CONFIDENTIAL

Clinical Study Phase 3 Protocol
OPI-NYXDLD-301
LYNX-1

RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-MASKED STUDY OF THE SAFETY AND EFFICACY OF NYXOL (0.75% PHENTOLAMINE OPHTHALMIC SOLUTION) IN SUBJECTS WITH DIM LIGHT VISION DISTURBANCES

Ocuphire Pharma, Inc.
37000 Grand River Avenue, Suite 120
Farmington Hills, MI 48335

Original: **October 28, 2020**
Amendment 1: **November 6, 2020**
Amendment 2: **March 25, 2021**

SUMMARY OF CHANGES FOR AMENDMENT 2

Bold underlined text shows additions; ~~strikethrough text~~ shows deletions. For changes that affect multiple sections of the protocol, the change is listed once at the first instance below, and each subsequent protocol section incorporating that change is also listed at that point. Administrative and minor editing changes not affecting the content or conduct of the protocol have been made; these are not listed. None of the changes made affect the risks to the subjects in this study.

Section: Location	Description of Change	Rationale for Change
Synopsis: Inclusion Criteria, p.13 5.1 Subject Inclusion Criteria, p.41	7. [redacted] under mesopic conditions (prior to illumination) in at least one eye. **This test may be repeated once following an additional 5 minutes of adaptation to the mesopic light conditions if the initial results do not meet this criterion.**	Global change to modify mesopic PD eligibility criterion from [redacted] mm and to clarify that one repeated screening of PD under mesopic conditions is acceptable during the Screening/Baseline visit
Synopsis: Inclusion Criteria, p.13 5.1 Subject Inclusion Criteria, p.41	8. ≤ ~~2~~30 ~~(20/100 Snellen or worse)~~ Early Treatment Diabetic Retinopathy Study (ETDRS) letters **(20/63 Snellen or worse)** in mLCVA score in at least one eye using the Precision Vision Illuminator Cabinet with 5% translucent contrast chart and a mesopic filter at 4 m.	Global change to modify mLCVA eligibility criterion from 20 letters (20/100 Snellen or worse) to 30 letters (20/63 Snellen or worse)
4.4.3 Study Medication Administration, p.37	**The first dose of study medication will be taken at 8PM to 10PM on the evening of the Baseline Visit (Day 1).** [redacted]	Global change to modify and clarify the contact lens discontinuation requirements for contact lens wearers
Synopsis: Exclusion Criteria, p.14 5.2 Subject Exclusion Criteria, p.42	12. Unwilling or unable to discontinue use of contact lenses ~~at screening until study completion, except for keratoconus subjects who may wear contacts up to 24 hours prior to~~ **on** their scheduled visits [redacted] **(for both types of lenses) before** ~~on~~ Day 8 and Day 15**.**	
7.2.1 Visit 1 (Screening/Baseline)/ Day 1, p.47	[redacted]	
7.2.1 Visit 1 (Screening/Baseline)/ Day 1, p.48	The first dose of study medication will be taken at 8PM to 10PM on the evening of the Baseline Visit (Day [redacted]	

<table>
<tr><td>7.2.2 Visit 2 (Treatment)/Day 8 ± 1 day), p.49</td><td>[redacted]</td><td rowspan="2"></td></tr>
<tr><td>7.2.3 Visit 3 (Treatment)/Day 15 ± 1 day), p.50</td><td>If[redacted]</td></tr>
<tr><td>Synopsis: Treatment Visits, p.17</td><td>Treatment visits will occur 2 times: Day 8 (~~+~~±1 day)/Visit 2 and Day 15 (~~+~~±1 day)/Visit 3.</td><td rowspan="5">Global change to remove the restriction that the Day 8 and Day 15 clinic visits have to be performed in the 8AM to 10AM time window and to open the visit window to ± 1 day</td></tr>
<tr><td>Synopsis: Study Medications, Dose and Mode of Administration, p.21</td><td>Nyxol® Eye Drops (Phentolamine Ophthalmic Solution):
One drop of Nyxol QD at or near bedtime (8PM to 10PM) OU for 14 days (~~+~~±1 day) for subjects randomized to active treatment.
Placebo (Nyxol vehicle):
One drop of placebo QD at or near bedtime (at 8PM to 10PM) OU for 14 days (~~+~~±1 day) for subjects randomized to placebo.</td></tr>
<tr><td>Synopsis: Duration of Subject Participation and Study, p.21</td><td>The total length of subject participation is approximately 3 weeks with 3 clinic visits and one telephone call follow-up summarized below:
Visit 1 (Screening/Baseline)/Day 1
Visit 2 (Treatment)/Day 8 (~~+~~±1 day) ~~at approximately 8AM to 10AM (+2 hours)~~
Visit 3 (Treatment)/Day 15 (~~+~~±1 day) ~~at approximately 8AM to 10AM (+2 hours)~~</td></tr>
<tr><td>Table 2. Screening, Baseline, Treatment, and Follow-Up Visits and Procedures, p.34</td><td><table><tr><th></th><th>Screening/ Baseline [a]</th><th>Treatment</th><th>Treatment</th><th>TC Follow-Up</th></tr><tr><td>Day</td><td>1</td><td>8 ~~+~~± 1 Day ~~(8—10 AM + 2 hr)~~</td><td>15 ~~+~~± 1 Day ~~(8—10 AM + 2 hr)~~</td><td>1 to 3 days after Visit 3</td></tr></table></td></tr>
<tr><td>4.5 Expected Duration of Subject Participation, p.38</td><td>The total length of subject participation is approximately 3 weeks, with 3 clinic visits and one telephone call follow-up summarized below:
Visit 1 (Screening/Baseline)/Day 1
Visit 2 (Treatment)/Day 8 (~~+~~±1 day)
Visit 3 (Treatment)/Day 15 (~~+~~±1 day)</td></tr>
</table>

7.2.2 Visit 2 (Treatment)/Day 8 ± 1 day), p.49	At Visit 2**,** ~~subjects should be scheduled for this visit between approximately 8AM and 10AM (+2 hour).~~ the medication box, complete with opened bottles and any unopened study medication, and diary will be returned to the study site where the site will account for opened and unopened study medication and the study medication box will be re-dispensed with the unopened medication.	
7.2.3 Visit 3 (Treatment)/Day 15 ± 1 day), p.50	At Visit 3, ~~subjects should be scheduled for this visit between approximately 8AM and 10AM (+2 hour).~~ the subject will bring their used dropper bottles with any unused medications and diary with them for purposes of drug accountability. The last day of study treatment is the day before Visit 3; no further study medication will be dispensed at Visit 3.	
7.2.1 Visit 1 (Screening/Baseline)/ Day 1. p.47	Prior to further screening, the subject must be asked to complete the subject questionnaire. [redacted]**,** ~~Then~~ subjects shall be assessed in each eye for PD and for mLCVA before and during illumination of the contralateral eye with a [redacted]") ([redacted]	To clarify that subjects need their refraction confirmed at the Screening/Baseline visit.
7.2.1 Visit 1 (Screening/Baseline)/ Day 1, p.48	**If the subject meets all eligibility criteria, they will be randomized to a treatment group. If a subject fails the screen, they can return for a rescreening (signing a new informed consent and assigning a new subject number) at the investigator's discretion.**	To clarify that rescreening of subjects who initially fail screening is acceptable.

SPONSOR SIGNATURE & CONTACTS

Study Title:	Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) in Subjects with Dim Light Vision Disturbances
Study Number:	OPI-NYXDLD-301
Original Protocol:	October 28, 2020
Amendment 1:	November 6, 2020
Amendment 2:	March 25, 2021

Person authorized to sign the protocol and protocol amendment(s) for the sponsor, Ocuphire Pharma, Inc.

