CONFIDENTIAL

Clinical Study Phase 2 Protocol

OPI-NYXG-201

ORION-1

Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution in Subjects with Open Angle Glaucoma or Ocular Hypertension

Ocuphire Pharma, Inc.
[redacted]

Version:	**02**
Original:	**March 14, 2019**
Amendment 1:	**April 8, 2019**

SPONSOR SIGNATURE & CONTACTS

Study Title:	Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution in Subjects with Open Angle Glaucoma or Ocular Hypertension
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Person authorized to sign the protocol and protocol amendment(s) for the sponsor, Ocuphire Pharma, Inc.

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12Apr2019

Date

INVESTIGATOR'S AGREEMENT

OPI-NYXG-201

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Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution in Subjects with Open Angle Glaucoma or Ocular Hypertension

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Investigator Agreement:

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice, the ethical principles set forth in the Declaration of Helsinki and with the U.S. Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312).

Signature: _____ Date: _____

Printed Name: _____

PROCEDURES IN CASE OF EMERGENCY

EMERGENCY CONTACT INFORMATION

Role in Study	Name	Contact Information
Clinical Study Leader	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]

ABBREVIATIONS AND TERMS

Abbreviation	*Full term*
AE	Adverse Event
AM	Ante Meridian – in the morning
ANCOVA	Analysis of Covariance
AR	All Randomized
BCDVA	Best Corrected Distance Visual Acuity
BP	Blood Pressure
°C	Degree Centigrade
CCLRU	Cornea and Contact Lens Research Unit
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
CRF	Case Report Form
CS	Contrast Sensitivity
CSR	Clinical Study Report
DCNVA	Distance Corrected Near Visual Acuity
ETDRS	Early Treatment Diabetic Retinopathy Study
°F	Degree Fahrenheit
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloric Acid
HR	Heart Rate
IB	Investigators' Brochure
ICF	Informed Consent Form

ICH	International Council for Harmonisation
IND	Investigational New Drug application
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-To-Treat
LASIK	Laser-Assisted in situ Keratomileusis
LDPE	Low Density Polyethylene
LSM	Least Squares Mean
logMAR	logarithm of the Minimum Angle of Resolution
mmHg	millimeters of mercury
MedDRA	Medical Dictionary for Regulatory Activities
NaOH	Sodium hydroxide
Nyxol	Phentolamine Mesylate Ophthalmic Solution 1 % (Nyxol®)
OAG	Open Angle Glaucoma
OD	Right eye
OHT	Ocular Hypertension
OR	Odds Ratio
OS	Left eye
OTC	Over-The-Counter
OU	Both eyes
PAS	Peripheral Anterior Synechiae
pH	Measure of acidity/alkalinity
PM	Post Meridian
POAG	Primary Open Angle Glaucoma
PP	Per Protocol
PRK	Photorefractive Keratectomy
Rx	Prescription

QD	Once daily
SAE	Serious Adverse Event
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Safety Population
TEAE	Treatment Emergent Adverse Event
TM	Trabecular Meshwork
US	United States
USP	United States Pharmacopeia
VA	Visual Acuity

1. STUDY SUMMARY

Study Number	**OPI-NYXG-201**
Clinical Phase	Phase 2
Type of Study	14 Day Safety and Efficacy
Name of Investigational Product	Nyxol Eye Drops - 1% Phentolamine Mesylate ophthalmic solution (Nyxol)
Duration of Study	Up to 7-8 weeks, including screening, washout, treatment and follow-up. Treatment period is 14 days.
Rationale	Phentolamine mesylate, the active drug in Nyxol, is a non-selective alpha-1 & alpha-2-adrenergic antagonist acting on the adrenergic nervous system and inhibits contraction of the smooth muscle. Some alpha-1-adrenergic antagonists have been shown to lower intraocular pressure (IOP) via the uveoscleral pathway and aqueous humor production. The major conventional outflow pathway includes the trabecular meshwork (TM), which has smooth-muscle-like properties and alpha-2-adrenergic receptors. Nyxol can potentially affect this pathway through smooth muscle relaxation of the TM, adding a complementary mechanism for IOP lowering. Previous Phase 2 clinical trials showed that Nyxol significantly reduces IOP in normotensive subjects after a single treatment.
Study Objectives	The objectives of this study are: • To evaluate the efficacy of Nyxol to lower IOP in Open Angle Glaucoma (OAG) and Ocular Hypertension (OHT). • To evaluate the ocular and systemic safety of Nyxol compared to its vehicle. • To evaluate additional efficacy of Nyxol to improve visual performance.
Design	Placebo-controlled, double-masked, multiple dose, Phase 2 study in approximately 40 randomized subjects with elevated IOP, evaluating safety and efficacy following administration of Nyxol QD at 8PM to 10PM in both eyes for 14 days.

Patient Population	40 subjects experiencing OAG or OHT.
Inclusion Criteria	Subjects may qualify in either eye. The eye with the higher IOP at the Qualification Visit at 8AM is designated as the study eye for the primary endpoint efficacy analysis. In the case where both eyes have the same IOP, the study eye will be the RIGHT eye. See Section 9 for more information on statistical analysis. ALL TREATMENTS WILL BE ADMINISTERED TO BOTH EYES (OU). 1. 18 years of age or greater. 2. Diagnosis of OAG or OHT. The diagnosis of OHT must be in BOTH eyes. For OAG it can be in either eye and OHT in the fellow eye. A reported history of untreated OHT with IOP ≥22mmHg and ≤ 30mmHg is preferred. 3. Untreated or treated OAG/OHT with 2 or fewer ocular hypotensive medications. 4. Untreated (post-washout) mean IOP ≥ 22mmHg and ≤30mmHg in the study eye at the Qualification Visit (8AM). 5. Corrected visual acuity in each eye +1.0 logMAR or better by Early Treatment Diabetic Retinopathy Study (ETDRS) in each eye (equivalent to 20/200 or better) at the Screening Visit and Qualification Visit. 6. Otherwise healthy and well-controlled subjects. 7. Able and willing to give signed informed consent and follow study instructions. 8. Able to self-administer study medication or to have study medication administered by a caregiver throughout the study period.

Exclusion Criteria	**Ophthalmic:** 1. Closed or very narrow angles (Grade 0-1, Shaffer) or angles that the investigator judges as occludable and/or with evidence of peripheral anterior synechiae (PAS) ≥ 180 degrees by gonioscopy within 6 months prior to Screening Visit in either eye. 2. Glaucoma: pseudo-exfoliation or pigment dispersion component, history of angle closure or narrow angles. Note: Previous laser peripheral iridotomy is NOT allowed. 3. Known hypersensitivity to any α-adrenoceptor antagonists. 4. Previous laser and/or non-laser glaucoma surgery or procedure in either eye. 5. Refractive surgery in either eye (i.e. radial keratotomy, PRK, LASIK, corneal cross linking). 6. Ocular trauma in either eye within the 6 months prior to Screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to Screening. 7. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at Screening in either eye. 8. Ocular medication in either eye of any kind within 30 days of Screening, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which can be used prior to Screening but cannot be used after Screening) or c) lubricating drops for dry eye (preservative-free artificial tears), which can be used throughout the study. 9. Clinically significant ocular disease in either eye as deemed by the investigator (i.e., corneal edema, uveitis, severe keratoconjunctivitis sicca) that might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month is not judged safe (i.e., cup-to-disc ratio > 0.8, severe visual field defect). 10. History of diabetic retinopathy.

11. Contact lens wear within 3 days prior to and for the duration of the study.

12. Central corneal thickness in either eye >600 µm at Screening.

13. Any abnormality in either eye preventing reliable applanation tonometry (e.g. central corneal scarring).

Systemic:

1. Known hypersensitivity or contraindication to α- and/or β-adrenoceptor antagonists (i.e. chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third degree heart block or CHF; severe diabetes).

2. Clinically significant systemic disease (i.e., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine or cardiovascular disorders) that might interfere with the study.

3. Participation in any investigational study within 30 days prior to Screening.

4. Use of any topical or systemic adrenergic or cholinergic drugs up to 30 days prior to Screening, or during the study unless the drug, dose and regimen has been consistent for the 30 days prior to Screening.

5. Changes in systemic medication that could have an effect on IOP within 30 days prior to Screening or anticipated during the study.

6. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the Screening and Qualification examinations and must intend to not become pregnant during the study.

7. Resting heart rate (HR) outside the normal range (50-110 beats per minute) at the Screening or Qualification Visit. HR may be repeated **once only** if outside the normal range

	following at least a 5 minute rest period in the sitting position. 8. Hypertension with resting diastolic blood pressure (BP) > 105 mmHg or systolic BP > 160 mmHg at the Screening or Qualification Visit. BP may be repeated **only once** if outside the specified range following at least a 5 minute rest period in the sitting position.

