]) and Eligibility 2 (Day [redacted]) Visits:
• [redacted]
[redacted]</td></tr>
</table>

	• [redacted] 5) Subjects who are on a PGA or NO-donating PGA therapy at Screening Visit must have a time-matched IOP increase of [redacted] in the study eye after the washout period at the Eligibility 1 and Eligibility 2 Visits. 6) Subjects with best-corrected visual acuity (BCVA), using Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, of [redacted] logMAR units (Snellen equivalent [redacted] 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	**Ocular** 1) Subjects with advanced glaucoma or subjects with a cup/disc ratio greater than [redacted] Subjects who are unable to reliably perform perimetry in either eye (see Appendix 2 for reliability criteria). 2) Subjects unwilling or unable to discontinue their current IOP-lowering medication(s). (An IOP-lowering medication with a shorter washout period is permitted between the Screening Visit and Eligibility 1 Visit) – see Table 1. Refer also to Table 2 for use of an IOP-lowering medication with a short washout period in non-randomized subjects during the Adaptive Dose Selection Period. 3) Subjects with narrow angles [redacted] according to Shaffer anterior chamber angle grading system) and subjects with angle closure, clinically significant peripheral anterior synechiae, congenital glaucoma, or a history of angle closure in either eye. 4) Subjects with an iris or pupil anomaly (e.g., synechiae, coloboma) preventing reliable assessment of pupil diameter in either eye. 5) Subjects whose central corneal thickness is less than [redacted] or greater than [redacted] in either eye. 6) Subjects with any condition that prevents reliable applanation tonometry in either eye (e.g., significant corneal surface abnormalities, scars, keratoconus). 7) Subjects with [redacted] conjunctival hyperemia in either eye at the 8AM assessment at the Eligibility 1 or Eligibility 2 Visits graded on high resolution, color photography scale. 8) Subjects with previous or currently active clinically significant corneal disease in either eye that could affect study outcome per Investigator's judgment. 9) Subjects with a history of [redacted]. 10) Subjects with any active or recurrent [redacted].

11) Subjects with a diagnosis of a clinically significant [redacted]

12) Subjects unwilling or unable to discontinue [redacted].

Ocular Surgery

13) Subjects with history of previous glaucoma [redacted]

14) [redacted]

15) [redacted]

16) [redacted]

17) [redacted]

Medication

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

19) Subjects with known contraindications to NO treatments (e.g., [redacted]

20) Subjects whose concomitant use of medications may interact with the safety or efficacy of a NO-donating compound [redacted]

21) Subjects who currently require treatment or are expected to require treatment with ocular or systemic corticosteroids during the study period [redacted]

22) Subjects with an anticipated need to initiate or modify medication [redacted]

23) Subjects who currently require treatment or are expected to require treatment with any ocular medications, [redacted]

	24) [redacted] **Other** 25) Subjects with a history or presence of uncontrolled systemic disease [redacted] 26) [redacted] 27) Subjects who were randomized in the [redacted]
Study Endpoints	**Efficacy Measures** Primary Endpoint: The primary efficacy endpoint for this trial is mean IOP reduction from time-matched baseline (based on Eligibility 1 and Eligibility 2 Visits) at the 8AM and 4PM time-points at the Week 2, 6 and Month 3 Visits in the study eye. The primary efficacy analysis is the non-inferiority comparison of the mean treatment effect between NCX 470 and latanoprost 0.005% in the study eye. A secondary efficacy analysis is the superiority comparison of the treatment effect between NCX 470 and latanoprost 0.005% in the study eye. [redacted] **Safety Measures** • Intraocular pressure • Slit-lamp biomicroscopy • Conjunctival hyperemia • Dilated ophthalmoscopy • Pachymetry • Perimetry • Pupil size • Iris color • Best-corrected visual acuity (BCVA) • Urine pregnancy tests (for females of childbearing potential) • Rate of discontinuation from the study • Treatment-Emergent Adverse Events
Statistical Methods	**Sample size determination and efficacy analyses:** The primary objective of this study is to demonstrate that mean IOP reduction from time-matched baseline (baseline minus follow-up) for NCX 470 (0.065% or 0.1%) is non-inferior to latanoprost ophthalmic solution, 0.005%. The secondary objective of this study is to demonstrate that mean IOP reduction from time-matched baseline for NCX 470 (0.065% or 0.1%) is superior to latanoprost.

An additional secondary objective is to demonstrate that NCX 470 is safe and well tolerated.

[redacted]