Mina Sooch, MBA
President & CEO
Ocuphire Pharma, Inc.
Tel: 248-681-9815 (Office)
[redacted]

[redacted]

Signature

3/25/21

Date

Benjamin Rubin, MD
Medical Monitor
[redacted]

[redacted]

Signa

3/25/2021

Date

INVESTIGATOR'S AGREEMENT

OPI-NYXDLD-301
LYNX-1

RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-MASKED STUDY OF THE SAFETY AND EFFICACY OF NYXOL (0.75% PHENTOLAMINE OPHTHALMIC SOLUTION) IN SUBJECTS WITH DIM LIGHT VISION DISTURBANCES

Original Protocol: **October 28, 2020**
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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 electronic records; electronic signatures (21 CFR 11, the protection of human subjects (21 CFR 50), financial disclosure by Clinical Investigators 921 CFR 54), 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	Ann Grace	[redacted]
Medical Monitor	Benjamin Rubin, MD	[redacted]

ABBREVIATIONS AND TERMS

Abbreviation	*Full term*
AE	adverse event
ANCOVA	analysis of covariance
ARP	All Randomized Population
ARVO	Association for Research in Vision and Ophthalmology
BAT	Brightness Acuity Tester
BCDVA	best-corrected distance visual acuity
BP	blood pressure
°C	degrees Celsius
CCLRU	Cornea and Contact Lens Research Unit
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CRA	clinical research associate
CRO	clinical research organization
CS	contrast sensitivity
°F	degree Fahrenheit
DCNVA	distance-corrected near visual acuity
DLD	dim light vision disturbances (also referred to as night vision disturbances or NVD)
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	heart rate
IB	Investigators' Brochure
ICH	International Council for Harmonisation
IND	Investigational New Drug
IOL	intraocular lens

IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intention-to-treat
IUD	intrauterine device
LASIK	laser-assisted in situ keratomileusis
LCVA	low-contrast visual acuity
LDPE	low-density polyethylene
logMAR	logarithm of the Minimum Angle of Resolution
LSM	least squares mean
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mHCVA	mesopic high-contrast visual acuity (BCDVA)
mLCVA	mesopic low-contrast visual acuity (BCDVA)
mITT	Modified intention-to-treat
Nyxol®	0.75% Phentolamine Ophthalmic Solution or 1% Phentolamine Mesylate Ophthalmic Solution
OD	oculus dexter (right eye)
OR	odds ratio
OS	oculus sinister (left eye)
OTC	over-the-counter
OU	oculus uterque (both eyes)
PD	pupil diameter
pHCVA	photopic high-contrast visual acuity (BCDVA)
pLCVA	photopic low-contrast visual acuity (BCDVA)
PP	Per Protocol
PRK	photorefractive keratectomy
QD	once daily
RK	radial keratectomy
RMS	root-mean square
SAE	serious adverse event

SOC	system organ class
SP	Safety Population
TEAE	treatment-emergent adverse event
US	United States
USP	United States Pharmacopeia
VA	visual acuity

1 STUDY SUMMARY

Study Number	**OPI-NYXDLD-301**
Clinical Phase	Phase 3
Type of Study	Randomized, placebo-controlled, double-masked, multiple-dose study of the safety and efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) in subjects with dim light vision disturbances (DLD).
Name of Investigational Product	Nyxol® Eye Drops – 0.75% Phentolamine Ophthalmic Solution
Duration of Study	Approximately 3 weeks, including screening, treatment, and follow-up.
Rationale	DLD, which includes night vision disturbances, affects patients under mesopic or scotopic conditions. [redacted] When the pupil dilates in people with DLD, peripheral aberrations scatter light rays resulting in these visual aberrations, a loss of mesopic low-contrast visual acuity (mLCVA) and contrast sensitivity (CS). It is proposed that a moderate pharmacologic reduction of pupil size (20-25%) by the application of an alpha-1 antagonist has the potential to mitigate DLD in many affected individuals. Phentolamine is a non-selective alpha-1 and alpha-2 adrenergic antagonist acting on the adrenergic receptors and inhibiting contraction of the smooth muscle. When topically applied, phentolamine inhibits contraction of the iris dilator muscle, resulting in a smaller pupil size. Previous Phase 2 clinical trials showed that Nyxol significantly decreases pupil diameter (PD) and improves mLCVA in DLD subjects after single- and multi-dose (14 days) treatment. Nyxol was generally well-tolerated in the eye (most common complaint was transient mild-to-moderate ocular hyperemia and eye irritation) and there were no clinically meaningful systemic effects as measured by heart rate (HR) and blood pressure (BP).

Study Objectives	The objectives of this study are: • To evaluate the efficacy of Nyxol to improve mLCVA in subjects with DLD • To evaluate the efficacy of Nyxol to improve visual performance • To evaluate the safety of Nyxol • To evaluate any additional benefits of Nyxol in treating DLD subjects The Sponsor intends to use this first Phase 3 registration study to evaluate Nyxol for the indication of "treatment of symptoms associated with dim light or night vision disturbances."
Design	Placebo-controlled, double-masked, multiple-dose, Phase 3 study in approximately 160 randomized subjects with DLD (approximately 136 that are evaluable for efficacy), evaluating safety and efficacy of Nyxol in subjects with DLD following administration of Nyxol once daily (QD) at or near bedtime (at 8PM to 10PM) in both eyes (OU) for 14 days. Following the successful completion of screening, each subject will be stratified by iris color (light/dark irides) and will then be randomized to treatment (masked) 1:1, Nyxol or placebo (vehicle). Treatment (Nyxol or placebo) will be administered OU by the subjects at or near bedtime each day. [redacted] The study eye and non-study eye, as well as binocular, will be evaluated at all appropriate assessments.
Subject Population	Approximately 160 randomized (approximately 136 that are evaluable for efficacy) subjects experiencing DLD
Inclusion Criteria	1. Males or females ≥ 18 years of age 2. Subject-reported DLD (likely subjects with a history of multifocal IOLs, post–laser-assisted in situ keratomileusis [LASIK], corneal scars, and keratoconus)

	3. Ability to comply with all protocol-mandated procedures independently and to attend all scheduled office visits 4. Otherwise healthy and well-controlled subjects 5. Able and willing to give written consent to participate in this study 6. Able to self-administer study medication 7. [redacted] This test may be repeated once following an [redacted] of adaptation to the [redacted] if the initial results do not meet this criterion. 8. ≤ 30 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/63 Snellen or worse) in mLCVA score in at least one eye using the Precision Vision Illuminator Cabinet with 5% translucent contrast chart and a mesopic filter at 4 m. 9. ≥ 10 ETDRS letters (≥ 2 lines) improvement in mLCVA in at least [redacted]
Exclusion Criteria	**Ophthalmic:** 1. Prior unresolved dry eye diagnosis, taking prescription drops for dry eye, or taking artificial tear drops routinely for dry eye 2. Prior history of fluctuating vision 3. Clinically significant ocular disease as deemed by the Investigator (e.g., untreated cataract, glaucoma, corneal edema, uveitis, severe keratoconjunctivitis sicca, retina degeneration, loss of visual field due to glaucoma or stroke, branch retinal vein occlusion, retina flare) that might interfere with the study 4. Known hypersensitivity to any topical alpha-adrenoceptor antagonists 5. Known allergy or contraindication to any component of the vehicle formulation 6. History of cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal

	7. Ocular trauma, ocular surgery (e.g., IOLs) or laser procedure (e.g., LASIK, photorefractive keratectomy [PRK]) within 6 months prior to screening 8. Use of any topical prescription or over-the-counter (OTC) ophthalmic medications of any kind (including artificial tear drops) within 7 days of screening until study completion, with the exception of lid scrubs with OTC products (e.g., OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.) 9. Recent or current evidence of ocular infection or inflammation in either eye (such as current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at screening in either eye). Subjects must be symptom free for at least 7 days. 10. History of diabetic retinopathy, diabetic macular edema, or dry or wet macular degeneration 11. History of any traumatic (surgical or nonsurgical) or non-traumatic condition affecting the pupil or iris (e.g., irregularly shaped pupil, neurogenic pupil disorder, iris atrophy, iridotomy, iridectomy, etc.) 12. Unwilling or unable to discontinue use of contact lenses on their scheduled visits at least 1 hour for soft contact lenses and at least 8 hours for hard gas-permeable contact lenses before ophthalmic assessments at screening, and at least 8 hours (for both types of lenses) before Day 8 and Day 15. 13. People with undiagnosed dry eye, at the determination of the Investigator. Dry eye evaluation should be based on one of the following dry eye tests: a. TearLabs osmolarity test (> 308 mOsm/L in either eye or an inter-eye difference ≥ 10 mOsm/L) b. Corneal fluorescein staining (≥ grade 2 in the inferior or ≥ grade 1 in the central zone using the National Eye Institute scale) c. Tear break-up time of < 5 seconds **Systemic:** 14. Known hypersensitivity or contraindication to alpha- and/or beta-adrenoceptor antagonists (e.g., chronic obstructive pulmonary disease or bronchial asthma; abnormally low BP or HR; second- or third-degree heart

	blockage or congestive heart failure [CHF]; severe diabetes as defined below) a. Predisposition to severe hypoglycemia (2 or more serious hypoglycemic episodes requiring assistance within the past year) b. Any hospitalization or emergency room visit due to poor diabetic control within the past 6 months c. Currently untreated diabetes mellitus or previously untreated subjects who initiated oral anti-diabetic medication or insulin within 3 months prior to Day 1 d. Any sign of diabetic retinopathy in either eye e. Uncontrolled diabetes mellitus defined by Hemoglobin A1c > 12% taken within the last 3 months 15. Clinically significant systemic disease (e.g., severe diabetes as previously defined, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere with the study 16. Initiation of treatment with or any changes to the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs within 7 days prior to screening or during the study 17. Participation in any investigational study within 30 days prior to screening and during the conduct of the study 18. Females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods include the use of at least one of the following: intrauterine device (IUD), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. A female is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential including those with post-tubal ligation must have a negative urine pregnancy test result at Visit 1 (Screening/Baseline), Visit 2 (Treatment), and Visit 3 (Treatment) examinations and must intend to not become pregnant during the study 19. Resting HR outside the specified range (50-110 beats per minute) at Visit 1 (Screening/Baseline). HR may be