Screening/Washout Visits	Subjects with an ophthalmic history of increased IOP (≥ 22mmHg and ≤30 mmHg) will be selected for study participation and be screened for study eligibility. After Screening, eligible subjects, if currently being treated with glaucoma medications, will be required to washout and refrain from administration of any glaucoma drugs for at least 28 days and no more than 35 days prior to the Qualification Visit. The washout subjects will be brought back at approximately two weeks after starting the washout period for an IOP safety check. In the judgement of the investigator, if there is any risk to the eye(s) of the subject, or if the mean IOP in either eye during washout is >30mmHg, then an appropriate rescue or prior medication will be administered, and the subject will be considered a screen failure. Adverse events occurring during the washout period will also be assessed at this visit. Subjects not previously treated with any glaucoma drugs will not require a washout period and may return the following day or up to 35 days later for their Qualification/Baseline Visit.
Qualification/Baseline Visit	After the washout, where applicable, a Qualification Visit will occur before dosing on Day 1. At the Qualification Visit, IOP eligibility will be determined with [redacted] at 8AM, 10AM, and 4PM (mean IOP at 8AM must be ≥ 22mmHg and ≤ 30mmHg, and ≥ 19 mmHg at 10AM and 4PM). IOP will be measured twice in both eyes at each timepoint and the mean value will be used in eligibility assessments. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. The eye with the higher IOP at the Qualification Visit at 8AM is designated as the study eye for the primary endpoint efficacy analysis. In the case where both eyes have the same IOP, the study eye will be the RIGHT eye. ALL TREATMENTS WILL BE ADMINISTERED TO BOTH EYES (OU). If the subject meets all eligibility criteria, then the Qualification Visit is the Baseline Visit. The subject will then be randomized into the study. The first dose of study medication will be taken at 8PM to 10PM on the Baseline Visit (Day 1).
Treatment-study Visits	Treatment-study visits will occur twice - on Day 8 ± 1 Day and Day 15 ± 1 Day. IOP evaluations will be performed at 8AM,

	10AM and 4PM on each of these days. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. Other assessments performed at these visits will include but are not limited to visual acuity, pupil diameter and safety measures.
Follow-up Visits	A Follow-up Visit will occur at 8AM ± 15 minutes on Day 16. Assessments performed at this visit include an IOP measurement at 8AM ± 15 minutes, visual acuity, pupil diameter, and safety measures. A Follow-up Visit phone call will occur on Day 22, seven days after the last dose. Concomitant medications, subject reported conjunctiva redness and adverse events (AEs) will be collected.
Number of Investigational Sites	Approximately 5 sites.
Estimated Total Sample Size	Approximately 40 randomized subjects, with approximately 36 completed subjects.
Sample Size Justification	A sample size of 36 completed subjects is needed for the study. Thirty-six completed subjects, who were originally randomized in a 1:1 ratio to the Nyxol 1% and the placebo groups, [redacted] between the Nyxol 1% and placebo groups in the change from Baseline to Day 15 in mean diurnal IOP (average of measurements at 8AM, 10AM, and 4PM). This calculation is based on a 2-sided t-test at the 5% level of significance ($\alpha = 0.05$) and a common standard deviation of 3.0. Additionally, it is assumed that there will be approximately 10% drop-out between Baseline/Day 1 and Day 15. To account for this drop-out, a total of 40 subjects will be randomized into the study.
Primary Efficacy Endpoint	The primary efficacy endpoint is the change from Baseline to Day 15 in mean diurnal IOP in the study eye. Mean diurnal IOP is the mean of the IOP measurements at all three timepoints (8AM, 10AM, 4PM).

Secondary Efficacy Endpoints	Secondary efficacy endpoints will be analyzed by study eye, fellow eye and all eyes (unless otherwise indicated) and will include: • Change from Baseline to Day 15 in mean diurnal IOP in the fellow eye and all eyes. • Change from Baseline to Day 8 in mean diurnal IOP. • Mean IOP at each post-treatment timepoint (8AM, 10AM and 4PM; on Day 8 and Day 15). • Change and percent change from Baseline to Day 8 and Day 15 in IOP at each timepoint (8AM, 10AM, 4PM), and Day 16 at 8AM. • Percentage of subjects achieving reductions from Baseline to Day 8 and Day 15 in IOP at 8AM of greater than or equal to 10%, 15%, 20%, 25% and 30%. • Percentage of subjects achieving Day 8, Day 15 and Day 16 IOP levels at 8AM of less than or equal to 16mmHg, 18mmHg, 20mmHg and 22mmHg. • Change and percent change from Baseline Day 8, Day 15, and Day 16 in IOP at 8AM. • Change and percent change to Days 8, 15, and 16 in pupil diameter at 8AM. • Percentage of subjects achieving reductions from Baseline to Day 8, Day 15 and Day 16 in pupil diameter at 8AM of greater than or equal to 10%, 15%, 20%, 25%, and 30%. • Change and percent change from Baseline to Day 8, Day 15, and Day 16 in best corrected distance visual acuity (BCDVA) (ETDRS high contrast) (photopic and mesopic) at 8AM. • Change and percent change from Baseline to Day 8, Day 15, and Day 16 in distance corrected near visual acuity (DCNVA) (ETDRS high contrast) (photopic and mesopic) at 8AM. • Percentage of subjects achieving improvements from Baseline to Day 8, Day 15, and Day 16 in BCDVA and DCNVA (photopic and mesopic) of greater than or equal to 1 line, 2 lines and 3 lines. All Secondary Endpoints related to IOP will be analyzed additionally in those subpopulations with Baseline IOP of <25mmHg and ≥25mmHg.

	For each subject at each timepoint (8AM, 10AM, 4PM), the IOP value is the average IOP (from the 2 measurements taken at that timepoint) in the study eye or in the fellow eye. The lighting conditions will be kept same from visit to visit. Every effort should be made to have the same clinician perform the IOP measurements at all timepoints and at all visits.
Primary Safety Endpoints	The primary safety measures are objective biomicroscopic and ophthalmoscopic examination, subjective ocular tolerability, and AEs. Other safety measures are systemic safety as measured by heart rate and blood pressure. Urine pregnancy tests for females of childbearing potential will be conducted. Please see Table 1 for details on measurements expected at each visit.
Study Medications, Dose and Mode of Administration	Nyxol Eye Drops: One drop of Nyxol in each eye daily at 8PM to 10PM for 14 days from Day 1 through Day 14 for subjects randomized to active treatment. Placebo (Nyxol vehicle): One drop of placebo in each eye daily at 8PM to 10PM for 14 days from Day 1 through Day 14 for subjects randomized to placebo.
Duration of Subject Participation and Study	The total length of subject participation is approximately 7-8 weeks with six clinic visits and one telephone call follow up summarized below: • Screening Visit (1 day). • Washout Visit/period (as necessary) (4-5 weeks with safety check visit at 2 weeks). • Qualification/Baseline Visit (1 day). • Treatment-study Visit Day 8 (1 week). • Treatment-study Visit Day 15 (1 week). • Follow-up clinic Visit on Day 16 (1 day). • Follow-up telephone call at Day 22 (1 week). The execution of the entire study (first subject screen through last randomized subject completed) is expected to be approximately 6 months.

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2. INTRODUCTION

2.1. Investigational products

The test product is Nyxol Eye Drops - 1% phentolamine mesylate ophthalmic solution (Nyxol), an alpha-1-adrenergic antagonist. Placebo control is Nyxol vehicle alone.

2.2. Findings from nonclinical and clinical studies

Detailed findings from nonclinical and clinical studies and potential risk are provided in the Investigators' Brochure (IB) (January 2019).

Single Dose Phase 2:

In NYX-SNV, treatment of 16 subjects with severe night vision disturbances with a single dose of 1% Nyxol resulted in [redacted]

Statistically significant improvements in several measurements of visual function as well as wavefront aberrometry were also reported. Modest, transient increases were seen in conjunctival and bulbar hyperemia.

Multiple Dose Phase 2:

In NYX-01a2, (Ocularis IND 70-499) 60 otherwise healthy subjects with reduced mesopic contrast sensitivity (CS), divided into three groups of twenty subjects each, received placebo, 0.5% or 1.0% Nyxol for 15 days, followed by an optional two week period where the subjects could use up to six doses of 1.0% Nyxol as needed.

IOP was measured 2 hours after the first dose on Day 1, and then again on Day 32 that was at least three days after the last dose. The mean absolute IOP and mean IOP changes post treatment on Day 1 were statistically significant between the treatment arms and the placebo arm.

[redacted]

More than 100 subjects have received active doses of Nyxol ranging from 0.2% to 1.0% in Phase 1 and Phase 2 clinical trials. There have been no serious adverse events. All treated subjects developed some degree of conjunctival hyperemia, an average of one point increase on a four point CCLRU scale (none, mild, moderate, severe). Most subjects went from mild to moderate. Three went from mild to severe. All redness resolved within 8 hours.

The anticipated benefits of the proposed study are reduction in IOP and improvement in the signs and symptoms of open angle glaucoma and ocular hypertension. The risks determined in previous ophthalmic studies are local hyperemia and conjunctival injection.

Systemic risks, principally tachycardia and hypotension, are known from parenteral administration of doses of 5 mg phentolamine mesylate (Regitine, Bedford, Ohio; see Regitine

Prescribing Information in IB) and local injectable administration of OraVerse (Novalar, San Diego, California; see OraVerse Prescribing Information in IB).

Design justification

The two primary mechanisms to lower IOP include decreasing the amount of aqueous humor production in the eye and increasing the outflow of aqueous humor from the eye[3]. Phentolamine is a non-selective alpha-adrenergic antagonist acting on the adrenergic nervous system and inhibits contraction of the smooth muscle. For example, phentolamine mesylate inhibits contraction of the iris dilator muscle, resulting in a smaller pupil size.

Alpha-adrenergic antagonists, including phentolamine, have been previously shown to lower IOP via the aqueous humor production and uveoscleral pathway respectively. The major conventional outflow pathway though includes the trabecular meshwork (TM), a tissue with contractile properties and α-2-adrenergic receptors. It is well accepted that relaxing of the TM is the optimal IOP lowering solution. Thus, the non-selective α-antagonist Nyxol is likely to relax the TM and lower IOP via this major outflow pathway.

Treatment of glaucoma focuses on one of the major risk factors: intraocular pressure (IOP), the pressure of the aqueous humor in the anterior chamber of the eye. IOP is a balance between production (inflow) and outflow of aqueous humor into and out of the anterior chamber. Aqueous humor is produced by the ciliary body. Adrenergic agonists, such as epinephrine generally decrease production of aqueous humor[3]. Paradoxically, prazosin and phentolamine, both adrenergic antagonists, also decrease production of aqueous humor and lower IOP[4].

The conventional outflow pathway for the aqueous humor includes - but is not limited to - the trabecular meshwork. The TM has smooth-muscle–like properties and is actively involved in aqueous humor dynamics through contractile mechanisms. Smooth-muscle–relaxing substances are known to increase outflow rates and reduce IOP without affecting the ciliary muscle, circumventing side effects such as accommodative changes or miosis[5]. Prazosin, an alpha-1-antagonist, has been shown to enhance uveoscleral outflow in rabbits[6]. Nyxol can potentially reduce IOP by increasing aqueous humor outflow via this pathway as well.