Interim Adaptive Analysis

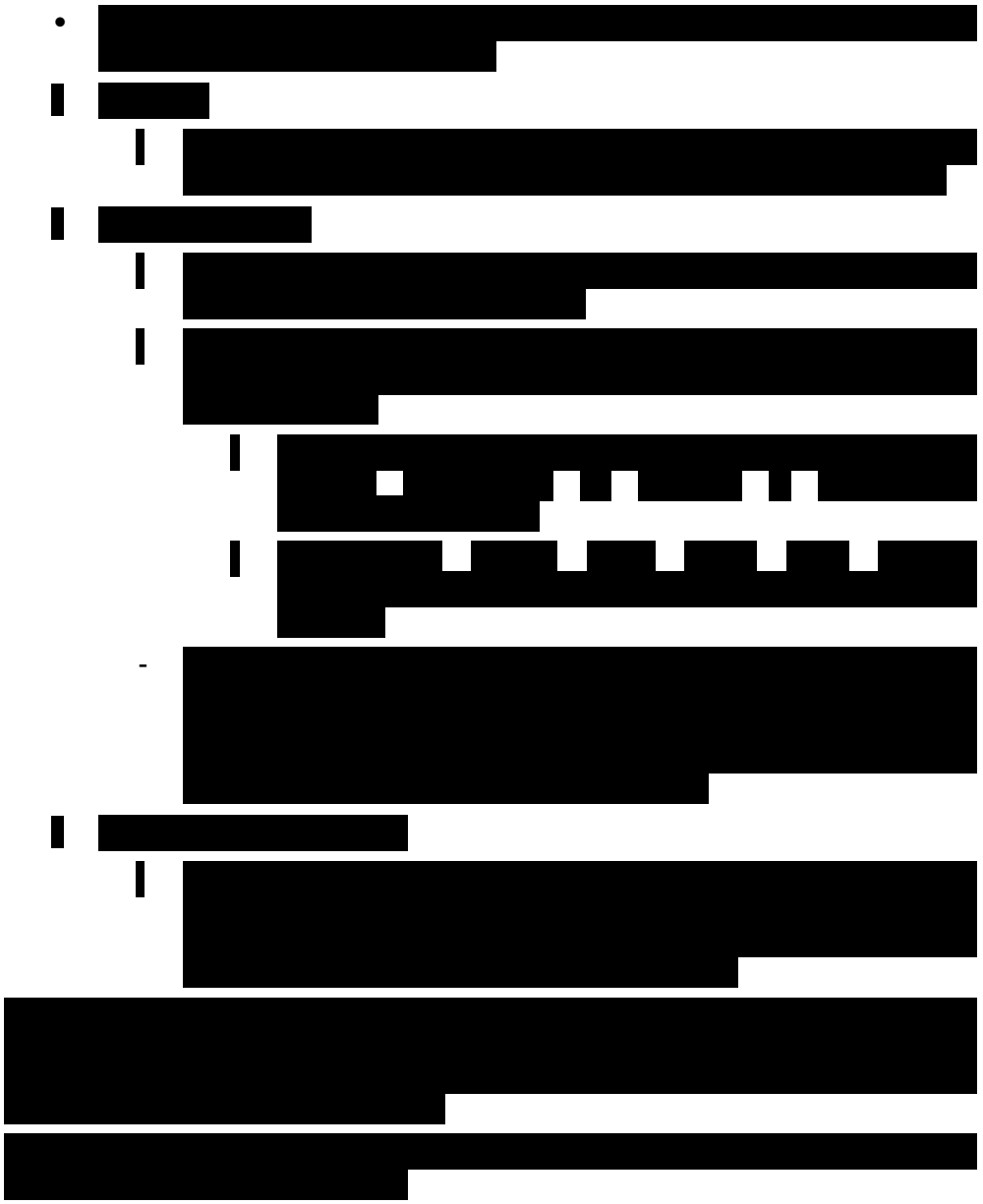
A planned unmasked interim adaptive analysis will be performed by a limited number of independent personnel once at least 30 subjects randomized in each of the three armshave completed the Week 2 Visit [redacted].

Information on the Adaptive Decision Committee (ADC) is provided in Section 11. Testing method and specifications regarding the decision rules for selecting the NCX 470 treatment dose will be detailed in the Statistical Analysis Plan and the Adaptive Decision Committee Charter.

Final Analysis

Primary Estimand

The primary comparisons in this trial will be between NCX 470 (0.065% or 0.1%) QD and latanoprost 0.005% QD at the 8AM and 4PM time points at the Week 2, Week 6, and Month 3 Visits in the ITT population with intercurrent events handled as described in the following estimand.



Efficacy Analyses

The primary analysis of the primary outcome will employ a linear model with mean IOP at the given visit (Week 2, Week 6, and Month 3) and time point (8AM and 4PM) as the response, baseline IOP as a covariate, and treatment as a main effect, using

	the intent to treat population with multiple imputation techniques used to impute missing data (fully detailed estimand statements and handling of intercurrent events will be provided in the statistical analysis plan). The primary analysis for superiority will be completed similarly. **Adjustments for Multiplicity**   **Safety Analyses** Safety analyses are based on the safety dataset. The safety population 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 (0.065% or 0.1%) 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. 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.

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 (Medeiros, 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.

The results of the first-in-man Phase 2 trial "Dolomites", NCX-470-17001 demonstrated that all tested concentrations of NCX 470 (0.021%, 0.042%, and 0.065%) QD met the primary

efficacy endpoint of non-inferiority to latanoprost 0.005% QD for reduction from baseline in mean diurnal IOP at Day 28. In pre-specified secondary efficacy analyses, NCX 470 0.065% was superior to latanoprost for mean IOP reduction from baseline at all 3 time points (8AM, 10AM and 4PM) on Day 28, with the difference reaching up to 1.4 mmHg. Mean IOP reduction from baseline at the 3 time points across Days 7, 14 and 28 ranged from 7.6 to 9.8 mmHg for NCX 470 0.065% compared with 6.3 to 8.8 mmHg for latanoprost. Additionally, all 3 concentrations of NCX 470 were well tolerated. The most frequent adverse event was conjunctival hyperemia. There were no treatment-related serious adverse events, and no evidence of treatment-related systemic side effects. The linearly increasing, dose-dependent IOP-lowering efficacy of NCX 470 without reaching a plateau, and the plateauing of ocular adverse events at the mid-dose of NCX 470 (0.042%) in the Phase 2 Dolomites trial (NCX-470-17001) indicated that a higher dose (0.1%) has the potential for greater IOP lowering without apparent significant additional risks. Therefore, an adaptive design will be utilized in the current trial whereby one of the NCX 470 doses (0.065% or 0.1%) will be discontinued during the adaptive evaluation, which will occur after at least 30 subjects randomized in each arm complete their Week 2 Visit.

1.2 Study Background

Nonclinical and Clinical Studies of NCX 470

A summary of all nonclinical and clinical studies with NCX 470 can be found in the Investigator's Brochure.

Description of the Study Medication

[redacted]

Description of Active Comparator

[redacted]

Justification of the Study Design

The proposed Phase 3 is a randomized, multi-regional, double-masked, parallel groups, active comparator-controlled clinical trial with adaptive dose selection.