	repeated **only once** if outside the specified range following at least a 5-minute rest period in the sitting position 20. Hypertension with resting diastolic BP > 105 mmHg or systolic BP > 160 mmHg at Visit 1 (Screening/Baseline). BP may be repeated **only once** if outside the specified range following at least a 5-minute rest period in the sitting position
Screening/Baseline Visit	Individuals who are potential subjects are identified by the study center to schedule the Screening Visit. The Screening Visit shall occur the same day as the Baseline Visit, where the dose of study treatment is given. Once a subject arrives 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, the informed consent form is signed, and a subject identification number is assigned. The start of screening includes an explanation of the study, a medical and ophthalmic history, demographics, and a review of prior/concomitant medications. During this time, eligibility for [redacted] shall be determined first. [redacted]) shall be determined and only eligible subjects will continue. This shall be followed by a urine pregnancy test for females of childbearing potential (Exclusion Criterion #18), and HR/BP (Exclusion Criteria #19-20). [redacted] [redacted]. Investigators should frequently remind subjects to blink between visual acuity assessments. The study eye of the subject [redacted] in order for the subject to not screen fail.

	Before further screening criteria, the following assessments shall be performed to establish baseline values: • Mesopic high-contrast visual acuity (mHCVA), photopic low-contrast visual acuity (pLCVA), and mesopic high-contrast distance-corrected near visual acuity (DCNVA) • Using an [redacted] and corneal topography measurements under [redacted] • Conjunctival hyperemia, assessed visually with a grading scale (0-3) using images from the Cornea and Contact Lens Research Unit (CCLRU; Investigators are cautioned to appropriately note all observations of conjunctival hyperemia on the biomicroscopy electronic Case Report Form at screening) • Slit lamp biomicroscopy The subject must also meet dry eye Exclusion Criterion #13 to be included in the study at the determination of the investigator. Specifically, subjects with undiagnosed dry eye may undergo a dry eye test. Final screening must include IOP measurement (using a Tono-Pen) and ophthalmoscopy. With the subject passing all eligibility criteria, the Screening Visit becomes the Baseline Visit. The subject will then be assigned a randomization number and randomized into the study. See Table 2 for details on measurements expected at each visit. The first dose of study medication must be taken by the subject at 8PM to 10PM on the Baseline Visit (Day 1). All treatments will be administered OU.
Treatment Visits	Treatment visits will occur 2 times: Day 8 (±1 day)/Visit 2 and Day 15 (±1 day)/Visit 3. mLCVA evaluations shall be performed on each of these days. [redacted] Other assessments as defined in Table 2 shall be performed at these visits.
Follow-up Visit	A follow-up visit (Visit 4) phone call will occur 1 to 3 days after Visit 3. Concomitant medications and adverse events (AEs) will be collected.

Number of Investigational Sites	Approximately 15 sites
Estimated Total Sample Size	Approximately 160 randomized subjects, with approximately 136 subjects that are evaluable for efficacy
Sample Size Justification	A sample size of approximately 136 subjects (68 per treatment group) that are evaluable for efficacy (i.e. who have a Day 8 mLCVA measurement) is needed for the study. [redacted] All subjects will be randomized into the study in a 1:1 ratio to one of the treatment arms (Nyxol or placebo), with a [redacted] It is assumed that there will be approximately 15% drop-out. To account for this drop-out, a total of approximately 160 subjects will be randomized into the study.
Primary Efficacy Endpoint	Percent of subjects with ≥ 15 ETDRS letters (≥ 3 lines) of improvement in the study eye compared to baseline in monocular mLCVA at Day 8 for the mITT population.
Secondary and Exploratory Efficacy Endpoints	Secondary efficacy endpoints (for the study eye, the non-study eye, the best of either eye, and binocular) will include: • [redacted] [redacted] [redacted] [redacted]

[redacted]

study eye, the best of either eye, and binocular) shall be collected and analyzed for the sites that have an OPD Scanner and will include but are not limited to:

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted], later
- [redacted]
- [redacted]

	[redacted] Subject will be allowed to acclimate to these lighting conditions (with the eyes open normally for a minimum of [redacted] prior to the set of PD, BCDVA, DCNVA, and wavefront error measurements). Subject will sit in the exam chair facing directly at the illuminated chart during the acclimation period and for all assessments. Room lights may be turned on for the scheduled remaining safety assessments (e.g., conjunctival hyperemia, AEs, subject questionnaire, etc.). The subject will be in the same room for all assessments, and every effort will be made to have the same person perform the measurements at all visits. All of the efficacy endpoints will be analyzed overall, and by [redacted] at all timepoints. The mLCVA endpoints will be analyzed by baseline PD [redacted] and higher-order aberrations subpoint. All efficacy endpoints will be analyzed by Modified Intention to Treat (mITT) and Per Protocol (PP) populations.
Safety Endpoints	The primary safety measures are conjunctival hyperemia and AEs. Analysis for conjunctival hyperemia includes change from baseline (Day 1) in the conjunctival hyperemia grading scale (CCLRU images) at each visit (Day 8 and Day 15), for study eye and non-study eye. Any increase of 2 units in conjunctival hyperemia between consecutive visits is considered an AE. Other safety measures include intraocular pressure (IOP), biomicroscopy, ophthalmoscopy, dry eye measurements, and

	systemic safety as measured by HR and BP. Urine pregnancy tests for females of childbearing potential will be conducted. Subject questionnaire values will be summarized by treatment group and visits (Day 1, Day 8, and Day 15). Measurements: • Conjunctival hyperemia will be assessed visually with a grading scale (0-3) using images from the CCLRU • IOP will be measured with the Tono-Pen • BP and HR will be measured manually or with available digital devices • Subject questionnaire will be a brief symptom survey
Study Medications, Dose and Mode of Administration	Nyxol® Eye Drops (Phentolamine Ophthalmic Solution): One drop of Nyxol QD at or near bedtime (8PM to 10PM) OU for 14 days (±1 day) for subjects randomized to active treatment. Placebo (Nyxol vehicle): One drop of placebo QD at or near bedtime (at 8PM to 10PM) OU for 14 days (±1 day) for subjects randomized to placebo.
Duration of Subject Participation and Study	The total length of subject participation is approximately 3 weeks with 3 clinic visits and one telephone call follow-up summarized below: • Visit 1 (Screening/Baseline)/Day 1 • Visit 2 (Treatment)/Day 8 (±1 day) • Visit 3 (Treatment)/Day 15 (±1 day) • Follow-up telephone call 1 to 3 days after Visit 3 The execution of the entire study (first subject screened through last randomized subject completed) is expected to be approximately 9 to 12 months.

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2 INTRODUCTION

2.1 Investigational Products

The test product is Nyxol® Eye Drops – 0.75% Phentolamine Ophthalmic Solution (Nyxol), a non-selective alpha-1 and alpha-2 adrenergic antagonist. Note that the concentration of 0.75% refers to phentolamine free base and is the same and used in place of 1% phentolamine mesylate drug substance, which was how Nyxol had been described in all prior studies. 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) (2020).

Nyxol has been assessed in 7 investigator-initiated and sponsored Phase 1 and Phase 2 clinical trials. Across all trials, 168 of 232 adult patients were exposed to at least one dose of Phentolamine Mesylate Ophthalmic Solution.

In prior clinical trials, Nyxol has demonstrated a consistent ability to decrease pupil by approximately 20% (~1–1.5 mm) under both mesopic and photopic conditions. Key pupil diameter (PD) data are summarized below (Table 1).

Table 1 Efficacy of 1% Nyxol in Reducing Pupil Diameter Under Mesopic Conditions in Phase 2 Trials

Study	Group	Mesopic Conditions				
		Pre-Treatment (Baseline) Pupil Diameter	**Post-Treatment Pupil Diameter**	**Change (%)**	**p-value compared to baseline**	**p-value compared to placebo**
NYX-SNV[1]	Placebo (N = 16)*	6.6 mm	6.4 mm	-0.2 mm (-3%)	p = 0.08	**p < 0.0001**
	1.0% Nyxol (N = 32)*	6.5 mm	5.2 mm	**-1.3 mm (-20%)**	**p < 0.0001**	
NYX-01a2[2]	Placebo (N = 38)*	6.25 mm	6.31 mm	0.07 mm (+1%)	p = 0.6	**p < 0.0001**
	1.0% Nyxol (N = 40)*	6.17 mm	5.31 mm	**-0.86 mm (-14%)**	**p < 0.0001**	
NYXG-201	Placebo (N = 20)	4.57 mm	4.52 mm	-0.05 mm (-1%)	p = 0.6178	**p < 0.0001**
	1.0% Nyxol (N = 19)	4.69 mm	3.70 mm	**-1.00 mm (-21%)**	**p < 0.0001**	

*Two eyes per subject were included to calculate the endpoint

Nyxol was observed to be well-tolerated at single doses up to and including 1.0% daily in each eye. This includes 59 patients who received multiple doses of up to 1% Nyxol for at

least 14 days. Safety of the patients in these trials was evaluated by adverse event (AE) monitoring, physical examinations, and vital sign assessments. Across all trials, no healthy volunteers or patients reported a treatment-emergent serious adverse event (SAE). No deaths occurred in any of the trials. No clinically meaningful changes were observed in physical examinations or vital signs, including blood pressure (BP) and heart rate (HR). AEs reported were mild to moderate in intensity, with the most common being transient conjunctival hyperemia and ocular irritation; however, Nyxol dosing at or near bedtime in the evening was observed to mitigate or minimize these side effects during the daytime.