Previous clinical studies of Nyxol conducted in normal healthy subjects or subjects with severe night vision complaints have shown that single doses and treatments for up to 30 days have resulted in statistically significant reductions in IOP in normotensive subjects, with no significant local or systemic adverse effects[2].

From a clinician's perspective, the currently available treatments for glaucoma have different limitations and risks that must be considered when tailoring the choice of treatment to an individual subject's needs and preferences. Some therapeutic classes have known systemic adverse effects, for example, beta-adrenergic antagonists (with cardiovascular and respiratory effects such as bradycardia, dyspnea, and wheezing)[7] and alpha-agonists (with central nervous system effects such as dry mouth, fatigue, sedation, and dizziness)[8]. Ocular side effects are common with topical agents and the acceptability of different side effects can vary by patient. With respect to efficacy, the Baltimore Eye Survey of 5308 subjects found that 78% of 10,444 eyes with primary OAG (POAG) had screening IOP of < 25 mmHg[9], indicating the importance of achieving efficacy at these lower IOP levels. A regimen that encourages compliance is also an important consideration. Clinicians and patients would benefit from having an additional therapeutic option for individualizing glaucoma treatment.

2.3. Route of administration, dosage regimen, and treatment period

As the intended route of administration for Nyxol is topical ocular, this is the route to be used in this study.

The dose selected for this study, 1%, was selected based upon preclinical safety studies and the results of the previous ophthalmic clinical studies described above.

The treatment period, 14 days, is selected on the basis of preclinical safety studies described in the IB in addition to optimal efficacy shown by other drugs[10].

2.4. Compliance

This study will be conducted in compliance with the protocol and in accordance with Good Clinical Practice, the ethical principles set forth in the Declaration of Helsinki and with the U.S. Code of Federal Regulations.

2.5. Study Population

A sample size of approximately 40 subjects at least 18 years of age and with OAG or OHT, will be randomized in a 1:1 ratio to the Nyxol 1% and placebo groups, with the expectation that approximately 36 subjects will complete the study.

3. OBJECTIVES AND PURPOSE

The objectives of this study are:

- To evaluate the efficacy of Nyxol to lower IOP in OAG and OHT.
- To evaluate the ocular and systemic safety of Nyxol compared to its vehicle.
- To evaluate additional efficacy of Nyxol to improve visual performance.

4. STUDY DESIGN

4.1. Primary and secondary endpoints

Efficacy:

The primary efficacy endpoint is the change from Baseline to Day 15 in mean diurnal IOP in the study eye. Mean diurnal IOP is the mean of the IOP measurements at all three timepoints (8AM, 10AM, 4PM).

ALL TREATMENTS WILL BE ADMINISTERED TO BOTH EYES AND IOP WILL BE MEASURED IN BOTH EYES.

The eye with the higher IOP at the Qualification Visit at 8AM is designated as the study eye. In the case where both eyes have the same IOP, the study eye will be the RIGHT eye. Baseline IOP evaluations will occur before dosing on Day 1. Treatment-study IOP evaluations will occur on Days 8 ± 1 Day and Day 15 ± 1 Day. Follow-up IOP evaluations will occur at 8AM ± 15 minutes on Day 16.

IOP measurements at the Baseline Visit and both Treatment-study Visits will be done at 8AM, 10AM and 4PM. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. IOP will be measured twice in both eyes at all time points. The mean IOP at each timepoint (8AM, 10AM, 4PM) is the average of the 2 IOP measurements at that timepoint. If the difference in the two IOP measurements is > 5 mmHg, a third measurement will be obtained, and the three values averaged.

Secondary efficacy endpoints will be analyzed by study eye, fellow eye and all eyes (unless otherwise indicated) and will include:

- Change from Baseline to Day 15 in mean diurnal IOP in the fellow eye and all eyes.
- Change from Baseline to Day 8 in mean diurnal IOP.
- Mean IOP at each post-treatment timepoint (8AM, 10AM and 4PM; on Day 8 and Day 15).
- Change and percent change from Baseline to Day 8 and Day 15 in IOP at each timepoint (8AM, 10AM, 4PM), and Day 16 at 8AM.
- Percentage of subjects achieving reductions from Baseline to Day 8 and Day 15 in IOP at 8AM of greater than or equal to 10%, 15%, 20%, 25% and 30%.
- Percentage of subjects achieving Day 8, Day 15 and Day 16 IOP levels at 8AM of less than or equal to 16mmHg, 18mmHg, 20mmHg and 22mmHg.
- Change and percent change from Baseline Day 8, Day 15, and Day 16 in IOP at 8AM.
- Change and percent change to Days 8, 15, and 16 in pupil diameter at 8AM.
- Percentage of subjects achieving reductions from Baseline to Day 8, Day 15 and Day 16 in pupil diameter at 8AM, of greater than or equal to 10%, 15%, 20%, 25%, and 30%.
- Change and percent change from Baseline to Day 8, Day 15, and Day 16 in best corrected distance visual acuity (BCDVA) (ETDRS high contrast) (photopic and mesopic) at 8AM.

- Change and percent change from Baseline to Day 8, Day 15, and Day 16 in distance corrected near visual acuity (DCNVA) (ETDRS high contrast) (photopic and mesopic) at 8AM.
- Percentage of subjects achieving improvements from Baseline to Day 8, Day 15, and Day 16 in BCDVA and DCNVA (photopic and mesopic) of greater than or equal to 1 line, 2 lines and 3 lines.

All Secondary Endpoints related to IOP will be analyzed additionally in those subpopulations with Baseline IOP of <25mmHg and ≥25mmHg.

The lighting conditions will be kept the same from visit to visit. Every effort should be made to have the same clinician perform the IOP measurements at all timepoints and at all visits.

Safety:

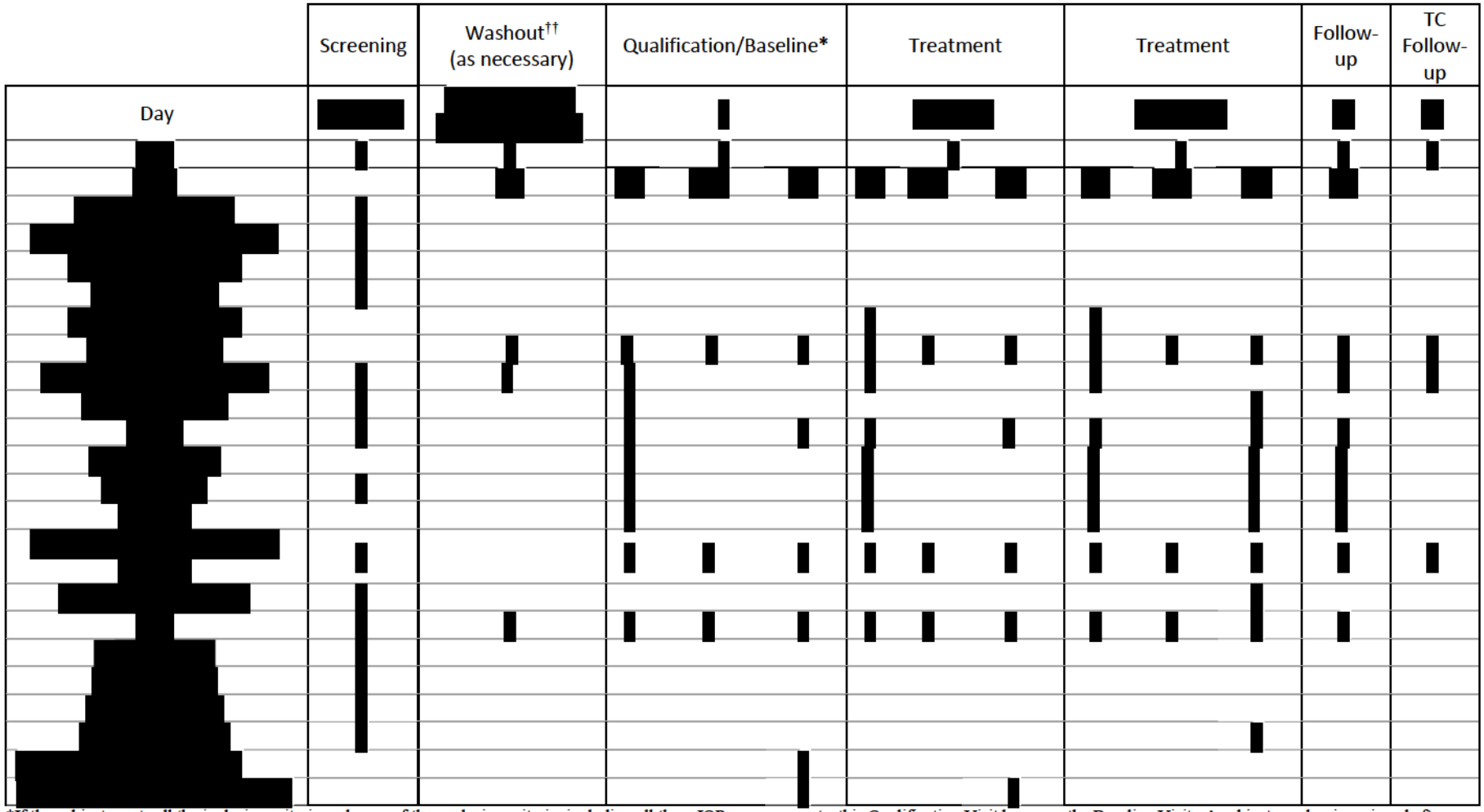
The primary safety measures are objective biomicroscopic and ophthalmoscopic examination, subjective ocular tolerability, and adverse events (AEs). Other safety measures are systemic safety as measured by heart rate and blood pressure. Urine pregnancy tests for females of childbearing potential will be conducted.