During the initial adaptive design dose-ranging phase, at least 30 subjects will be randomized in each arm in a 1:1:1 ratio to receive NCX 470 ophthalmic solution (0.065% or 0.1%), or latanoprost ophthalmic solution, 0.005% QD in the evening, one drop in each eye.

- NCX 470 ophthalmic solution, 0.065% (minimum 30 subjects randomized)
- NCX 470 ophthalmic solution, 0.1% (minimum 30 subjects randomized)
- Latanoprost ophthalmic solution, 0.005% (minimum 30 subjects randomized)

[redacted]

The adaptive dose selection will be made at the end of the Adaptive Dose Selection Period during which at least 30 randomized subjects in each arm complete their Week 2 Visit [redacted]

- [redacted]

[redacted]

Justification of the Route of Delivery

The topical ophthalmic route of delivery selected for the NCX 470 is the same as for the topical ophthalmic IOP-lowering product VYZULTA. NCX 470 and VYZULTA have the same postulated mechanism of action, both comprised of a PGA and a NO-donating moiety. [redacted]

Justification of the Dose Selection for NCX 470

The IOP-lowering effect of NCX 470 was initially established in normotensive beagle dogs and ocular hypertensive non-human primates. In these nonclinical models, topical ophthalmic formulations of NCX 470 0.042%, formulated to be equimolar to topical ophthalmic formulation of 0.03% bimatoprost, demonstrated 2.0 to 3.5 mmHg superiority in IOP-lowering effect compared to 0.03% topical ophthalmic bimatoprost.

Therefore, clinical dose ranging in the Phase 2 trial was centered on the mid dose of 0.042% NCX 470 (equimolar with 0.03% bimatoprost); a low dose of 0.021% NCX 470 (equimolar to 0.015% bimatoprost); and a high dose of 0.065% NCX 470 (equimolar to 0.05% bimatoprost).

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

The results of the Phase 2 trial “Dolomites”, NCX-470-17001 demonstrated that all tested concentrations of NCX 470 (0.021%, 0.042%, and 0.065%) QD met the primary efficacy endpoint of non-inferiority to latanoprost 0.005% QD for reduction from baseline in mean diurnal IOP at Day 28. In pre-specified secondary efficacy analyses, NCX 470 0.065% was superior to latanoprost for mean IOP reduction from baseline at all 3 time points (8AM, 10AM

and 4PM) on Day 28, with the difference reaching up to 1.4 mmHg. Mean IOP reduction from baseline at the 3 time points across Days 7, 14 and 28 ranged from 7.6 to 9.8 mmHg for NCX 470 0.065% compared with 6.3 to 8.8 mmHg for latanoprost. Additionally, all 3 concentrations of NCX 470 were well tolerated. The most frequent adverse event was conjunctival hyperemia. There were no treatment-related serious adverse events, and no evidence of treatment-related systemic side effects. NCX 470 showed linearly increasing IOP-lowering efficacy with each incremental concentration of NCX 470 without reaching a plateau, with a conjunctival hyperemia dose-response which plateaued at the middle dose (0.042%). The separation of the dose-response curves in IOP lowering vs. conjunctival hyperemia showed a favorable therapeutic index thereby allowing for a higher concentration of NCX 470 (i.e., 0.1%) to be evaluated in this trial alongside the highest dose tested (0.065% NCX 470) in the Phase 2 Dolomites trial. An adaptive design will be utilized wherein one of the NCX 470 doses will be discontinued during the adaptive evaluation, which will occur after at least 30 randomized subjects in each arm complete their Week 2 Visit.

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. Latanoprost has been used as comparator in the Phase 2 dose-ranging study NCX-470-17001 and NCX 470 0.065% demonstrated its superiority to this standard-of-care treatment for mean IOP reduction from baseline at all 3 time points (8AM, 10AM and 4PM) at the Week 4 Visit, with the difference reaching up to 1.4 mmHg. Therefore, latanoprost 0.005% is a reasonable choice for an active comparator for the NCX 470 Phase 3 program.

Selection of the Study Population

A total of approximately 670 male and female adults with OAG or OHT in both eyes will be randomized in this clinical study at approximately 50 investigative sites in the US and approximately 1 to 3 investigative sites in China. Up to 15 additional sites may be added based on enrollment rates.

[redacted]

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 Phase 2 NCX-470-17001 trial, as well as the clinical development and marketing experience of bimatoprost, latanoprost, and latanoprostene bunod ophthalmic solutions.

[redacted] For further information, please refer to the Investigator Brochure for NCX 470.

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.

The results of the Phase 2 “Dolomites” trial, NCX-470-17001 demonstrated that all tested concentrations of NCX 470 (0.021%, 0.042%, and 0.065%) QD met the primary efficacy endpoint of non-inferiority to latanoprost 0.005% QD for reduction from baseline in mean diurnal IOP at the Week 4 Visit. In pre-specified secondary efficacy analyses, NCX 470 0.065% was superior to latanoprost for mean IOP reduction from baseline at all 3 time points (8AM, 10AM and 4PM) at the Week 4 Visit, with the difference reaching up to 1.4 mmHg. Mean IOP reduction from baseline at the 3 time points across the Week 1, 2 and 4 Visits ranged from 7.6 to 9.8 mmHg for NCX 470 0.065% compared with 6.3 to 8.8 mmHg for latanoprost. Additionally, all 3 concentrations of NCX 470 were well tolerated. The most frequent adverse event was conjunctival hyperemia. There were no treatment-related serious adverse events, and no evidence of treatment-related systemic side effects. NCX 470 showed increased IOP-lowering efficacy with each incremental concentration of NCX 470, with a conjunctival hyperemia dose-response which plateaued at the mid-dose (0.042%). The separation of the dose-response curves in IOP lowering vs. conjunctival hyperemia showed a favorable therapeutic index thereby allowing for a higher concentration of NCX 470 (i.e., 0.1%) to be evaluated in this trial alongside the highest dose tested (0.065% NCX 470) in the Phase 2 trial.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary Objective

The primary objective is to demonstrate that NCX 470 (0.065% or 0.1%) QD is non-inferior to latanoprost 0.005% QD based on mean IOP reduction from time-matched baseline at the 8AM and 4PM time points at the Week 2, Week 6 and Month 3 Visits.