Phase 2 Trial in Patients With Severe NVD (NYX-SNV):

NYX-SNV was a double-masked, randomized, placebo-controlled, single-dose trial assessing the tolerability and effect of a single topical drop of 1.0% solution of phentolamine mesylate in Tears Naturale II in each eye or Tears Naturale II (placebo) on PD, contrast sensitivity (CS), visual acuity (VA), and wavefront aberrometry. A total of 24 patients (median age of 39) with severe night vision complaints were randomly assigned 2:1 to treatment groups (active treatment, n = 16; placebo control, n = 8). Patients had to demonstrate at least a 2-line improvement in low-contrast visual acuity (LCVA) in dim light during illumination of the contralateral eye at screening. Each group was treated with one drop of test article in each eye. The primary endpoint was a statistically significant improvement in the mean change in monocular CS scores under mesopic conditions at each of 5 spatial frequencies. Key secondary endpoints included measurements of LCVA under mesopic and photopic conditions, change in PD, and percent of subjects with an improvement in CS (at multiple frequencies), which were recorded at baseline (prior to treatment administration) and approximately 2 hours after administration.

The planned United States (US) Food and Drug Administration (FDA) primary endpoint was percent of subjects with 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (3 lines) of improvement in mesopic LCVA (mLCVA) at a single timepoint. In this trial, even with a small sample size, there was a positive trend of 15-letter (3-line or greater) improvement in mLCVA (19% Nyxol vs 0% for placebo, $p = 0.16$) and photopic low-contrast visual acuity (pLCVA) (19% Nyxol vs 0% for placebo, $p = 0.16$). Additionally, greater fractions of Nyxol-treated eyes registered a 1-line (5-letter or greater) improvement in mLCVA (69% vs 31% for placebo, $p = 0.029$) and pLCVA (63% vs 13% for placebo, $p = 0.017$), as well as a 2-line (10-letter or greater) improvement in mLCVA (34% vs 6% for placebo, $p < 0.03$) and pLCVA (28% vs 0% for placebo, $p < 0.02$).

Other distance VA measurements were made, including mesopic distance high-contrast visual acuity (mHCVA) and photopic distance high-contrast visual acuity (pHCVA). Greater fractions of Nyxol-treated eyes registered a 2-line (10-letter or greater) statistically significant improvement in mHCVA (25% vs 0% for placebo, $p < 0.03$), with a notable but not statistically significant trend in pHCVA (19% vs 0% for placebo, p = NS). Differences in mean change in VA between treatments were also seen. There were statistically significant improvements with 1% Nyxol from pre-treatment across all mean VA measurements ($p < 0.0001$). Further, mean mLCVA showed statistically significant improvement for both treatment groups 2 to 3 hours post-treatment, with the mean

magnitude of improvement for phentolamine mesylate–treated patients being over twice that of placebo-treated patients (8.0 vs 3.1 letters, respectively; $p = 0.035$).

Additionally, mean PD decreased at a statistically significant amount of an average of 1.3 mm ($p < 0.0001$), or ~20%, for phentolamine mesylate–treated patients, whereas mean PD of placebo-treated patients did not significantly change between pre-treatment and post-treatment. The difference in mean change between treatment groups was also statistically significant (1.1 mm, $p < 0.0001$) (Table 1). In a *post-hoc* analysis that helped inform the Phase 3 trial design, there was an average of ~1.5 mm PD reduction in patients with baselines above 6 mm, compared to ~1 mm reduction in patients with baselines below 6 mm. Measurements were taken 2 to 3 hours after dosing.

Total wavefront root-mean square (RMS) error is the summation of all aberrations measured with a wavefront device (VISX-CustomVue Aberrometer), delineated in µm (microns), RMS error for short. Higher-order RMS error is the summation of higher-order aberrations, including trefoil, coma, and spherical aberrations that because of their complex nature cannot be corrected with regular corrective lenses. Reduction in higher "errors" would be consistent with improvements in dim light vision disturbances (DLD). In a *post-hoc* analysis with the purposes to help inform future trials and commercial efforts, the difference in change between Nyxol and placebo treatment arms for both total RMS (0.42 µm, $p = 0.0004$) and higher-order RMS (0.17 µm, $p < 0.0001$) were statistically significant, with Nyxol-treated eyes showing improvement with a larger reduction in error.

In summary, in NYX-SNV, 1% Nyxol demonstrated statistically significant reductions in PD and improvement in LCVA under photopic and mesopic lighting conditions, as well as individual CS frequency improvements. Treatment with 1% Nyxol further exhibited a statistically significant reduction in aberration errors (errors that affect light transmission in specific PD sizes).

It is important to note that similar results were found in NYX-01a2, which was a 15-day, double-masked, randomized, placebo-controlled trial in patients with severe DLD. The NYX-01a2 trial demonstrated a dose response favoring 1% Nyxol. Further, statistically significant reductions in PD, trends in improvement in LCVA under bright and dim lighting conditions were shown. Durability of effect on PD was observed 24 hours later for Nyxol with daily morning doses.

Phase 2 Trial in a Glaucomatous and Presbyopic Population (ORION-1, NYXG-201):

ORION-1 (NYXG-201) was a double-masked, randomized, placebo-controlled, multi-center trial of 1% Nyxol compared with placebo ophthalmic solution for 14 days in patients with open-angle glaucoma or ocular hypertension. After screening was performed based on inclusion and exclusion criteria, a total of 39 elderly patients (median age of 63) were randomized into the trial (Nyxol arm, n = 19; placebo arm, n = 20). These patients were either treatment-naïve or were previously taking intraocular pressure (IOP)-lowering medication that was washed out for 30 days prior to dosing. Patients took their study medication (Nyxol or placebo) in both eyes (OU) between 8PM to 10PM every evening for 14 days. Assessments were made on Day 1, Day 8, Day 15, and Day 16. The primary efficacy endpoint was change in mean diurnal IOP at Day 15 from baseline. Mean diurnal

IOP is the mean of the IOP measurements at 3 timepoints (8AM, 10AM, 4PM). Secondary efficacy endpoints included change in PD, change in distance-corrected near visual acuity (DCNVA), and change in best-corrected distance visual acuity (BCDVA), as well as additional IOP analyses. Safety assessments included measurements of conjunctival redness (using the Cornea and Contact Lens Research Unit [CCLRU] grading 4-point scale [0-3]), AEs, HR, BP, concomitant medications, and pregnancy. Highlights of this trial were presented at the 2020 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO).

In this study, Nyxol had statistically significant PD reductions under photopic and mesopic conditions that were sustained for 36 hours post-dosing. A statistically significant number of patients with Nyxol compared to placebo demonstrated ≥ 1 line of improvement in DCNVA, with a trend for 2- and 3-line improvements at all time points. There was no statistical difference in conjunctival hyperemia compared to placebo. In summary, daily evening dosing of Nyxol was found to be well tolerated with no daytime conjunctival redness and demonstrated improvement in DCNVA with sustained PD reduction in a glaucomatous and presbyopic population. Smaller pupil size can have beneficial effects in improving symptoms of patients with DLD, which is relevant to the LYNX-1 trial.

2.3 Design Justification

DLD, which includes night vision disturbances, affects patients under mesopic or scotopic conditions. DLD involves photic phenomena, such as glare, halos, and starbursts, which can be a result of a combination of ocular aberrations and light scatter, as well as the effect of multiple images simultaneously superimposed onto the retina, as in the case of multifocal intraocular lenses (IOLs; Rosen 2005).

These visual disturbances can be debilitating to a variety of everyday activities, especially driving. The light emitted by traffic lights and other cars scatters and obscures most of the visual field, making driving in dim light conditions hazardous. Glare, in particular, can be dangerous while driving.

Several surveys suggest that DLD are a clinically relevant concern.