4.2. Description and schedule of visits and procedures

Approximately 40 subjects with either OAG or OHT will be randomized, for a target of 36 completed subjects. Subjects will be randomized in a 1:1 ratio to receive 1 % Nyxol or placebo once daily for 14 days beginning at 8PM to 10PM on Day 1 and continuing through Day 14. Efficacy evaluations (IOP) will take place at the Baseline and the Treatment-study Visit days (Day 8 ± 1 Day and Day 15 ± 1 Day) at 8AM, 10AM, and 4PM. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. There will be Follow-up Visits on Day 16 at 8AM ± 15 minutes and by phone on Day 22 (7 days after the last Treatment-study Visit).

Study procedures are shown in detail in Table 1:

Table 1: Screening, Washout, Qualification, Treatment-study, and Follow-Ups Visits and Procedures



*If the subject meets all the inclusion criteria and none of the exclusion criteria, including all three IOP measurements, this Qualification Visit becomes the Baseline Visit. A subject number is assigned after the subject is qualified.
**New test (VF 24-2 or 30-2 are acceptable) is required to evaluate screening criteria if the information is not available from a previous test within the last six months.
***Contact or Non-Contact Pachymetry can be performed providing the same type of pachymeter is used throughout the study for all subjects at an individual site.
†IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments.
††Subjects not previously treated with any glaucoma drugs will not require a washout period and may return the following day or up to 35 days later for their Qualification/Baseline Visit.

4.3. Measures taken to minimize/avoid bias

This is a double masked, placebo controlled study with 1:1 randomization.

4.4. Study medications

Nyxol (1%) is a sterile, non-preserved, isotonic, buffered aqueous solution containing phentolamine mesylate (1.0%), mannitol and sodium acetate. Placebo is Nyxol vehicle, consisting of non-preserved, isotonic, buffered aqueous solution containing mannitol and sodium acetate. The study medications may be adjusted with NaOH (USP) or HCl (USP) to pH 4.8. The product is packaged in a one ml LDPE dropper bottle containing 0.6 ml for single dose use.

4.4.1. Packaging and labeling

Nyxol (1%) and vehicle will be supplied as a clear, colorless to slightly brown, non-preserved aqueous solutions in one ml dropper bottles containing 0.6 ml. Each bottle will be labeled with investigational labels with the study number, subject initials and other relevant information, including a statement "Caution – New Drug – Limited by Federal (US) Law to Investigational Use".

4.4.2. Storage of study medication

Prior to dispensing to the subject, all investigational material must be stored in a secure location with strictly limited access documented by signature of authorized persons who may dispense investigational materials. The products should be stored refrigerated (2°C to 8°C, 36°F to 46°F) until the day before use or until provided to the subject. Study medication must not be frozen and must be protected from light. The subject should be instructed that the product may be kept at room temperature once dispensed (up to 25°C, 77°F).

4.4.3. Study medication accountability

4.4.3.1. Receipt and disposition of study medication

The Investigator or designee (e.g., study coordinator or pharmacist) will maintain a full accountability record for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study drug using the inventories supplied by the Sponsor. Each subject will receive sufficient study medication for the duration of the trial. A Study Medication Box will be dispensed at Baseline Visit (Day 1). As described in Section 7.2.3, the subject will empty any remaining contents from the unit-dose dropper bottle following each instillation and will return in baggies in the original boxes ALL opened bottles as well as any unopened study medication at Treatment-study Visits (Day 8 ± 1 Day and Day 15 ± 1 Day). At the Day 8 Visit, the box will be re-dispensed to the subject following study drug accountability and removal of opened study medication materials. Study medication accountability will again be conducted at the Day 15 Visit, but the box will not be re-dispensed. The Investigator or designee will account for all received and returned study medication. The monitor will review dispensing and study medication accountability records during site visits and at the completion of the study and note any discrepancies. All investigational study medication must be stored in a secure facility, with access limited to the Investigator and authorized staff.

4.4.3.2. Return of study medication

When the study is completed or is terminated by Ocuphire, all study material including used and unused study medication bottles will be returned to Ocuphire (or its designee) or destroyed under the direction of same. All study medication accounting procedures must be completed before the study is considered completed. A final study medication disposition will be completed by the study coordinator.

4.5. Expected duration of subject participation

The total length of subject participation is approximately 7-8 weeks with six clinic visits and one telephone call summarized below:

- Screening Visit (1 day).
- Washout Visit/period (as necessary) (4-5 weeks with safety check visit at 2 weeks).
- Qualification/Baseline Visit (1 day).
- Treatment-study Visit Day 8 (1 week).
- Treatment-study Visit Day 15 (1 week).
- Follow-up clinic Visit on Day 16 (1 day).
- Follow-up telephone call on Day 22 (1 week).

The execution of the entire study (first subject screen through last randomized subject completed) is expected to be approximately 6 months.

4.6. Randomization and procedure for breaking the code

A randomization code for allocating the study treatments will be prepared by a masked biostatistician not connected with the study.

At the initiation of study related procedures, every potential subject is assigned a ***Screening number*** in numerical order. Once a subject is qualified for the study (Qualification/Baseline Visit) the subject is assigned a ***randomization number*** in the order provided by the biostatistician.

The study medications will be masked to both Investigator and study subjects, as well as Ocuphire. Treatment assignments will be masked to the Investigator, Ocuphire, and the subjects. Only in case of medical emergency or occurrence of serious adverse events (SAE) will the randomization code be unmasked by the study pharmacist and made available to the Investigator, Ocuphire, and/or other personnel involved in the monitoring or conduct of this study.

4.7. Collection of data

The source documentation for all data collected in the study will maintained by the investigator in the subject files at the study site. All original data collected during this trial is to be recorded on paper case report forms (CRFs) and then electronically entered into the database following study completion. The paper CRF is considered to be the source documentation for this study.

4.8. Completed subject

A completed subject is defined as one who completes all planned dosing and procedures through Day 22.

4.9. Non-completing subject

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator and/or the Medical Monitor prior to completing all of the study procedures required in this protocol. Any subject may decide to voluntarily withdraw from the study at any time without prejudice.

4.9.1. Study medication discontinuation

The study medication may be discontinued for the following reasons:

- **Adverse Events:** Adverse events including clinically significant laboratory abnormalities and intercurrent diseases reported by the subject or observed by the investigator with documentation on the case report form (CRF).
- **Death:** If a subject dies, the adverse event that caused the death should be documented on the CRF and be noted as serious and fatal.
- **Disallowed concurrent medication:** Any medication not allowed by the protocol would be a protocol violation.
- **Lack of efficacy:** A subject may elect to discontinue participation in the study for a perceived lack of efficacy.
- **Investigator decision:** A subject may be discontinued for reasons other than those bulleted previously if the investigator thinks it is not in the best interest of the subject to continue.
- **Other:** If there is any other reason for subject discontinuation this should be noted on the CRF.

The reason for premature study medication discontinuation should be entered onto the appropriate CRF. In the event that discontinuation of study medication occurs after a completed single dose, the Investigator will make every attempt to complete all subsequent safety assessments at Day 15 and Day 22.

4.9.2. Reasons for Withdrawal from Study

- Subject withdraws consent.
- Subject is non-compliant, e.g. missed three or more daily use of medication.
- Subject is lost to follow-up.
- Subject withdraws for other reason.

4.9.3. Entire study terminated

The entire study may be terminated by Investigators or the Sponsor. Prompt, written notice of reasonable cause to the other party (Sponsor or Investigators, respectively) is required. Prompt notice to the IRB and to regulatory authorities is also required.

4.9.4. Actions after discontinuation

All subjects who discontinue study medication due to a report of an AE **must** be followed-up and provided appropriate medical care until their signs and symptoms have remitted or stabilized or until abnormal laboratory findings have returned to acceptable or pre-study limits.

For any subject who chooses to withdraw consent or who is non-compliant, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for the Follow-up Visit.

4.10. Completed study

The study is completed when all randomized subjects have completed the study, all CRFs have been completed, and all CRF data entered into the database. Final DB lock will occur after the last randomized subject completes, all data has been entered and all queries resolved.

4.11. Procedure after the completion of the study

When the study is completed, Oculos will provide Ocuphire and the IRB with a brief (i.e., one to three pages) report, containing a description of the study, the number of subjects enrolled, the number of subjects completed the number of subjects who dropped out and why, efficacy findings and adverse events.

5. SUBJECT INCLUSION AND EXCLUSION CRITERIA

Subjects may qualify in either eye. The eye with the higher IOP at the Qualification/Baseline Visit at 8AM is designated as the study eye. In the case where both eyes have the same IOP, the study eye will be the RIGHT eye. See Section 9 for more information on statistical analysis. ALL TREATMENTS WILL BE ADMINISTERED TO BOTH EYES (OU).

5.1. Subject inclusion criteria

1. 18 years of age or greater.
2. Diagnosis of OAG or OHT. The diagnosis of OHT must be in BOTH eyes. For OAG it can be in either eye and OHT in the fellow eye. A reported history of untreated OHT with IOP $\geq$ 22mmHg and $\leq$ 30mmHg is preferred.
3. Untreated or treated OAG/OHT with 2 or fewer ocular hypotensive medications.
4. Untreated (post-washout) mean IOP $\geq$ 22mmHg and $\leq$ 30mmHg in the study eye at the Qualification Visit (8AM).
5. Corrected visual acuity in each eye +1.0 logMAR or better by Early Treatment Diabetic Retinopathy Study (ETDRS) in each eye (equivalent to 20/200 or better).
6. Otherwise healthy and well controlled subjects.
7. Able and willing to give signed informed consent and follow study instructions.
8. Able to self-administer study medication or to have study medication administered by a caregiver throughout the study period.