[redacted]

2.2 Study Endpoints

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

- IOP
- Slit-lamp biomicroscopy
- Conjunctival hyperemia
- Dilated ophthalmoscopy
- Pachymetry
- Perimetry
- Pupil size
- Iris color
- Best Corrected Visual Acuity (BCVA)
- Urine pregnancy tests (for females of childbearing potential)
- Rate of discontinuation from the study
- Treatment-Emergent Adverse Events

2.3 Efficacy Evaluations

Primary Endpoint: The primary efficacy endpoint for this trial is mean IOP reduction from time-matched baseline (based on Eligibility 1 and Eligibility 2 Visits) at the 8AM and 4PM time-points at the Week 2, 6 and Month 3/Exit Visits in the study eye

[redacted]

2.4 Safety Evaluations

Evaluations of safety include but are not limited to the collection of: adverse events, IOP, slit lamp biomicroscopy parameters, conjunctival hyperemia, dilated ophthalmoscopy parameters, pachymetry, perimetry, pupil size, iris color, BCVA, pregnancy tests (for women of child bearing potential (WOCBP)) and rate of discontinuation from the trial.

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]

[redacted]

3. STUDY DESIGN

3.1 Overall Study Design

This is a randomized, multi-regional, double-masked, parallel-group, active comparator-controlled, Phase 3 clinical trial with adaptive dose selection. This trial will be conducted in approximately 50 sites in the United States and [redacted] China. [redacted]

Subjects will be assessed for initial eligibility at the Screening Visit (Figure 1). Subjects currently being treated with an IOP-lowering medication 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 [redacted] and the Eligibility 2 Visit (Day [redacted]) with diurnal IOP measurements at 8AM, 10AM, and 4PM at both visits. The baseline IOP for study eligibility will be based on the study eye IOP measurements from the Eligibility 1 and Eligibility 2 Visits. Subjects meeting eligibility requirements will be randomized at the end of the Eligibility 2 Visit.

During the initial adaptive design dose-ranging phase, at least 30 subjects will be randomized in each arm in a 1:1:1 ratio to receive NCX 470 ophthalmic solution (0.065% or 0.1%), or latanoprost ophthalmic solution, 0.005% QD in the evening, one drop in each eye.

- NCX 470 ophthalmic solution, 0.065% (minimum 30 subjects randomized)
- NCX 470 ophthalmic solution, 0.1% (minimum 30 subjects randomized)
- Latanoprost ophthalmic solution, 0.005% (minimum 30 subjects randomized)

[redacted]

- [redacted]

- [redacted]

[redacted]

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

Approximately 640 subjects will be studied for 3 months [redacted]

A subject will be considered as having completed the study after completion of the Month 3/ Exit Visit (Day 90 [± 3 days]). The overall study duration is estimated to be approximately 12 to 15 months from the first subject enrolled until completion of the last subject. The maximum duration of subject participation (from the Screening Visit to the Month 3/Exit Visit) is approximately 139 days (or approximately 167 days for subjects for whom the washout period may be extended during the Adaptive Dose Selection Period).

[redacted]

[redacted]

*

3.2 Washout Period for Majority of the Study Subjects

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. [redacted]

[redacted]

The minimum washout period will begin at the Screening Visit and will be completed at the Eligibility 1 Visit (day [redacted] (Figure 1). The time between the Screening Visit and the Eligibility 1 Visit should not [redacted] for any subject.

After the Eligibility 1 Visit there will be an additional [redacted] 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 should [redacted].

[redacted]

For treatment-naïve subjects the Eligibility 1 Visit will be scheduled a minimum of 5 days after the Screening Visit.

[redacted]

Table 1: Minimum Washout Period(s) for IOP-Lowering Medications

IOP-Lowering Medication	Minimum Washout Period
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

3.3 Washout Period and Handling of Eligibility 1 and Eligibility 2 Study Visits for the Study Subjects during Adaptive Dose Selection Period

[redacted]

[redacted]

Table 2: [redacted]

Scenario	Handling
[redacted] od	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

Scenario	Handling
[redacted]	• [redacted]
4. [redacted]	• [redacted]
5. [redacted]	• [redacted]

4. SUBJECT SELECTION

4.1 Number of Subjects and Sites

This study will be conducted at approximately 50 clinical sites in the US and [redacted] in China. [redacted] 670 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 [redacted]) **and** the Eligibility 2 Visit (Day [redacted]):

- [redacted]

4.3 Inclusion Criteria

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

1) Subjects [redacted] years old. Subject must 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 [redacted]
3) If treated for OAG or OHT, treatment nature and dose regimen must have been stable [redacted]
4) Subjects will meet the following IOP requirements at the Eligibility 1 (Days [redacted] and Eligibility 2 (Day [redacted]) Visits:
   - [redacted]
5) [redacted]
6) Subjects with best-corrected visual acuity (BCVA), using Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, of [redacted] logMAR units (Snellen equivalent [redacted]) 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:

Ocular

1) Subjects with advanced glaucoma or subjects with a cup/disc ratio greater than [redacted] or [redacted] Subjects who are unable to reliably perform perimetry in either eye (see Appendix 2 for reliability criteria).
2) Subjects unwilling or unable to discontinue their current IOP-lowering medication(s). (An IOP-lowering medication with a shorter washout period is permitted between the Screening Visit and Eligibility 1 Visit – see Table 1. Refer also to Table 2 for use of an IOP-lowering medication with a short washout period in non-randomized subjects during the Adaptive Dose Selection Period.
3) Subjects with narrow angles [redacted] Shaffer anterior chamber angle grading system) and subjects with angle closure, clinically significant peripheral anterior synechiae, congenital glaucoma, or a history of angle closure in either eye.
4) Subjects with an iris or pupil anomaly (e.g., synechiae, coloboma) preventing reliable assessment of pupil diameter in either eye.
5) Subjects whose central corneal thickness is less than [redacted] or greater than [redacted] in either eye.
6) Subjects with any condition that prevents reliable applanation tonometry in either eye (e.g., significant corneal surface abnormalities, scars, keratoconus).
7) Subjects with [redacted] conjunctival hyperemia in either eye at the 8AM assessment at the Eligibility 1 or Eligibility 2 Visits graded on high resolution, color photography scale.
8) Subjects with previous or currently active clinically significant corneal disease in either eye that could affect study outcome per Investigator's judgment.
9) Subjects with a history of severe dry eye in either eye.
10) Subjects with any active or recurrent intraocular infection, inflammation, iritis or uveitis in either eye.
11) Subjects with a diagnosis of a clinically significant retinal disease [redacted]
12) Subjects unwilling or unable to discontinue [redacted]

Ocular Surgery

13) Subjects with history of previous glaucoma or angle surgery [redacted]

14) [redacted]

15) [redacted]

16) Subjects with history of previous complicated cataract surgery [redacted]

17) Subjects who had incisional ocular surgery or severe trauma in either eye within the previous 6 months [redacted]

Medication

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

19) Subjects with known contraindications to NO treatments [redacted]

20) Subjects whose concomitant use of medications may interact with the safety or efficacy of a NO-donating compound [redacted]

21) Subjects who currently require treatment or are expected to require treatment with ocular or systemic corticosteroids [redacted]

22) Subjects with an anticipated need to initiate or modify medication [redacted]

23) Subjects who currently require treatment or are expected to require treatment with any ocular medications, [redacted]

24) [redacted]

Other

25) Subjects with a history or presence of uncontrolled systemic disease [redacted]

26) [redacted]

27) Subjects who were randomized in the Phase 2 NCX-470-17001 clinical trial.

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, including investigational ophthalmic products, used in the 12 months prior to the Screening Visit must be recorded. Additionally, all medications used between the Screening Visit and the Month 3/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 (see Table 1). Additionally, an IOP-lowering medication with a short washout period (e.g., a topical carbonic anhydrase inhibitor such as AZOPT) is permitted in non-randomized subjects during the Adaptive Dose Selection Period.

The use of over-the-counter artificial tears or antihistamine eye drops is allowed provided they are administered a minimum of 5 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 Month 3/Exit Visit subjects must not receive:

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [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, latanoprost ophthalmic solution, 0.005%, is a sterile, preserved, isotonic, buffered ophthalmic aqueous solution containing 0.005% latanoprost. [redacted]

XALATAN® (latanoprost ophthalmic solution) 0.005% will be used as the active comparator in China and an FDA-approved generic of latanoprost ophthalmic solution, 0.005% will be used as the active comparator in the US.

6.3 Packaging of the Study Medication

[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 [redacted] assigned for a given subject 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 the local language, as applicable, and will comply with US federal regulations and other local regulations, as applicable, for investigational drug product. The [redacted] boxes will be labeled minimally with the following information: protocol number, investigational product name(s), quantity, storage conditions, and Caution statement: *New Drug - Limited by Federal Law to Investigational Use*. The [redacted] label will minimally consist of two parts and list the unique kit number which will correspond to the treatment assignment; the second part of the 2-part label will contain masking information which is only to be revealed in the event of an emergency unmasking by the investigator upon approval by the Sponsor or designee.

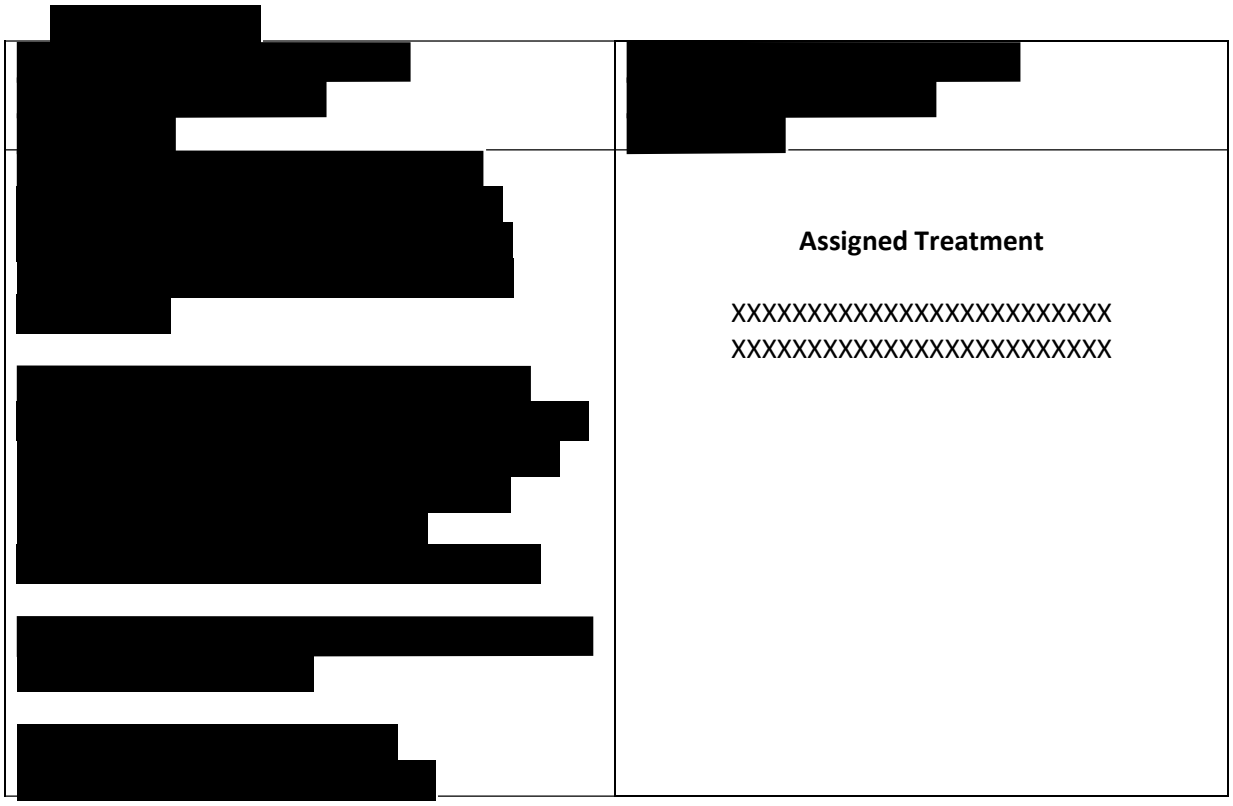
The [redacted] and individual bottles will be labeled minimally with the protocol number and unique kit number which will correspond to the treatment assignment.