- More than half (53%) of vision-corrected Americans admit they feel uncomfortable when driving in the dark (Fejer and Girgis, 1992).
- Up to 3% of patients with refractive procedures are unable to function visually at night (Pop and Payette, 2004; Fan-Paul, 2002; Holladay, 1999; Monestam and Lundqvist, 2006).
- As many as 20% of people with multifocal IOLs complain of night vision disturbances (van Alphen, 1976).
- In one study of 297 drivers given vision tests that correlate with accidents, 45% of the drivers who reported difficulty driving at night were unable to perform any of the tests with glare (Puell, 2004).

The effects of DLD can be mitigated by miosis, where the smaller pupil blocks the unfocused, peripheral aberrant rays of light, selectively allowing passage of the more centrally focused rays (Martinez, 1998). A miotic change in the pupil size can be achieved by modulating 1 of 2 or both opposing sets of muscles – the iris sphincter muscles controlled by the cholinergic nervous system and the iris dilator muscles controlled by the adrenergic nervous system (Yoshitomi, 1985; Steinhauer, 2004). An alpha-1 antagonist approach will act on the iris dilator muscle and produce a miotic effect (Yu, 2002). It is proposed that a moderate pharmacologic reduction of pupil size (20–25%) by the application of an alpha-1 antagonist has the potential to mitigate DLD in many affected individuals.

The biggest challenge for the treatment of DLD is the lack of safe, tolerable, convenient, and effective treatments. Despite a large number of addressable patients with moderate-to-severe DLD, there is no FDA-approved treatment on the market for DLD. Some commonly used tools such as tinted glasses are not effective, and in fact, may worsen patients' vision at night. Off-label use of approved miotic agents, such as regular-strength pilocarpine, are unsuitable for the treatment of DLD because they reduce pupil size to a degree that may impede safe night vision and may cause loss of accommodation (Isopto prescribing information).

Phentolamine is a non-selective alpha-1 and alpha-2 adrenergic antagonist acting on adrenergic receptors and is known to inhibit contraction of the iris dilator muscle, resulting in a smaller pupil size.

Previous Phase 2 clinical trials showed that 1.0% Phentolamine Mesylate Ophthalmic Solution (0.75% Phentolamine Ophthalmic Solution) significantly decreases PD and improves mLCVA in DLD subjects after single- and multi-dose (14 days) treatment. Phentolamine Ophthalmic Solution was generally well-tolerated in the eye (the most common complaint was mild-to-moderate ocular hyperemia and eye irritation) and there were no clinically meaningful systemic effects as measured by HR and BP.

2.4 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 for one drop of Nyxol selected for this study, 0.75%, was based upon: 1) preclinical safety studies, 2) the results of the previous ophthalmic clinical studies described above and in the IB, and 3) clinical studies conducted with varying doses of drugs in the same class (Hogan, 1997).

Treatment (Nyxol or placebo) will be administered OU. Subjects will have one drop of treatment administered in each eye.

Note that 0.75% Phentolamine Ophthalmic Solution, which expresses the phentolamine mesylate concentration in free base, is the new nomenclature being used in place of 1% Phentolamine Mesylate Ophthalmic Solution, which was how Nyxol had been described in prior studies.

2.5 Compliance

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

2.6 Study Population

A sample size of approximately 160 DLD subjects ≥ 18 years of age will be randomized in a 1:1 ratio to 1 of 2 masked treatment arms (Nyxol or placebo), with the expectation that approximately 136 subjects will be evaluable for efficacy. Randomization will be stratified by iris color (light/dark irides; Appendix 1). The subjects will be recruited from approximately 15 investigational sites.

3 OBJECTIVES AND PURPOSE

The LYNX-1 study is a randomized, placebo-controlled, double-masked, multiple-dose study of the safety and efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) in subjects with DLD.

The objectives of this study are:

- To evaluate the efficacy of Nyxol to improve mLCVA in subjects with DLD
- To evaluate the efficacy of Nyxol to improve visual performance
- To evaluate the safety of Nyxol
- To evaluate any additional benefits of Nyxol in treating DLD subjects

The Sponsor intends to use this first Phase 3 registration study to evaluate Nyxol for the indication of [redacted]

4 STUDY DESIGN

4.1 Primary and Secondary Endpoints

Efficacy:

The primary efficacy endpoint is the percent of subjects with ≥ 15 ETDRS letters (≥ 3 lines) of improvement in the study eye compared to baseline in monocular mLCVA at Day 8.

The eye with the greatest mLCVA improvement [redacted] The study eye and non-study eye, as well as binocular, will both be evaluated at all appropriate assessments.

All treatments will be administered OU.

Secondary efficacy endpoints (for the study eye, the non-study eye, the best of either eye, and binocular) will include:

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

Exploratory efficacy endpoints (for the study eye, the non-study eye, the best of either eye, and binocular) will be collected and analyzed for the sites that have an OPD Scanner and will include but are not limited to:

- [redacted]

In addition, data captured by OPD Scan III per subject per applicable visit will be generated. These data include graphs, heatmaps, vision simulations, numerical data, point spread function, Zernike graphs, VA-ETDRS simulations, angle kappa, etc. Exploratory analyses may be completed using these data.

Measurements (Appendix 2):

- [redacted]

Safety:

The primary safety measures are conjunctival hyperemia and AEs.

Analysis for conjunctival hyperemia includes change from baseline (Day 1) in the conjunctival hyperemia grading scale (CCLRU images) at each visit (Day 8 and Day 15), for study eye and non-study eye. Any increase of 2 units in conjunctival hyperemia between consecutive visits is considered an AE.

Other safety measures include IOP, biomicroscopy, ophthalmoscopy, dry eye measurements, and systemic safety as measured by HR and BP. Urine pregnancy tests for females of childbearing potential will be conducted.

Subject questionnaire values will be summarized by treatment group and visits (Day 1, Day 8, and Day 15).

Measurements:

- Conjunctival hyperemia will be assessed visually with a grading scale (0-3) using images from the CCLRU.
- IOP will be measured with the Tono-Pen.
- BP and HR will be measured manually or with available digital devices.
- Subject questionnaire will be a brief symptom survey (Appendix 3).

4.2 Description and Schedule of Visits and Procedures

A sample size of approximately 160 DLD subjects ≥ 18 years of age will be randomized in a 1:1 ratio to 1 of 2 treatment arms (Nyxol or placebo), with the expectation that approximately 136 subjects will be evaluable for efficacy. Randomization will be stratified by iris color (light/dark irides). Study procedures are shown in detail in Table 2.

Table 2 Screening, Baseline, Treatment, and Follow-Up Visits and Procedures

	[redacted]
Day	
Visit	
Informed consent	
Subject ID number assigned	
Medical/ophthalmic history [b]	
Demographics	
Drug accountability and review of subject diary	
Concomitant medications [c]	
Urine pregnancy test [d]	
Heart rate/Blood pressure [e]	
[redacted]	
[redacted]	
[redacted]	

	Screening/Baseline [a]	Treatment	Treatment	TC Follow-Up
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		[redacted]	
Adverse events	X	X	X	X
Randomization number assigned	X			
Medications dispensed/Re-dispensed	X	X		
Diary dispensed/Re-dispensed	X	X		

Abbreviations: BAT, Brightness Acuity Tester; BCDVA, best-corrected distance visual acuity; CCLRU, Cornea and Contact Lens Research Unit; DCNVA, distance-corrected near visual acuity; mLCVA, mesopic low-contrast visual acuity

[redacted]

4.3 Measures Taken to Minimize/Avoid Bias

This is a placebo-controlled, double-masked, 1:1 randomized, 2-arm, Phase 3 study.

4.4 Study Medications

Study Medication Identification

Established name	Phentolamine mesylate – parent phentolamine
CAS registry number	65-28-1 – parent 50-60-2
Chemical class	An alpha-adrenergic antagonist, it is a member of the following classes: imidazoles, of phenols, is a tertiary amino compound and a substituted aniline
Chemical name	3-[N-(4,5-dihydro-1H-imidazol-2-ylmethyl)-4-methylanilino]phenol;methanesulfonic acid
Molecular formula	$C_{18}H_{23}N_3O_4S$ – parent $C_{17}H_{19}N_3O$
Molecular weight	377.140 – parent 281.352
Drug name/formulation	Nyxol / aqueous isotonic solution
Concentration active	1% – parent 0.75%
Manufacturer drug substance	[redacted]
Manufacturer drug product, placebo	[redacted]
Storage requirements	[redacted] Stored in a secured location (locked) with no access for unauthorized personnel at site

Formulation

Nyxol (0.75% Phentolamine Ophthalmic Solution) is a clear, colorless to slightly brown, sterile, non-preserved, isotonic, buffered aqueous solution containing 1% phentolamine mesylate (equivalent to 0.75% phentolamine free base), [redacted] Placebo for Nyxol is a clear, colorless, sterile, non-preserved, isotonic, buffered aqueous solution containing [redacted]. The pH of the study medications may be adjusted with [redacted] (United States Pharmacopeia [USP]) and/or [redacted] (USP) to [redacted]

4.4.1 Packaging and Labeling

The investigational products, active and placebo, are packaged in a unit-of-use 1 mL low-density polyethylene (LDPE) dropper bottles with a fill volume specification of 0.6 mL for single-dose investigational use. Each bottle is wrapped with an aluminum foil overwrap impermeable to water and oxygen and will be labeled with an investigational label showing the study protocol number 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 and Dispensing

Prior to dispensing, 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.