5.2 Subject exclusion criteria

Excluded from the study will be individuals with the following characteristics in either eye:

Ophthalmic:

1. Closed or very narrow angles (Grade 0-1, Shaffer[1]) or angles that the investigator judges as occludable and/or with evidence of peripheral anterior synechiae (PAS) $\geq$ 180 degrees by gonioscopy within 6 months prior to Screening Visit in either eye.
2. Glaucoma: pseudo-exfoliation or pigment dispersion component, history of angle closure, or narrow angles. Note: Previous laser peripheral iridotomy is NOT allowed.
3. Known hypersensitivity to any α-adrenoceptor antagonists.
4. Previous laser and/or non-laser glaucoma surgery or procedure in either eye.
5. Refractive surgery in either eye (i.e. radial keratotomy, PRK, LASIK, corneal cross linking).
6. Ocular trauma in either eye within the 6 months prior to Screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to Screening.
7. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at Screening in either eye.

8. Ocular medication in either eye of any kind within 30 days of Screening, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which can be used prior to Screening but cannot be used after Screening) or c) lubricating drops for dry eye (preservative-free artificial tears), which may be used throughout the study.
9. Clinically significant ocular disease in either eye as deemed by the investigator (i.e., corneal edema, uveitis, severe keratoconjunctivitis sicca) that might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month is not judged safe (i.e., cup-to-disc ratio > 0.8, severe visual field defect).
10. History of diabetic retinopathy.
11. Contact lens wear within 3 days prior to and for the duration of the study.
12. Central corneal thickness in either >600 µm at Screening.
13. Any abnormality in either eye preventing reliable applanation tonometry (e.g. central corneal scarring).

Systemic:

1. Known hypersensitivity or contraindication to α- and/or β-adrenoceptor antagonists (i.e. chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third degree heart block or CHF; severe diabetes).
2. Clinically significant systemic disease (i.e., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine or cardiovascular disorders) that might interfere with the study.
3. Participation in any investigational study within 30 days prior to Screening.
4. Use of any topical or systemic adrenergic or cholinergic drugs up to 30 days prior to Screening, or during the study unless the drug, dose and regimen has been consistent for the 30 days prior to Screening.
5. Changes in systemic medication that could have an effect on IOP within 30 days prior to Screening or anticipated during the study.
6. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the Screening examination and must intend to not become pregnant during the study.
7. Resting heart rate (HR) outside the normal range (50-110 beats per minute at the Screening or Qualification Visit. HR may be repeated **once only** if outside the specified range following at least a 5 minute rest period in the sitting position.
8. Hypertension with resting diastolic blood pressure (BP) > 105 mmHg or systolic BP > 160 mmHg at the Screening or Qualification Visit. BP may be repeated **once only**

if outside the specified range following at least a 5 minute rest period in the sitting position.

6. TREATMENT OF SUBJECTS

Approximately 40 subjects with either OAG or OHT will be enrolled, with a target completion of 36 subjects. Patents will be randomized in a 1:1 ratio to receive 1 % Nyxol or placebo once daily for 14 days beginning at 8PM to 10PM on Day 1 (Baseline Visit) and continuing through Day 14. IOP evaluations will take place at 8AM, 10AM, and 4PM on Day 8 ± 1 Day and on Day 15 ± 1 Day, and at 8AM on Day 16. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. There will be a Follow-up phone telephone call 7 days after the last Treatment-study Visit (Day 22).

6.1. Treatment adherence

All subjects will be instructed on the importance of following the once-a-day dosing regimen. Beginning the day of the Baseline Visit (Day 1) subjects will instill one drop of study medication in each eye at 8PM to 10PM and repeat this procedure 13 times for a total of 14 doses. Subjects are to bring unused bottles into the study site on the Day 8 Visit and the Day 15 Visit. Treatment adherence will be measured by counting the dropper bottles at the start of the study, and those remaining at each study visit.

6.2. Concomitant medications

As noted in the exclusion criteria (Section 5.2), the following are prohibited:

- Use of ocular medication within 30 days of the Screening Visit, or anticipated use during the study, with the exception of lubricating drops for dry eye (preservative-free artificial tears), which may be used throughout the study.
- Use of any topical or systemic adrenergic or cholinergic drugs up to 30 days prior to Screening, or during the study unless the drug, dose and regimen has been consistent for the 30 days prior to Screening (Appendix 1). A large number of drugs, both prescription and over-the-counter, contain active ingredients that can affect intraocular pressure. This would include many eye drops, such as Visine, that would be used to reduce redness, most cough or cold preparations, antihistamines and bronchodilators, most nose-drops, most blood-pressure medications, many drugs used for migraines, and many other products. ***If there is any question about whether a medication is acceptable, Ocuphire or the Medical Monitor should be consulted before proceeding.***
- Changes in systemic medication that could have an effect on ocular autonomic tone 30 days prior to Screening or anticipated during the study.

Intermittent use of over-the-counter (OTC) ***preservative-free*** artificial tear lubricant products is acceptable. However, no other ocular medications (OTC or prescription) are allowed within 30 days of the Screening Visit, or during the study.

Topical or systemic therapy with agents that could have an effect on IOP is to be consistent in dose, regimen and agent within the 30 days prior to Screening and throughout the study. For example, a subject can be treated with a systemic adrenoceptor antagonist as long as the particular agent and its dose and regimen had been consistent for the thirty 30 days prior to Screening, and there was no reason to believe that alteration would be necessary at some point later during the study.

Use of all medications should be documented on the appropriate CRF. Investigators are encouraged to contact Ocuphire or the Medical Monitor for any questions regarding

allowed medications. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by Ocuphire.

All medications which the subject has taken within 30 days prior to the Screening Visit and during the study will be recorded in the CRF. The name of the drug, dose, route of administration, duration of treatment and indication will be recorded for each medication. For combination products (e.g., Contac®), the brand name is required. For non-combination products, the generic name is desired. The use of routine ophthalmic diagnostic pharmaceutical agents (e.g., fluorescein and local anesthetic) will be allowed, and individual documentation not required. Any change in dosing parameters should also be recorded in the CRF.

7. ASSESSMENT OF EFFICACY

7.1. Specification of the efficacy parameters

The primary efficacy endpoint is the change from Baseline to Day 15 in mean diurnal IOP. Mean diurnal IOP is the mean of the IOP measurements at all three timepoints (8AM, 10AM, 4PM).

IOP is measured with the Goldmann Applanation Tonometer, using a two-person method (one-person physically applies the tonometer, while another reads the result)[11].

The eye with the higher IOP at the Qualification Visit at 8AM is designated as the study eye. In the case where both eyes have the same IOP, the study eye will be the RIGHT eye. Baseline evaluations will occur before dosing on Day 1; Treatment-study evaluations will occur on Day 8 ± 1 Day and Day 15 ± 1 Day; follow-up evaluations will occur at 8AM on Day 16.

IOP measurements at the Baseline Visit and both Treatment-study Visits will be performed at 8AM, 10AM and 4PM. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. IOP will be measured twice in both eyes at each timepoint. The mean value at each timepoint for the study eye will be used in efficacy assessments. If the difference in the two IOP measurements is > 5mmHg, a third measurement will be obtained, and the three values averaged.

7.2. Assessing, recording, and analyzing of efficacy parameters

IOP, visual acuity, and ophthalmological examinations will be measured at the Screening Visit, the Qualification/Baseline Visit, the Treatment-study visits, and Follow-up Visit.

Efficacy Endpoint	Equipment Name	Measurement (Unit)	Procedure
IOP	[redacted]	mmHg	[redacted]

Distance VA		Letters	
Near VA		Jaeger	
Pupil diameter		mm	

For this study photopic and mesopic light conditions are considered to be "with the lights on or with the lights off". There are no specific light conditions required other than the same light conditions should be used throughout the study.

7.2.1.Screening

Individuals who are potential subjects will be contacted by the study center to schedule the Screening visit. This visit may occur anytime but at least 28 days and no more than 35 days before dosing.

Once subjects arrive at the study center, a member of the study center staff will interview the individual as to their qualifications for participation in the study, and if the subject wishes to continue, a Screening number is assigned, and the Informed Consent form is signed. Screening includes an explanation of the study, a medical and ophthalmic history, visual acuity exam, heart rate and blood pressure, and a review of concomitant medications. The second step in screening includes procedures such as a urine pregnancy test and a complete ophthalmic examination, including IOP, biomicroscopy, gonioscopy, pachymetry, and visual field (if one has not been done within the last 6 months).

Contact or non-contact pachymetry can be performed providing the same type of pachymeter is used throughout the study for all subjects at an individual site.

Visual field tests of 24-2 or 30-2 are acceptable.

7.2.2. Washout Period

After Screening, study participants will be required to refrain from administration of any glaucoma drugs for at least 28 days and no more than 35 days prior to the Qualification/Baseline Visit. The washout subjects will be brought back in approximately two weeks after the Screening Visit for an IOP safety check. In the judgement of the investigator, if there is any risk to the eye(s) of the subject, or if the mean IOP in either eye is >30mmHg, then an appropriate rescue or prior medication will be administered, and the subject will be considered a screen failure. Adverse events occurring during the washout period and a review of concomitant medications will also be assessed at this visit.

Unmedicated subjects who meet the inclusion/exclusion criteria after screening do not have a washout period. These subjects may return the following day or up to 35 days later for their Qualification/Baseline Visit.

7.2.3. Qualification Visit/Baseline (Day 1)

At the Qualification/Baseline Visit, the subject will be asked how do his/her eyes feel, and if there have been any changes in their medical condition, or concomitant medications since their last visit. Any adverse changes in the condition of the subject at this visit are recorded in the Medical/Ophthalmic History CRF.

At the Qualification/Baseline Visit:

- Females of childbearing potential will take a urine pregnancy test at 8AM.
- Review of concomitant medications at 8AM.
- IOP measurements using a [redacted] at the Baseline visit and both Treatment-study visits will be done at 8AM, 10AM and 4PM. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. IOP will be measured twice in both eyes at each timepoint. The mean value at each timepoint for the study eye will be used in efficacy assessments. If the difference in the two IOP measurements is >5 mmHg, a third measurement will be obtained, and the three values averaged.
- Pupil diameter, using a [redacted], near visual acuity using a standard chart held at 14 inches and distance visual acuity with ETDRS are measured at 8AM.
- Resting HR and BP are measured at 8AM and 4PM. Blood pressure, using the same arm, same cuff size appropriate for arm circumference throughout the study, and heart rate should be measured after at least 3 minutes rest in the sitting position. If HR or BP are outside the normal range (see Exclusion Criteria – Systemic #7 and #8), they may be repeated only once following at least a 5 minute rest period in the sitting position.
- Eye redness (conjunctival hyperemia) visually checked at 8AM, 10AM and 4PM using [redacted]
- Adverse events will be reviewed at each timepoint.