The [redacted] 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).

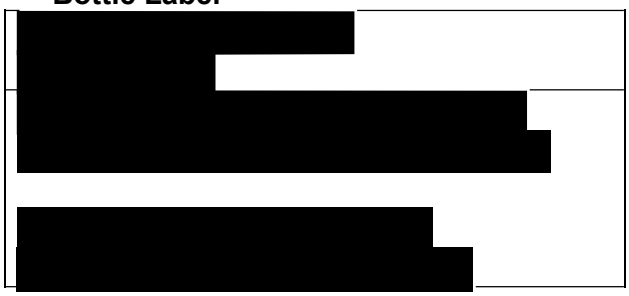
The [redacted], the [redacted], and the bottles will be labeled as described below:



The [redacted] will also have a storage temperature sticker to clearly indicate whether the kit and its contents should be stored at room temperature or refrigerated.

[redacted]

Bottle Label



[redacted]

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.

[redacted]

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 log.

It is the responsibility of the unmasked site designee to maintain detailed study medication accountability records. The importance of returning the kits with all dispensed 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] by the Sponsor or its representative. At the Screening Visit, the site will assign [redacted] to each subject and record it in the screening log. The site will then register the subject in the EDC system in which they will be issued a [redacted]

At the Eligibility 2 Visit (Day 1), [redacted]

[redacted]

The subjects, investigators, site staff measuring IOP or evaluating safety parameters, the Sponsor, the Medical Monitor, and the CRO personnel interacting with the clinical sites (or handling study data) will be masked to the treatment assignment. **The unmasked site designee will only perform handling of study medication, and a limited set of procedures** [redacted]

IRT assignment is based on a randomization schedule created by an unmasked statistician.

6.8 Study Medication Dispensing and Collection

For each subject fulfilling eligibility criteria, the clinical site staff will access the EDC and 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]

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

In the event a subject needs a replacement kit, utilize the IRT. If a subject's study medication is lost or destroyed, the subject will be assigned a [redacted] from within that [redacted] will be dispensed.

Subjects will be instructed to return their study medication [redacted] only to the site's unmasked site designee at the Week 6 and Month 3/Exit Visits. An inventory will be conducted by the unmasked site designee during the conduct of the trial.

6.9 Instructions for Use and Administration

The study medication must be administered one drop in each eye by the subject or caregiver, **at [redacted] from the evening of the Eligibility 2 Visit (Day [redacted]) to the evening prior to the subject's last study visit.**

No study medication will be administered by the investigational site staff.

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

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 the 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 2, Week 6, and Month 3/Exit 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 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 [redacted] 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 [redacted] months for non-ophthalmic and [redacted] months for ophthalmic medications
- [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]

[redacted]

7.2 Eligibility 1 Visit (Day [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [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 [redacted]

[redacted]

[redacted]

7.3 Eligibility 2 Visit (Day)

Eligibility 2 Visit will occur days after the Eligibility 1 Visit. Additionally, Eligibility 2 Visit will occur no more than days from the Screening Visit (except during the Adaptive Dose Selection Period as noted in Table 2).

- Record any AEs which occurred since the last visit and during this visit
- Record any changes in concomitant medication(s), medical/ophthalmic history
-
- Dispense subject diary and subject dosing instructions

7.4 Week 2 Visit (Day 14)

- Record any AEs which occurred since the last visit and during this visit
- Record any changes in concomitant medication(s), medical/ophthalmic history
-

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Review the subject diary for compliance and collect it; dispense new subject diary and dosing instructions

7.5 Week 6 Visit (Day 42 [redacted]

- Record any AEs which occurred since the last visit and during this visit
- Record any changes in concomitant medication(s), medical/ophthalmic history
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Review the subject diary for compliance and collect it; dispense new subject diary and dosing instructions

[redacted]

Note: If a subject, who was randomized to the discontinued dose of NCX 470, is discontinued at the Week 6 Visit, the Month 3/Exit Visit assessments should be performed and documented.

7.6 Month 3 Visit (Day 90 [redacted] Exit Visit

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

- [redacted]
- Review subject diary for compliance and collect it
- Utilize IRT/EDC to exit the subject

7.7 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, changes in medical/ophthalmic conditions
- [redacted]

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

Note that completion of an Unscheduled Visit eCRF is not required for subjects returning to complete perimetry on a separate day from the initial Screening Visit.

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.

Subjects may be rescreened for participation in the trial following Sponsor's approval.

8.2 Subject Completion

A subject is considered to have completed the study at the end of the Month 3/Exit Visit.

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 <u>may</u> 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 <u>must</u> 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 treatment period, the Month 3/Exit Visit assessments should be performed and documented.