[redacted] medication must not be frozen and must

be protected from light. All investigational study medication must be stored in a secure facility, with access limited to the Investigator and authorized staff.

4.4.3 Study Medication Administration

Study medication will be dispensed by the Investigator or designee at the site on Visit 1 (Screening/Baseline).

The subject will instill one drop once daily (QD) at or near bedtime (8PM to 10PM) OU for 14 days (+ 1 day). The first dose of study medication will be taken at 8PM to 10PM on the evening of the Baseline Visit (Day 1). If the subject wears contact lenses, they must be removed prior to dosing and not replaced until the next morning at the earliest.

4.4.4 Study Medication Accountability

4.4.4.1 Receipt and Disposition of Study Medication

The Investigator or designee (e.g., study coordinator or pharmacist) shall 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 Visit 1 (Screening/Baseline; Day 1). As described in Section 7.2.1, the subject will empty any remaining contents from the unit-dose dropper bottle following each instillation. The subject should then empty the remaining contents and return the opened bottle to its foil pouch and place it in the medication box for return to the study site. All opened bottles as well as any unopened study medication will be returned at Visit 2 (Treatment; Day 8) and Visit 3 (Treatment; Day 15).

At Visit 2, the box will be re-dispensed to the subject following study drug accountability and removal of opened study medication materials. Study medication accountability shall again be conducted at Visit 3, but the box will not be re-dispensed. The Investigator or designee must 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.

4.4.4.2 Return of Study Medication

When the study is completed or is terminated by Ocuphire, all study materials, including used and unused study medication bottles, must 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 3 weeks, with 3 clinic visits and one telephone call follow-up summarized below:

- Visit 1 (Screening/Baseline)/Day 1
- Visit 2 (Treatment)/Day 8 (±1 day)
- Visit 3 (Treatment)/Day 15 (±1 day)
- Follow-up telephone call 1 to 3 days after Visit 3

The execution of the entire study (first subject screened through last randomized subject completed) is expected to be approximately 9 to 12 months.

4.6 Randomization and Procedure for Breaking the Code

A randomization code for allocating subjects to treatment will be prepared by a masked biostatistician not connected with the study. Subjects will be stratified by iris color (light/dark irides).

At the initiation of study-related procedures, every subject who is screened is assigned a ***subject identification number*** in numerical order within site. Once a subject is qualified for the study, the subject is assigned a ***randomization number*** in the order provided by the biostatistician.

The study medications will be masked to Investigators, study staff, study subjects, the clinical research organization (CRO), and Ocuphire. Only in case of medical emergency or occurrence of SAEs will the randomization code be unmasked by the Medical Monitor 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

Study-specific data that have been outlined in the protocol will be entered into the clinical database by individual(s) designated by the Investigator. Data are verified electronically using a series of online programmed edit checks that have been created by the Clinical Data Manager and programmed by the Clinical Data Programmer or designee. Data discrepancies will be brought to the attention of the clinical team and investigated by the study monitor and site staff. Study monitors will review and verify a targeted subset of data collected in the electronic Case Report Form (eCRF) against any applicable source documentation during remote review or scheduled monitoring visits. The specific data selected for source data verification will be detailed in Clinical Monitoring Plan. The study monitor will work closely with the site staff to address any discrepancies that have been found so that proper resolutions can be made and documented in the clinical database. An audit trail within the system will track all changes made to the data.

4.8 Completed Subject

A completed subject is defined as one who completes all planned procedures through the end of Visit 3.

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:** AEs include clinically significant laboratory abnormalities and intercurrent diseases reported by the subject or observed by the Investigator with documentation on the eCRF.
- **Death:** If a subject dies, the AE that caused the death should be documented on the eCRF 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 eCRF.

The reason for premature study medication discontinuation should be entered onto the appropriate eCRF.

4.9.2 Reasons for Withdrawal From Study

- Subject withdraws consent.
- 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 Ocuphire. Prompt, written notice of reasonable cause to the other party (Ocuphire or Investigators, respectively) is required. Prompt notice to the Institutional Review Board (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 medical assessments 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 the Day 8 Visit 2 mLCVA and other measurements are assessed prior to discontinuation, in addition to a follow-up telephone call that includes assessments for AEs, concomitant medications, and subject-evaluated conjunctival hyperemia.

4.10 Completed Study

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

4.11 Procedure After the Completion of the Study

When the study is completed, the CRO will provide Ocuphire and the Investigator with a brief (i.e., 1-3 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 AEs.

5 SUBJECT INCLUSION AND EXCLUSION CRITERIA

5.1 Subject Inclusion Criteria

1. Males or females ≥ 18 years of age
2. Subject-reported DLD (likely subjects with a history of multifocal IOLs, post–laser-assisted in situ keratomileusis [LASIK], corneal scars, and keratoconus)
3. Ability to comply with all protocol-mandated procedures independently and to attend all scheduled office visits
4. Otherwise healthy and well-controlled subjects
5. Able and willing to give written consent to participate in this study
6. Able to self-administer study medication
7. [redacted]
8. ≤ 30 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/63 Snellen or worse) in mLCVA score in at least one eye using the [redacted]
9. [redacted]

5.2 Subject Exclusion Criteria

Excluded from the study will be individuals with the following characteristics:

Ophthalmic (in either eye):

1. Prior unresolved dry eye diagnosis, taking prescription drops for dry eye, or taking artificial tear drops routinely for dry eye
2. Prior history of fluctuating vision
3. Clinically significant ocular disease as deemed by the Investigator (e.g., untreated cataract, glaucoma, corneal edema, uveitis, severe keratoconjunctivitis sicca, retina degeneration, loss of visual field due to glaucoma or stroke, branch retinal vein occlusion, retina flare) that might interfere with the study
4. Known hypersensitivity to any topical alpha-adrenoceptor antagonists
5. Known allergy or contraindication to any component of the vehicle formulation
6. History of cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal
7. Ocular trauma, ocular surgery (e.g., IOLs), or laser procedure (e.g., LASIK, photorefractive keratectomy [PRK]) within 6 months prior to screening

8. Use of any topical prescription or over-the-counter (OTC) ophthalmic medications of any kind (including artificial tear drops) within 7 days of screening until study completion, with the exception of lid scrubs with OTC products (e.g., OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.)
9. Recent or current evidence of ocular infection or inflammation in either eye (such as current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at screening in either eye). Subjects must be symptom free for at least 7 days.
10. History of diabetic retinopathy, diabetic macular edema, or dry or wet macular degeneration
11. History of any traumatic (surgical or nonsurgical) or non-traumatic condition affecting the pupil or iris (e.g., irregularly shaped pupil, neurogenic pupil disorder, iris atrophy, iridotomy, iridectomy, etc.)
12. Unwilling or unable to discontinue use of contact lenses on their scheduled visits at least 1 hour for soft contact lenses and at least 8 hours for hard gas-permeable contact lenses before ophthalmic assessments at screening, and at least 8 hours (for both types of lenses) before Day 8 and Day 15
13. People with undiagnosed dry eye, at the determination of the Investigator. Dry eye evaluation should be based on one of the following dry eye tests:
    a. TearLabs osmolarity test (> 308 mOsm/L in either eye or an inter-eye difference ≥ 10 mOsm/L)
    b. Corneal fluorescein staining (≥ grade 2 in the inferior or ≥ grade 1 in the central zone using the National Eye Institute scale)
    c. Tear break-up time of < 5 seconds

Systemic:

1. Known hypersensitivity or contraindication to alpha- and/or beta-adrenoceptor antagonists (e.g., chronic obstructive pulmonary disease or bronchial asthma; abnormally low BP or HR; second- or third-degree heart blockage or congestive heart failure [CHF]); severe diabetes as described below)
    a. Predisposition to severe hypoglycemia (2 or more serious hypoglycemic episodes requiring assistance within the past year)
    b. Any hospitalization or emergency room visit due to poor diabetic control within the past 6 months
    c. Currently untreated diabetes mellitus or previously untreated subjects who initiated oral anti-diabetic medication or insulin within 3 months prior to Day 1
    d. Any sign of diabetic retinopathy in either eye
    e. Uncontrolled diabetes mellitus defined by Hemoglobin A1c > 12% taken within the last 3 months

2. Clinically significant systemic disease (e.g., severe diabetes as previously defined, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere with the study
3. Initiation of treatment with or any changes to the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs within 7 days prior to screening or during the study (Appendix 4)
4. Participation in any investigational study within 30 days prior to screening and during the study
5. Females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods include the use of at least one of the following: intrauterine device (IUD), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. A female is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential including those with post-tubal ligation must have a negative urine pregnancy test result at Visit 1 (Screening/Baseline), Visit 2 (Treatment), and Visit 3 (Treatment) examinations and must intend to not become pregnant during the study
6. Resting HR outside the specified range (50–110 beats per minute) at Visit 1 (Screening/Baseline). HR may be repeated **only once** if outside the specified range following at least a 5-minute rest period in the sitting position
7. Hypertension with resting diastolic BP > 105 mmHg or systolic BP > 160 mmHg at Visit 1 (Screening/Baseline). BP may be repeated **only once** if outside the specified range following at least a 5-minute rest period in the sitting position

6 TREATMENT OF SUBJECTS

Approximately 160 DLD subjects ≥18 years of age will be randomized in a 1:1 ratio to 1 of 2 treatment arms (Nyxol or placebo), with the expectation that approximately 136 subjects will be evaluable for efficacy. Randomization will be stratified [redacted]. There will be no treatment administered on Visit 4 (follow-up phone call).