To continue in the study, the subject must have a mean IOP ≥ 22 mmHg at 8AM and ≥ 19 mmHg at 10AM and 4PM in the study eye **after the washout period** (if required) at the Qualification Visit (8AM).

Subjects may qualify in either eye. The eye with the higher IOP at the Qualification Visit at 8AM is designated as the study eye for the efficacy endpoints. In the case where both eyes have the same IOP, the study eye will be the RIGHT eye. See Section 9 for more information on statistical analysis. ALL TREATMENTS WILL BE ADMINISTERED TO BOTH EYES (O.U.).

If the subject meets all of the inclusion criteria and none of the exclusion criteria, including all three timepoint IOP measurements, this qualification visit becomes the Baseline Visit, a subject number is assigned, and he/she is randomized into the study.

Site personnel will demonstrate the proper instillation technique to the subject at the Qualification/Baseline Visit (Day 1) and the subject will self-administer a dose of artificial tears at the study site, instilling 1 drop in each eye from the unit-dose bottle (Note: if a drop is not instilled into the eye, the subject should wait approximately 10-15 seconds and administer a second drop). The subject should be in a seated position and should tilt his or her head backward for administration of the study medication. The bottle of study medication should be held at an almost vertical position above the eye while the lower eyelid is pulled down gently, and 1 drop is placed into the conjunctival cul-de-sac. The tip of the bottle should not touch the eye. After a drop is instilled in each eye, the subject should keep the eyes gently closed for approximately 30 seconds. After successful instillation of the drop in each eye, the subject should carefully empty any remaining contents as directed.

The subject is given their study medication dropper bottles, and with instructions when to administer the eye drop (8PM to10PM), and when to return to the clinic.

Each subsequent evening of dosing, the subject will administer one drop to each eye from a single new unit-dose bottle and close the eyes gently for 30 seconds, then empty the remaining contents and store the opened bottle in the baggie provided and place it in the medication box for return to the study site at the Day 8 Visit. Each subsequent evening of dosing (approximately 24 hours between doses), the subject will follow the same procedures. At the Day 8 visit the medication box, complete with opened bottles and any unopened study medication will be returned to the study site where the baggies of opened medication will be removed, and the study medication box will be re-dispensed with the unopened medication. During the second week of treatment, subjects will continue to administer one drop of study medication to each eye every night using a new bottle for each dose, then emptying the remaining contents of that bottle and storing the opened bottles in the baggies and placing them back in the box to return to the study site at the Day 15 Visit. The Day 15 visit will be the last day of study treatment; no further study medication will be dispensed at this visit.

The subject should be instructed to contact the investigator should adverse events of concern occur (e.g., shortness of breath, fainting, etc.). If the event is life-threatening, then the subject should go to the emergency room.

7.2.4. Study Day 8 ± 1 Day

On Study Day 8, the subject should bring their used dropper bottles with any unused medications with them for purposes of drug accountability. At the end of the Study Day 8 Visit the study medication box will be re-dispensed with the unopened medication.

The subjects will be asked if they had any problems with their eyes from the last visit, and if there have been any changes in their medical condition, or concomitant medications since their last visit. ***Any changes in the condition of the subject are recorded as an adverse event.***

In addition, on Study Day 8:

- Review of concomitant medications at 8AM.
- IOP measurements will be done at 8AM, 10AM and 4PM. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. IOP will be measured twice in both eyes at each timepoint. The mean value at each timepoint for the study eye will be used in efficacy assessments. If the difference in the two IOP measurements is > 5mmHg, a third measurement will be obtained, and the three values averaged.
- Pupil diameter, near and distance visual acuity, resting heart rate and blood pressure are measured at 8AM. Blood pressure, using the same arm, same cuff size appropriate for arm circumference throughout the study, and heart rate should be measured after at least 3 minutes rest in the sitting position. If HR or BP are outside the normal range (see Exclusion Criteria – Systemic #7 and #8), they may be repeated only once following at least a 5 minute rest period in the sitting position.
- Eye redness (conjunctival hyperemia) visually checked at each timepoint using [redacted] scale.
- Adverse Events will be reviewed at each timepoint.

7.2.5. Study Day 15 ± 1 Day

On Study Day 15, the subject should bring their used dropper bottles and any unused medications with them for purposes of drug accountability.

The subjects will be asked if they had any problems with their eyes from the last visit, and if there have been any changes in their medical condition, or concomitant medications since their last visit. ***Any changes in the condition of the subject are recorded as an adverse event.***

In addition, on Study Day 15:

- Review of concomitant medications and a urine pregnancy test at 8AM.
- IOP measurements will be done at 8AM, 10AM and 4PM. All IOP measurements have a window of ± 15 minutes with at least 2 hours between the 8AM and 10AM assessments. IOP will be measured twice in both eyes at each timepoint. The mean value at each timepoint for the study eye will be used in efficacy assessments. If the difference in the two IOP measurements is >5 mmHg, a third measurement will be obtained, and the three values averaged.
- Pupil diameter, near and distance visual acuity, resting heart rate and blood pressure are measured at 8AM. Blood pressure, using the same arm, same cuff size appropriate for arm circumference throughout the study, and heart rate should be measured after at least 3 minutes rest in the sitting position. If HR or BP are outside the normal range (see

Exclusion Criteria – Systemic #7 and #8), they may be repeated only once following at least a 5 minute rest period in the sitting position.

- Eye redness (conjunctival hyperemia) visually checked at each timepoin [redacted]
- Adverse Events will be reviewed at each timepoint.
- Distance and near visual acuity, pupil diameter, and a complete ophthalmic examination, including biomicroscopy will also be performed at 4 PM.

Subjects completing their Day 15 Visit should be instructed **not** to resume their original glaucoma medication(s) until after completion of the Day 22 Follow-up phone call.

7.2.6. Follow-up Visit (Day 16)

The subjects will be asked if they had any problems with their eyes from the last visit, and if there have been any changes in their medical condition, or concomitant medications since their last visit. ***Any changes in the condition of the subject are recorded as an adverse event.***

In addition, on Study Day 16:

- Review of concomitant medications at 8AM.
- IOP is measured twice in the study eye at 8AM ± 15 minutes and the two values are averaged. If the difference in the two IOP measurements is >5 mm Hg, a third measurement is obtained, and the three values are averaged.
- Pupil diameter, near and distance visual acuity, resting heart rate and blood pressure are measured at 8AM. Blood pressure, using the same arm, same cuff size appropriate for arm circumference throughout the study, and heart rate should be measured after at least 3 minutes rest in the sitting position. If HR or BP are outside the normal range (see Exclusion Criteria – Systemic #7 and #8), they may be repeated only once following at least a 5 minute rest period in the sitting position.
- Eye redness (conjunctival hyperemia) visually checked at each timepoint using [redacted]
- Adverse Events will be reviewed at 8AM.

Subjects completing their Day 16 Visit should be reminded **not** to resume their original glaucoma medication(s) until after completion of the Day 22 Follow-up phone call.

7.2.7. Follow-up phone call (Day 22)

One week after their last dose, subjects will be called and asked if they had any problems with their eyes from the last visit including whether their eyes are red, and if there have been any changes in their medical condition, or concomitant medications since their last visit. ***Any changes in the condition of the subject are recorded as an adverse event.***

If an adverse event/reaction is unresolved at the time of the last visit or if a subject reports a worsening of symptoms, every effort should be made to follow up until the adverse event/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

All subjects should be advised to resume their glaucoma medications during this follow-up phone call.

7.2.8. Unscheduled Visits

An Unscheduled Visit may be any visit to the Investigator other than the specific visits requested in the protocol as possibly required for the subject's ophthalmic condition. The Investigator will perform all procedures necessary to evaluate the study participant at these visits and record any adverse events in the CRF.

As noted in Section 4.9, every possible effort should be made by investigators to assure that subjects who discontinue early from the study have a final visit that includes all examinations listed for the Follow-up Visit.

7.2.9. Visit variation

Visits on Day 8 and 15 may be 1 day early or late. If the visit is late, the subject should be advised to take an additional dose from one of the 2 spare dropper bottles provided in the study medication box the night before the visit. The subject should then empty the remaining contents and store the opened bottle in the baggie provided and place it in the medication box for return to the study site at their next visit. If the Day 15 Visit occurs one day early or late, the Day 16 Visit and the Day 22 telephone call should be adjusted accordingly.

8. ASSESSMENT OF SAFETY

8.1. Specification of safety parameters

The assessment of safety and tolerability is the secondary objective of this study. The assessment of safety will be evaluated by:

- Conjunctival hyperemia measured with a [redacted]
  [redacted]
- Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva and anterior chamber. Fluorescein staining to be used.
- Ophthalmoscopy. Dilated fundus exam including optic nerve, macula, vessels and periphery.
- Heart rate and blood pressure. Blood pressure should be measured using the same arm and same cuff size appropriate for arm circumference throughout the study. BP and heart rate should be measured after at least 3 minutes rest in the sitting position. If HR or BP are outside the normal range (see Exclusion Criteria – Systemic #7 and #8), they may be repeated only once following at least a 5 minute rest period in the sitting position.
- Adverse events.

8.2. Assessing, recording, and analyzing safety parameters

The timing for recording safety parameters may be found in Section 4.2, Table 1: Schedule of Visits and Procedures.

8.3. Adverse events

All AEs and SAEs that occur following consent and until the final study visit should be collected and recorded on the AE or SAE CRF page. Only treatment-emergent adverse events/adverse reactions will be summarized (see Section 9.3.5).