If a subject withdraws their consent during the study treatment period, all efforts should be taken to complete Month 3/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.

[redacted]

Study medication must be returned by the subject to the site unmasked designee, as applicable.

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.

8.6 Subjects Discontinued Per Protocol Following Adaptive Evaluation

Subjects, who were randomized to the discontinued dose of NCX 470, must discontinue at the next scheduled study visit following the completion of the Adaptive Dose Selection Period. [redacted]

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. Subjects must not undergo any elective, or plan any non-urgent procedures for the study duration and 30 days following the last treatment administration.

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.

All AEs that occur from the signing of the ICF on the day of the Screening Visit through the Month 3/Exit Visit 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 completion) 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 3 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

A final analysis plan containing detailed statistical methods, including accounting for multiplicity, will be generated and finalized prior to database lock following the completion of the 3-month safety and efficacy evaluation period. There will be a single final statistical analysis plan for this multi-regional trial.

Additionally, an interim analysis plan containing detailed statistical methods, including accounting for multiplicity, will be generated and finalized prior to the interim analysis supporting the adaptive evaluation of at least 30 subjects in each treatment arm through Week 2.

11.1 Determination of Sample Size and Power Calculations

The primary objective of this study is to demonstrate that mean IOP reduction from time-matched baseline (baseline minus follow-up) for NCX 470 (0.065% or 0.1%) is non-inferior to latanoprost ophthalmic solution, 0.005%.

[redacted]

- [redacted]

[redacted]

11.2 Analysis Population

For the 3-month 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 3-month 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 3-month 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, 0.065%
- NCX 470 ophthalmic solution, 0.1%
- Latanoprost ophthalmic solution, 0.005%

11.4 Collection and Derivation of Primary Efficacy Assessments

At the Screening Visit, IOP will be measured at 8AM [redacted] min., 10AM [redacted] min., or 4PM ± [redacted] min. From the Eligibility 1 Visit to the Month 3 Visit, IOP will be measured at 8AM [redacted] min., 10AM [redacted] min. and 4PM [redacted] min. IOP measurements will be conducted in both eyes.

Handling of missing values:

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

11.5 Hypothesis and Methods of Analysis

11.5.1 Primary Efficacy Analysis

The primary efficacy assessment is the non-inferiority analysis of the difference in the treatment effect between NCX 470 and latanoprost 0.005% for mean IOP reduction from time-matched baseline at the 8AM and 4PM time-points at the Week 2, Week 6 and Month 3 Visits in the study eye.

Efficacy will be assessed by the primary variable:

Mean reduction from baseline (average of Eligibility 1 and Eligibility 2 Visits) in time-matched IOP at the 8AM and 4PM time points at the Week 2, Week 6 and Month 3 Visits.

The primary analysis of the primary outcome will employ a linear model with mean IOP at the given visit (Week 2, Week 6, and Month 3) and time point (8AM and 4PM) as the response, baseline IOP as a covariate, and treatment as a main effect, using the ITT population with multiple imputation techniques used to impute missing data.

The primary analysis for superiority will be completed similarly.

Adjustments for Multiplicity

[redacted]

[redacted]

Detailed statistical methodology will be provided in the Statistical Analysis Plan.

Primary Estimand

The primary comparisons in this trial will be between NCX 470 (0.065% or 0.1%) QD and latanoprost 0.005% QD at the 8AM and 4PM time points at the Week 2, Week 6, and Month 3 Visits in the [redacted] population with intercurrent events handled as described in the following estimand.

- [redacted]
  - [redacted]
  - [redacted]:
    - [redacted]
      - [redacted]
        - [redacted]
        - [redacted]
      - [redacted]
- [redacted]
  - [redacted]

[redacted]

[redacted]

Interim Adaptive Analysis

[redacted]

Adaptive Decision Committee

[redacted]

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.

[redacted]

11.5.2 Secondary Efficacy Analyses

[redacted] Detailed statistical methodology for the secondary efficacy analyses will be provided in the Statistical Analysis Plan.

11.5.3 Safety Analysis

Safety analyses are based on the safety dataset. The safety population 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 0.065, NCX 470 0.1% 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.

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.

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 masked Clinical Research Associate (CRA) will monitor the study on a periodic basis by having regular contacts with the investigational sites, including on-site and/or remote 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.

Additionally, an unmasked CRA will monitor the site on a regular basis to ensure that all study medication is stored in a secure area and in accordance with the storage conditions indicated on the label of the outer kits. The unmasked CRA will also provide oversight of temperature excursions. Finally, the unmasked CRA will monitor the site to ensure that study medication is only dispensed to randomized subjects, and that all dispensed and returned study medication is recorded by the unmasked site designee on an inventory log.

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.

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 Plan (MP). 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.

13.6 Audits and Inspections

Authorized representatives of Nicox or the company representing Nicox, a regulatory authority, or an IRB/IEC 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 (e.g., Subject's data records, diagnostic tests) 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 for subjects in the U.S. and appropriate local guidelines, requirements, and regulations for the subjects in China, 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 publicly 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.

14.7 Coordinating Investigator

The Coordinating Investigator for this trial is [redacted]

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.

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APPENDIX 1: TIME AND EVENTS TABLE

Table 3: Times and Events Schedule	**Screening Visit**	**Eligibility 1 Visit** Day [redacted]			**Eligibility 2 Visit** Day [redacted]			**Week 2 Visit** Day 14 [redacted] days)			**Week 6 Visit** Day 42 [redacted] days)			**Month 3/ Exit Visit** Day 90 [redacted] days)		
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**
Informed consent	X															
Screening number (IRT/EDC)	X															
Demographics	X															
Medical/Ophthalmic history/Changes in MH/OH	X	X			X			X			X			X		
Concomitant medications[a]	X		X			X			X			X			X	
[redacted]	X	X									X			X		
[redacted]	X															
[redacted]	X	X			X			X			X			X		
[redacted]	X	X			X			X			X			X		
[redacted]	X[l]														X	
[redacted]	X	X			X			X			X			X		
[redacted]	X	X			X			X			X			X		
[redacted]	X				X									X		
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X						X			X[k]						X
[redacted]	X															
[redacted]y	X															X
[redacted]	X															
Adverse events[g]	X		X			X			X			X			X	
Randomization (IRT/EDC)[h]							X									
Dispense study medication[i]							X						X			
Collect study medication											X			X		
Dispense/collect subject diary[j]							X		X			X			X	
Study exit (IRT/EDC)															X	

(a) [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.