6.1 Treatment Adherence

All subjects must be instructed on the importance of following the once-daily dosing regimen and maintaining their dosing diaries. Beginning the day of Visit 1 (Screening/Baseline; Day 1) subjects will instill one drop of study medication in the evening (at 8PM to 10PM) at or near bedtime OU. Subjects will repeat this instillation, using one bottle per day, 13 or 14 more times for a total of up to 15 doses over the course of the study. Subjects are to bring all opened bottles as well as any unopened study medication into the study site at Visit 2 and Visit 3. Treatment adherence will be measured by counting the dropper bottles at the start of the study and those remaining at each study visit. Subjects will also bring their diary to Visit 2 and Visit 3 and dosing will be reviewed by study staff.

6.2 Concomitant Medications

As noted in the exclusion criteria (Section 5.1), use of any topical prescription or OTC ophthalmic medications of any kind within 7 days of screening, with the exception of lid scrubs with OTC products (e.g., OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.), is prohibited. Many drugs, both prescription and OTC, contain active ingredients that can affect PD. 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 BP medications, many drugs used for migraines, and many other products.

Additionally, initiation of treatment with or any changes to the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs (Appendix 4) within 7 days prior to screening, or during the study, is prohibited. However, a subject can be treated with a systemic adrenoceptor antagonist, for example, as long as the particular agent and its dose and regimen had been consistent for the 7 days prior to screening, and there was no reason to believe that alteration would be necessary at some point later during the study.

If there is any question about whether a medication is acceptable, the Medical Monitor should be consulted before proceeding.

Use of all medications shall be documented on the appropriate eCRF. Investigators are encouraged to contact 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 taken by the subject within 30 days prior to the Screening Visit and during the study will be recorded in the eCRF. 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®, Cosopt®), 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 should be documented. Any change in dosing parameters should also be recorded in the eCRF.

7 ASSESSMENT OF EFFICACY

7.1 Specification of the Efficacy Parameters

The primary efficacy endpoint is the percent of subjects with ≥ 15 ETDRS letters (≥ 3 lines) of improvement in the study eye compared to baseline in monocular mLCVA at Day 8.

[redacted]The study eye and non-study eye, as well as binocular, will be evaluated at all appropriate assessments. Secondary efficacy endpoints can be found in Section 4.1.

All of the efficacy endpoints will be analyzed overall, and by light/dark irides at all timepoints. The mLCVA endpoints will be analyzed by baseline PD [redacted]) and [redacted] subpoint.

7.2 Assessing, Recording, and Analyzing Efficacy Parameters

VA, PD, and wavefront error (total and higher order) will be measured at Visit 1 (Screening/Baseline), Visit 2 (Treatment), and Visit 3 (Treatment) as described in Section 4.1.

[redacted] to the set of PD, BCDVA, DCNVA, and wavefront error measurements). Subject will sit in the exam chair facing directly at the illuminated chart during the acclimation period and for all assessments. Room lights may be turned on for the scheduled remaining safety assessments (e.g., conjunctival hyperemia, AEs, subject questionnaire, etc.). The subject will be in the same room for all assessments, and every effort will be made to have the same person perform the measurements at all visits.

7.2.1 Visit 1 (Screening/Baseline)/Day 1

Individuals who are potential subjects are identified by the study center to schedule the Screening Visit. The Screening Visit should occur the same day as the Baseline Visit, where the dose of study treatment is given.

Once a subject arrives 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, the informed consent form is signed, and a subject identification number is assigned.

If the subject wears soft contact lenses, they must be removed for at least 1 hour prior to ophthalmic assessments. If the subject wears hard gas-permeable contact lenses, they must be removed for at least 8 hours prior to testing.

The start of screening includes an explanation of the study, a medical and ophthalmic history, demographics, and a review of prior/concomitant medications. During this time, eligibility for [redacted] must be determined first. Then, ophthalmic and non-ophthalmic criteria ([redacted]) shall be determined and only eligible subjects will continue. This shall be followed by a urine pregnancy test for females of childbearing potential [redacted] and HR/BP ([redacted]).

Prior to further screening, the subject must be asked to complete the subject questionnaire. Subjects should then have their refraction confirmed using the High contrast distance chart as detailed in the Study Procedures Manual. Following a [redacted], subjects shall be assessed in each eye for PD and for mLCVA before and during illumination of the [redacted] ([redacted]

[redacted] OD shall be the study eye. Investigators should frequently remind subjects to blink between visual acuity assessments.

The study eye of the subject must meet [redacted] in order for the subject to not screen fail.

Before further screening criteria, the following assessments shall be performed to establish baseline values:

- mHCVA, pLCVA, and mesopic high-contrast DCNVA
- [redacted] corneal topography measurements under [redacted], and other data captured
- Conjunctival hyperemia, assessed visually with a grading scale (0–3) using images from the CCLRU (Investigators are cautioned to appropriately note all observations of conjunctival hyperemia on the biomicroscopy eCRF at screening)
- Slit lamp biomicroscopy

The subject must also meet dry eye Exclusion Criterion #13 to be included in the study at the determination of the investigator. Specifically, subjects with undiagnosed dry eye may undergo a dry eye test (one of the below):

a. TearLabs osmolarity test (> 308 mOsm/L in either eye or an inter-eye difference ≥ 10 mOsm/L)
b. Corneal fluorescein staining (≥ grade 2 in the inferior or ≥ grade 1 in the central zone using the National Eye Institute scale)
c. Tear break-up time of < 5 seconds

Final screening must include IOP measurement (using a Tono-Pen) and ophthalmoscopy.

With the subject passing all eligibility criteria, the Screening Visit becomes the Baseline Visit. The subject will then be assigned a randomization number and randomized into the study.

Through the screening process at Visit 1, all assessments will have been completed as defined in Table 2. A summary of the screening process is outlined in Appendix 5.

If the subject meets all eligibility criteria, they will be randomized to a treatment group. If a subject fails the screen, they can return for a rescreening (signing a new informed consent and assigning a new subject number) at the investigator's discretion.

Site personnel will then demonstrate the proper instillation technique to the subject. The subject at home 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 medication dropper bottles in a kit and instructions regarding when to administer the eye drop (8PM to 10PM QD), and when to return to the clinic. All treatments will be administered OU.

[redacted]

The first dose of study medication will be taken at 8PM to 10PM on the evening of the Baseline Visit (Day 1). If the subject wears contact lenses, they must be removed prior to dosing and not replaced until the next morning at the earliest.

Each subsequent evening of dosing, the subject will administer 1 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 foil pouch and place it in the medication box for return to the study site at Visit 2 (Day 8). Each subsequent evening of dosing (approximately 24 hours between doses), the subject will follow the same procedures.

The subject should be instructed to contact the Investigator should AEs 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.

7.2.2 Visit 2 (Treatment)/Day 8 (± 1 day)

If the subject wears contact lenses, [redacted] prior to ophthalmic assessments. At Visit 2, the medication box, complete with opened bottles and any unopened study medication, and diary will be returned to the study site where the site will account for opened and unopened study medication and 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 since the last visit, 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 are recorded as an AE.***

In addition, at Visit 2 subjects shall have the following assessments, as defined in Table 2:

- Females of childbearing potential must take a urine pregnancy test.
- Subject must have HR and BP assessments.
- Subject shall be assessed using the subject questionnaire.
- Pupil diameter
- Subject shall be assessed for mLCVA, mHCVA, pLCVA and DCNVA (mesopic, high-contrast conditions) as mentioned in Section 4.1.
- OPD Scan measurements (for those sites with OPD Scan III), wavefront aberrometry (total and higher-order RMS) and corneal topography measurements under mesopic conditions, and other data captured
- Eye redness (conjunctival hyperemia) will be assessed visually with a grading scale (0-3) using images from the CCLRU.
- Subject will have an IOP assessment.