All treatment-emergent adverse events/adverse reactions occurring during the study (i.e. once the subject has received one dose of study medication) **must** be documented, regardless of the assumption of causal relationship, on the respective CRF. All treatment-emergent adverse events/adverse reactions must be documented from the time the subject receives the **first dose** of study medication until the subject's participation in the study has been completed. If a subject has ongoing adverse events/adverse reactions at the time of study completion, the ongoing adverse events/adverse reactions **must** be followed-up and provided appropriate medical care until the signs and symptoms have remitted or stabilized or until abnormal laboratory findings have returned to acceptable or pre-study limits.

Documentation of adverse events/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome.

8.3.1. Adverse event definitions

The following definitions of terms apply to this section:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered ''serious'' if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered ''unexpected'' if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Any medical condition present prior to administration of the masked study medication which remains unchanged or improved should NOT be recorded as an adverse event at subsequent visits.

As noted in Section 7.2.1, any change in their Baseline health status that is not considered to be an adverse event should be recorded on the Medical History page of the CRF (e.g., the subject has been diagnosed with cancer).

The study medication relationship for each adverse event/adverse reaction should be determined by the Investigator using these explanations:

- **Not Related:** The event is clearly related to other factors such as subject's clinical condition, therapeutic interventions, concomitant disease or therapy administered to the subject and does not follow a known response pattern to the product.
- **Possibly Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.
- **Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, **and** either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

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

- 1 = Mild: present, but not distressing, and no disruption of normal daily activity.
- 2 = Moderate: discomfort sufficient to reduce or affect normal daily activity.
- 3 = Severe: incapacitating, with inability to work or perform normal daily activity.

A change in severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe or from severe to moderate. In either case the start or stop dates should be recorded.

Action taken in response to an adverse event is coded as:

- 1=None.
- 2=Study medication interrupted.
- 3=Study medication discontinued.
- 4=Non-drug therapy.
- 5=New OTC or Rx drug added.
- 6=Hospitalized (< 24 hours).
- 7=Hospitalized (≥ 24 hours).

Outcome of an adverse event is coded as:

- 1=Recovered without sequelae.
- 2=Stable and ongoing.
- 3=Ongoing.
- 4=Death.
- 5=Unknown/ Lost to follow-up.

The term "severe" is used to describe the intensity (severity, see above) of an event/reaction; the event/reaction itself may be of relatively minor medical significance (such as severe headache). This is not the same as a "Serious" Adverse Event, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to the subject's life or vital functions. "Serious"ness (NOT severity) serves as a guide for defining regulatory reporting obligations.

In previous clinical studies of Nyxol the most frequently reported adverse event was conjunctival hyperemia. **In the present study, investigators are cautioned to use the appropriate verbatim term on the adverse event form to describe this observation:**

- **Redness related to instillation that is transient (i.e., is no longer present 2 hours after instillation) = "conjunctival erythema upon instillation".**
- **Redness that is NOT transient (i.e., is present 2 hours after instillation) = "conjunctival hyperemia".**

Investigators are also cautioned to appropriately note all observations of conjunctival hyperemia (also called conjunctival erythema) on the biomicroscopy CRF.

Expedited reporting of Serious and Unexpected Adverse Events: All treatment emergent SAEs (related and unrelated) will be recorded from the first administration of study medication, Baseline Visit (Day 1), until the final study visit, following the end of treatment exposure. Any SAEs "suspected" to be related to the investigational product and discovered by the Investigator at any time after the study should be reported.

Any SAE that occurs must be reported to Oculos within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to Oculos as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the site with a copy emailed to OG201 Safety@Oculoscr.com. The Investigator must assess the SAE relationship and complete the SAE form. Oculos may request additional information. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy will be emailed to OG201 Safety@Oculoscr.com. In addition, all SAEs should be recorded on the Adverse Event CRF page with the serious question marked "Yes".

It is the investigator's responsibility to notify the approving IRB of any SAEs on a timely basis as instructed by the Sponsor following the Sponsor's determination of causality. All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event. The Sponsor/Oculos will report all SAEs to the US Food and Drug Administration (FDA) on the appropriate

schedule depending if the event is drug related or not drug related, expected, unexpected (based on the available information in the Investigator's Brochure).

Any death occurring during the study and follow up period must be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to study drug, the SAE resulting in the death must be reported to Oculos. A death occurring after completion of the study including the Safety Follow-up Visits, that is not reasonably associated with study drug administration, does not require completion of the SAE form.

8.3.2. Follow-up of subjects after adverse events

If an adverse event/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. If a non-serious adverse event/adverse reaction is unresolved at the time of the last visit, an effort will be made to follow up until the adverse event/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

9. STATISTICS

9.1. Sample Size

A sample size of 36 total completed subjects is needed for the study. Thirty-six completed subjects, who were originally randomized in a 1:1 ratio to the Nyxol 1% and the placebo groups, [redacted] Additionally, it is assumed that there will be approximately 10% drop-out between Baseline/Day 1 and Day 15. To account for this drop-out, a total of 40 subjects will be randomized into the study.

9.2. Analysis Populations

Full Analysis Set (FAS): The FAS will include all randomized subjects who have received at least 11 doses of study medication without missing 2 consecutive doses and have both a Baseline and a Day 15 IOP measurement. This population is also known as the Per Protocol (PP) population. The FAS will be used to analyze efficacy endpoints.

All Randomized Population (AR): The AR population will include all randomized subjects. This population is also known as the intent-to-treat (ITT) population. The AR population will be used in confirmatory efficacy analyses.

Safety Population (SP): The SP will include all randomized subjects who have received at least one dose of study medication. The SP will be used to summarize safety variables.

9.3. Statistical Methods

9.3.1. General Considerations

All continuous variables will be summarized by treatment and timepoint (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical variables will be summarized by treatment and timepoint (as applicable) using frequency counts and percentages.

All study data will be listed by treatment, subject and timepoint (as applicable).

All statistical tests will be performed using a significance level of 5% (two-tailed). Given the large number of secondary efficacy endpoints, the p-values for those analyses will be considered descriptive.

9.3.2. Demographic and Baseline Characteristics

Demographic and Baseline characteristics such as age, race, gender, and history of ocular surgery and procedures, will be summarized by treatment group using the FAS and the AR population. These data will also be provided in by-subject listings.

9.3.3. Subject Disposition

Subject disposition, including randomization, and completion and withdrawal from the study will be summarized using the AR population. These data will also be provided in by-subject listings.

9.3.4. Medical History and Prior/Concomitant Medications

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group using the FAS.

Prior medications (medications with an end date prior to the date of randomization) and concomitant medications (medications with a start or end date after the date of randomization) will be coded using MedDRA and will both be summarized by treatment group using the FAS.

Medical history and prior and concomitant medications will also be provided in by-subject listings.

9.3.5. Analysis of Efficacy

Efficacy will be assessed using the FAS with subjects included in the treatment group they were randomized to, regardless of the treatment they actually received. For the analysis of the primary efficacy endpoint, observed case data will be used (no imputation will be performed for missing efficacy data) for the primary analysis. Confirmatory analyses will be performed using the AR population, with imputation performed for missing data. For the analysis of the secondary efficacy endpoints, only observed case data will be used. If warranted, confirmatory analyses using the AR population with imputation for missing data will also be performed for the secondary efficacy endpoints.

For all efficacy endpoints, Baseline is defined as the pre-dose value from the Baseline Visit/Day 1. If there is no pre-dose value from Day 1, then Baseline will be the value from the Screening Visit.

IOP will be measured twice in both eyes at each timepoint. The mean value at each timepoint for the study eye will be used in efficacy assessments. If the difference in the two IOP measurements is >5 mmHg, a third measurement will be obtained, and the three values averaged. The lighting conditions will be kept same from visit to visit.

Diurnal IOP is the mean of all three measurements (8AM, 10AM, and 4PM) on a specific day.

All efficacy data will be summarized by treatment group, study day and timepoint (8AM, 10AM, 4PM), as appropriate.

The primary efficacy endpoint is the change from Baseline to Day 15 in mean diurnal IOP. The primary efficacy endpoint will be analyzed using [redacted]

Secondary efficacy endpoints (for the study eye unless otherwise noted) are indicated in Section 4.1.

For each of the continuous secondary efficacy endpoints, [redacted]

For each of the secondary efficacy endpoints related to percentage of subjects (or percentage of eyes) meeting certain criteria, the analysis will be performed using a logistic regression with treatment and Baseline included as independent factors. For each analysis, the percentage of subjects (or eyes) in each treatment group meeting the criteria, the odds ratio (OR) with 95% CI and p-value will be provided. For all of these endpoints, the FAS will be used with subjects included in their randomized treatment group regardless of the treatment they actually received.

9.3.5. Analysis of Safety

No statistical analysis of safety data will be performed in this study. Safety will be assessed using the SP with subjects included in the treatment group they actually received, regardless of their randomized treatment. Observed case data will be used; no imputation will be performed for missing safety data.

For all safety endpoints, Baseline is defined as the pre-dose value from the Baseline Visit/Day. If there is no pre-dose value from Day 1, then Baseline will be the value from the Screening Visit.

Biomicroscopy results, and ophthalmoscopy results will be summarized by treatment group using the SP. As both eyes are treated in the study; both eyes will be included in the summarizations for visual acuity, biomicroscopy, and ophthalmoscopy. Separate summary tables will be created for the study eye versus the fellow eye.

Heart rate and blood pressure values and change from Baseline in the values will be summarized by treatment group and timepoint (8AM on Day 8, Day 15 and Day 16; 4PM on Day 15).

Verbatim descriptions of AEs will be coded using MedDRA. Only treatment-emergent AEs (TEAEs; those that occur after the first dose of study medication *or increasing in severity after initiation of study medication*) will be summarized. TEAEs and serious AEs (SAEs) will be summarized by treatment group, by system organ class (SOC), severity, and relationship to study medication. Deaths, withdrawal from study medication due to AEs, and withdrawal from the study due to AEs will each by summarized by treatment group. Note that in MedDRA, ocular events are coded to the SOC of "special senses". Thus, using SOC in the summaries will provide a separation of ocular and non-ocular adverse events.