1. URINE PREGNANCY TEST

Urine pregnancy test is to be conducted on site by study staff per the instructions on the pregnancy kit at Screening, Eligibility 1, Week 6 and Month 3/Exit Visits.

2. 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.

2.1 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 [redacted].

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.

2.2 Best Corrected Visual Acuity (BCVA)

[redacted]

[redacted]

3. [redacted]

4. PUPIL SIZE

Measurement of pupil diameter will be performed at the Screening, Eligibility 1, Eligibility 2, Week 2, Week 6 and Month 3/Exit Visits using a pupillary gauge.

Measurement of pupil size should occur after assessment of BCVA and using the same illumination for each subject visit at each visit throughout the course of this study.

Measurement of pupil diameter should occur to the nearest 0.5 mm using a pupillary gauge while the subject fixates on a distant, non-accommodative target. To avoid stimulating the accommodative response and consequential constriction, the pupillary gauge should be held away from the visual axis of the subject.

[redacted]

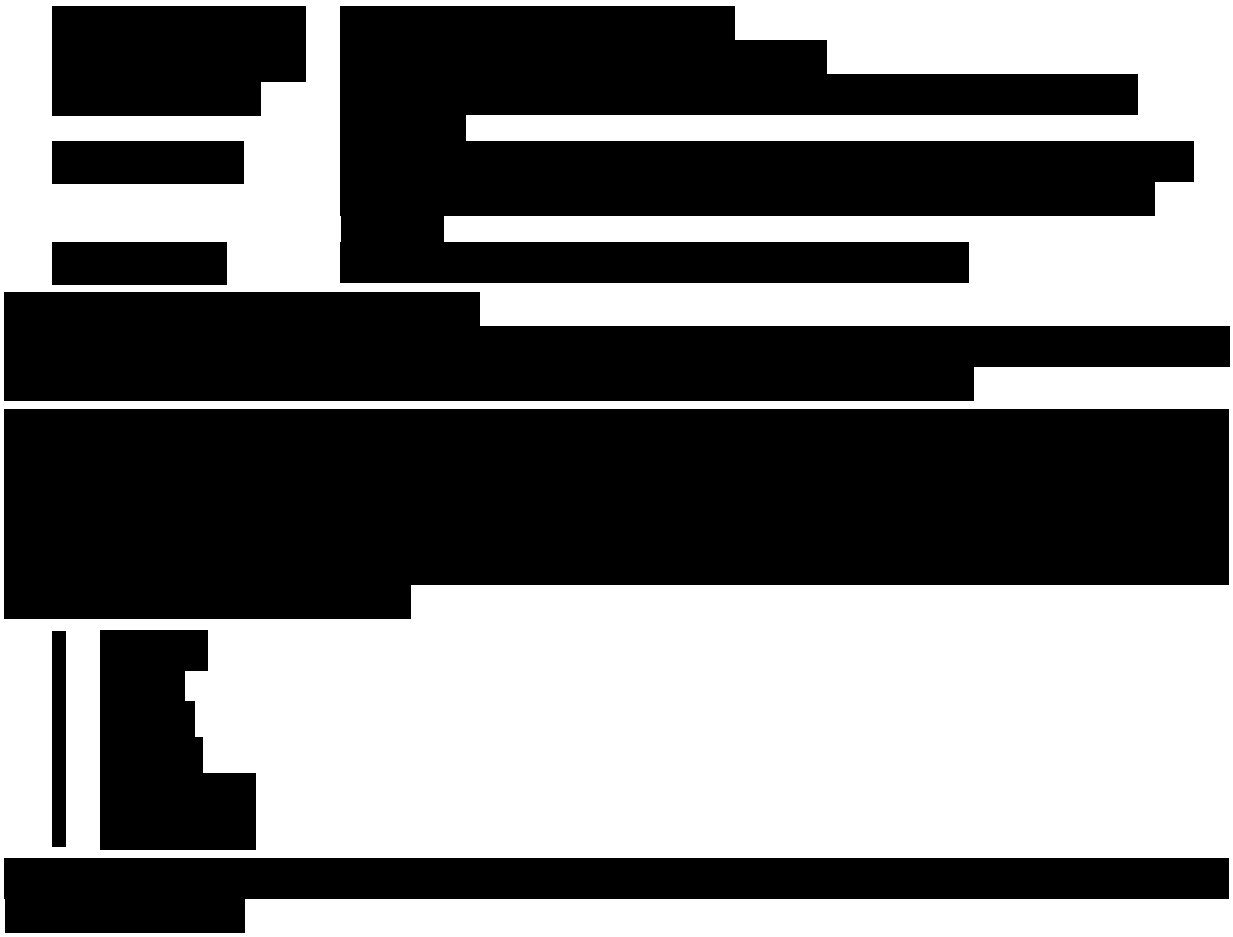
7. [redacted]

8. INTRAOCULAR PRESSURE (IOP)

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

Intraocular pressure will be taken [redacted]

Pachymetry will be performed by trained personnel [redacted].



12. INTERACTIVE RESPONSE TECHNOLOGY (IRT)

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

APPENDIX 3: GENERAL INSTRUCTIONS FOR COMPLETION OF SAE FORMS

1. [redacted]

[redacted]