All safety data will be provided in by-subject listings.

9.4. Procedure for accounting for missing, unused, or spurious data

For the summarization and analysis of efficacy data, the focus will be on observed case data only. No imputation will be performed for missing data. As appropriate, confirmatory efficacy analyses will be performed using imputation for missing data;

details of the imputation will be included in the study Statistical Analysis Plan. For the summarization of safety data, observed case data only will be used.

9.5. Procedure for reporting deviations from the statistical plan

Any deviations from the statistical plan will be described and a justification given in the final Clinical Study Report (CSR).

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The Investigator will permit study-related monitoring visits, audits, IRB review, and regulatory inspection(s) by providing direct access to source data and documents.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The progress of the study will be monitored by on-site, written, and telephone communications between personnel at the Investigator's site and the Medical Monitor. The Investigator will allow Ocuphire, the Study Monitor, and the Medical Monitor to inspect all CRFs, subject records (source documents), signed consent forms, records of study medication receipt, storage, preparation, and disposition, and regulatory files related to this study.

12. ETHICAL CONSIDERATIONS AND GCP COMPLIANCE

12.1. GCP compliance

The proposed study is subject to all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not necessarily limited to, the approval of Institutional Review Boards, the Helsinki Declaration, U.S. FDA Law, ICH GCP guidelines, obtaining prospective informed consent, monitoring of the conduct of the study and the completeness of the CRFs by Ocuphire or its designee(s), and appropriate record retention by the Investigator.

12.2. Institutional Review Board (IRB)

This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IRB prior to initiation of the study. Written IRB approval must adequately identify the protocol and informed consent. In addition to approving the protocol, the IRB must also approve the Subject Information and Consent Form, as well as any advertising tools that will be used for the study. Written approval also must indicate whether approval was granted based on full committee review or expedited review. Copies of all approved materials, all correspondence with the IRB and written approval from the IRB must be made available to Ocuphire, *prior* to the start of subject enrollment into the study.

12.3. Protocol Deviations/Violations

If the Investigator desires to modify the procedures and/or design of the study, he or she must contact and obtain the consent and approval of Ocuphire and the IRB, regarding the proposed changes, prior to their implementation. Changes implemented after obtaining this approval will be considered Protocol Deviations. Changes implemented without prior approval will be considered Protocol Violations.

12.4. Informed consent requirements

Written informed consent will be obtained from each subject. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The investigator is responsible for ensuring that no subject is subject to any study-related examination or activity before that subject has given informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject.

It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact on their subsequent care.

The investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian will be required to sign and date the informed consent form.

A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site. Signed informed consent must be obtained prior to the conductance of any study procedures.

13. DATA HANDLING AND RECORD KEEPING

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and U.S. Food and Drug Administration (FDA) guidelines for the handling and analysis of data for clinical trials.

13.1. Data Entry

All study data will be entered into a paper CRF. CRFs are considered to be the source documents for this study. Data will be entered from the CRF into the study database.

13.2. Data quality control and reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the Clinical Investigator and Ocuphire for resolution. The study database will be updated in accordance with the resolved query reports. All changes to the study database will be documented.

13.3. Archiving of data

Archived versions of the database will be saved by Ocuphire consistent with ICH Good Clinical Practices Guidelines, complying with whichever of the requirements is longer. Ocuphire will notify the investigator when documents should be returned.

13.4. Records retention

The Investigator's site and clinical laboratory will retain all records related to the study in compliance with ICH Good Clinical Practices Guidelines.

13.5. Amendments to the protocol

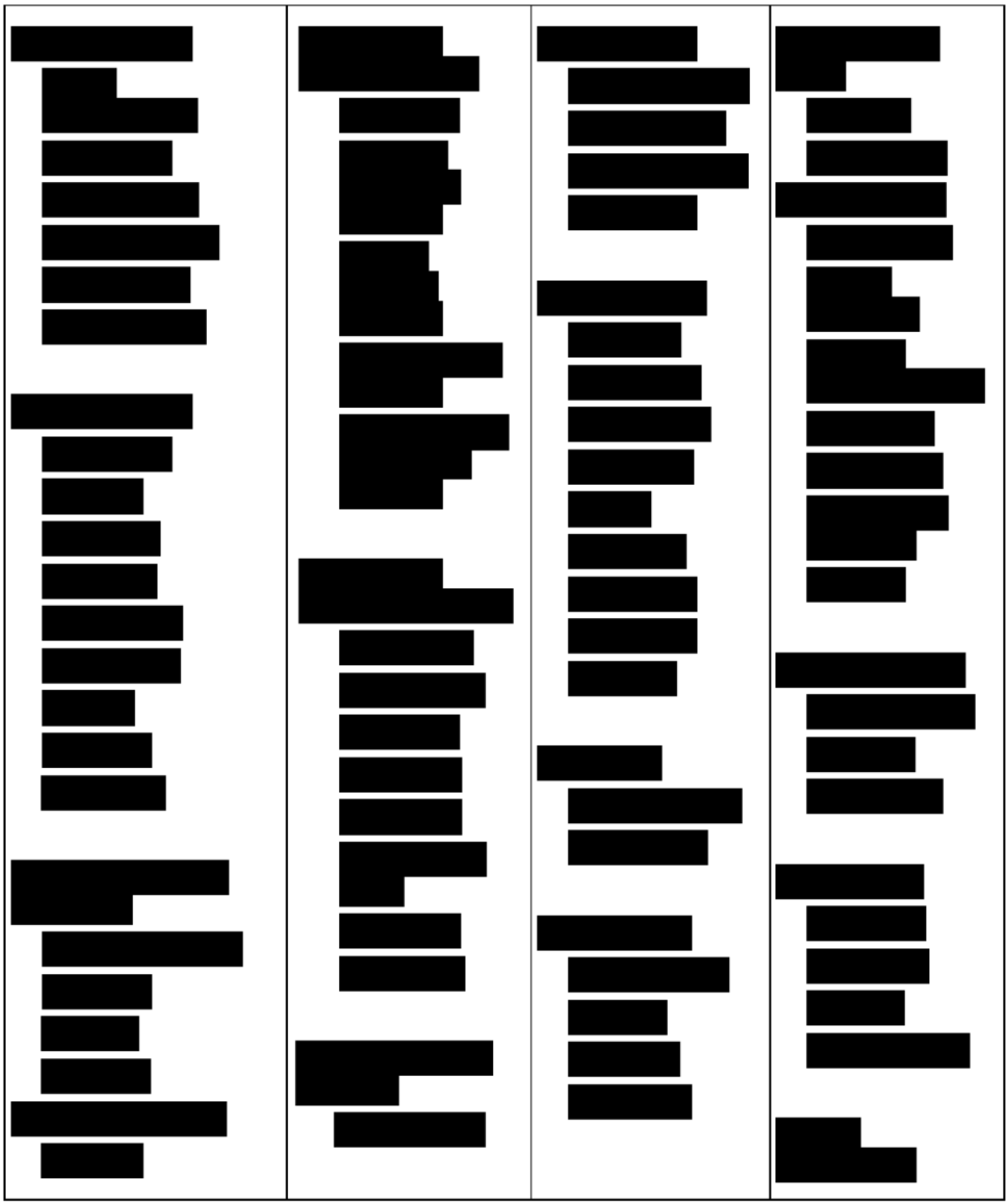
Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

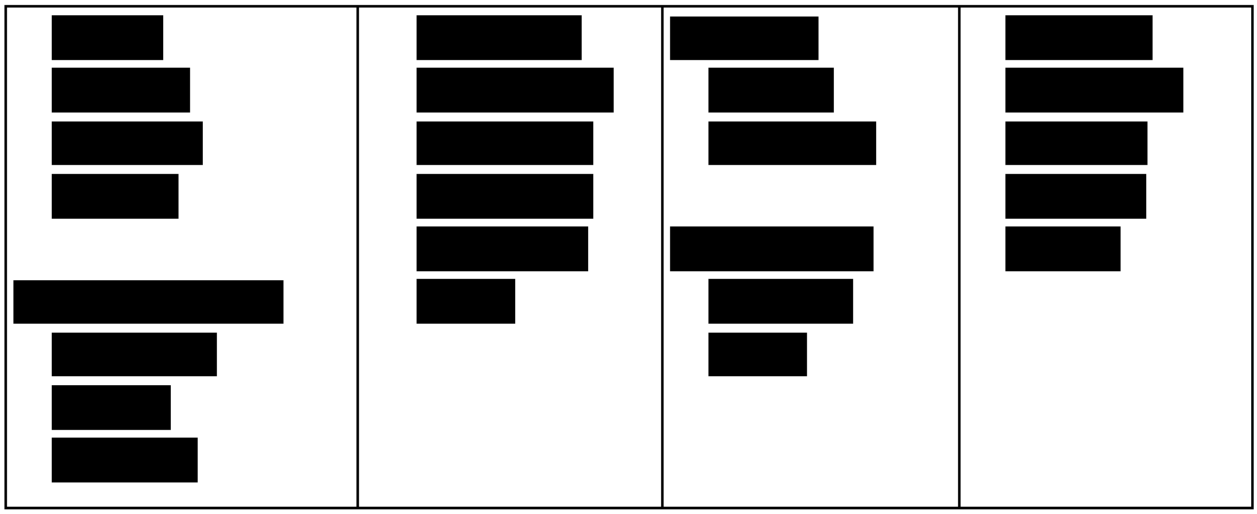
The investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by Ocuphire and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study [e.g., change in monitor(s), change of telephone number(s)].

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

APPENDIX 1: ADRENERGIC AND CHOLINERGIC DRUGS

The following drugs are examples of drugs which cannot be used up to 30 days prior to Screening, or during the study unless the drug, dose and regimen has been consistent for the 30 days prior to Screening. ***This list is not inclusive of all drugs in these classes. If there is any doubt, please consult with Ocuphire or the Medical Monitor.***





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