7.2.3 Visit 3 (Treatment)/Day 15 (± 1 day)

During the second week of treatment, subjects will continue to administer 1 drop of study medication OU every night using a new bottle for each dose, then emptying the remaining contents of that bottle, return the opened bottle to its foil pouch and place it in the medication box for return to the study site at their next visit.

If the subject wears contact lenses, they must be removed for a minimum of 8 hours prior to ophthalmic assessments. At Visit 3, the subject will bring their used dropper bottles with any unused medications and diary with them for purposes of drug accountability. The last day of study treatment is the day before Visit 3; no further study medication will be dispensed at Visit 3.

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 adverse changes in the condition of the subject are recorded as an AE.***

In addition, at Visit 3 subjects will have the following assessments, as defined in Table 2:

- Females of childbearing potential must take a urine pregnancy test.
- Subject must have HR and BP assessments.
- Subject shall be assessed using the subject questionnaire.
- Pupil diameter
- Subject shall be assessed for mLCVA, mHCVA, pLCVA, and DCNVA (mesopic, high-contrast conditions) as mentioned in Section 4.1.
- OPD Scan measurements (for those sites with OPD Scan III), wavefront aberrometry (total and higher-order RMS) and corneal topography measurements under mesopic conditions, and other data captured
- Eye redness (conjunctival hyperemia) shall be assessed visually with a grading scale (0-3) using images from the CCLRU.
- Subject shall be assessed using biomicroscopy.
- Subject must have an IOP assessment.
- Subject shall be assessed using ophthalmoscopy.

7.2.4 Follow-Up Phone Call Visit 4

Up to 3 days after Visit 3, 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 AE.***

If an AE/adverse 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 AE/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

7.2.5 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 AEs in the eCRF.

As noted in Section 4.9.4, every possible effort should be made by Investigators to assure that subjects who discontinue early from the study have a telephone follow-up that includes assessments of AEs, concomitant medications, and subject-evaluated conjunctival hyperemia.

7.2.6 Visit Variation

Visit 2 on Day 8 and Visit 3 on Day 15 may each be 1 day late. If the visit is late, the subject should be advised to take an additional dose from 1 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 return the opened bottle to its foil pouch and place it in the medication box for return to the study site at their next visit. The follow-up telephone call may occur up to 3 days after Visit 3.

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 CCLRU images using a 4-point scale (0-3) (Appendix 6).
    - None (0) = Normal; appears white with a small number of conjunctival blood vessel easily observed
    - Mild (+1) = Prominent, pinkish-red color of both the bulbar and palpebral conjunctiva
    - Moderate (+2) = Bright, scarlet red color of the bulbar and palpebral conjunctiva
    - Severe (+3) = Beefy red with petechiae, dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage
- Biomicroscopy of the anterior segment includes evaluation of cornea, conjunctiva, and anterior chamber. Fluorescein staining will be used.
- IOP is measured with the Tono-Pen.
- Ophthalmoscopy direct or indirect fundus exam without dilation includes optic nerve, macula, vessels, and periphery (note: Use of 90 D lens (indirect) is allowed).
- HR and BP are measured as per the site's normal equipment and procedures.
- AEs
- Brief subject questionnaire (Appendix 3)

8.2 Assessing, Recording, and Analyzing Safety Parameters

The timing for recording safety parameters may be found in Table 2.

8.3 Adverse Events and Serious 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 eCRF page. Only treatment-emergent adverse events/adverse reactions (TEAEs) will be summarized (Section 9.3.5).

All AEs/adverse reactions occurring during the study (i.e., once the subject has signed the informed consent/assent) **must** be documented, regardless of the assumption of causal relationship, on the respective eCRF. All TEAEs/adverse reactions must be documented from the time the subject receives the study medication until the subject's participation in the study has been completed. If a subject has ongoing AEs/adverse reactions at the time of study completion or discontinuation from the study, the ongoing AEs/adverse reactions **must** be followed-up and provided appropriate medical care until the signs and symptoms

have remitted or stabilized or until medical assessments have returned to acceptable or pre-study limits.

Documentation of AEs/adverse reactions includes start date and end date, severity, relationship to study medications, action(s) taken, seriousness, and outcome.

8.3.1 Adverse Event Definitions

The following definitions of terms apply to this section:

Adverse event. An AE is any untoward medical occurrence associated with the use of a study medication in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporarily associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational drug under evaluation and the comparator product or vehicle placebo that is given or administered during any phase of the study.

Medical conditions/diseases present before starting the investigational treatment are only considered AEs if they worsen after starting the investigational treatment. Abnormal test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by open-ended questioning of the subject at each visit during the study. At each clinic assessment/visit, study personnel should ask the following question: “Have you had any problems since your last assessment/visit?”. AEs also may be detected when they are volunteered by the subject during or between visits or through study assessments.

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

SAE or serious suspected adverse reaction. An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or Ocuphire, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

- Other medically important serious event

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 and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that is unrelated to the medication under study and has not worsened since the start of the study, is not considered an SAE.

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

Unexpected adverse event or unexpected suspected adverse reaction. An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB 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 AEs or suspected adverse reactions that are mentioned in the IB 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.

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

- Not related
- Unlikely related
- Possibly related
- Probably related
- Definitely related
- Unknown

Unless the relationship is considered to be "Not related" or "Unlikely related" and there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study medication and the occurrence of the AE, then the AE should be considered "related".

If the relationship between the AE/SAE and the investigational product is determined by Ocuphire to be anything other than "Not related" or "Unlikely related" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Severity of an AE is defined as a qualitative assessment of the level of discomfort of an AE as is determined by the Investigator or reported to him/her by the subject. The assessment of severity 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 an end date for the previous severity and a new start and end 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 end times/dates should be recorded.

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

Action taken in response to an AE is coded as:

- Dose increased: An indication that a medication schedule was modified by addition; either by changing the frequency, strength, or amount.
- Dose not changed: An indication that a medication schedule was maintained.
- Dose reduced: An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
- Dose interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
- Not applicable: Determination of a value is not relevant in the current context
- Unknown: Not known, not observed, not recorded, or refused

Additional other action taken:

- Concomitant medication
- Hospitalization

Outcome of an AE is coded as:

- Fatal: The termination of life as a result of an AE
- Not recovered/not resolved: One of the possible results of an AE outcome that indicates that the event has not improved or the subject recuperated
- Recovered/resolved: One of the possible results of an AE outcome that indicates that the event has improved or the subject has recuperated
- Recovered/resolved with sequelae: One of the possible results of an AE outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury
- Recovering/resolving: One of the possible results of an AE outcome that indicates that the event is improving
- Unknown: Not known, not observed, not recorded, or refused

In previous clinical studies of Nyxol, the most frequently reported AE was conjunctival hyperemia.

In the present study, any increase of 2 units in conjunctival hyperemia between consecutive visits is considered an AE.

Investigators are cautioned to use the appropriate verbatim term on the AE 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”

Expedited reporting of Serious and Unexpected Adverse Events: All SAEs (related and unrelated) will be recorded following subject signature of the informed consent/assent and until the Follow-up Visit. Any SAEs “suspected” to be related to the study medication and discovered by the Investigator at any time **after** the study should be reported.

Any SAE that occurs must be reported to the CRO 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 the CRO 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 [redacted] The Investigator must assess the SAE relationship and complete the SAE form. The CRO 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 [redacted] In addition, all SAEs should be recorded on the AE eCRF 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 Ocuphire following Ocuphire'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. Ocuphire will report all SAEs to the 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 IB).

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 medication, the SAE resulting in the death must be reported to the CRO. A death occurring after completion of the study, including the Safety Follow-up Visits, that is not reasonably associated with study medication administration does not require completion of the SAE form.

8.3.2 Follow-Up of Subjects After Adverse Events

If an AE/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. All SAEs ongoing at the time of the last visit or discontinuation from the study will be followed up until the AE/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 approximately 136 subjects (68 per treatment group) that are evaluable for efficacy (i.e. who have a Day 8 mLCVA measurement) is needed for the study.

[redacted]

All subjects will be randomized into the study in a 1:1 ratio to 1 of the 2 treatment arms (Nyxol or placebo), [redacted]

It is assumed that there will be approximately 15% drop-out. To account for this drop-out, a total of approximately 160 subjects will be randomized into the study.

9.2 Analysis Populations

Modified Intention-to-Treat: The mITT will include all randomized subjects who received at least 1 dose of study medication. The mITT will be used for the primary endpoint analysis and to analyze efficacy endpoints.

Per Protocol Population: The PP population includes all subjects in the mITT who received at least 5 doses of study medication during the first 7 days of dosing including the day prior to Day 8, have a Baseline and a Day 8 mLCVA measurement, and have no major protocol deviations. The PP population will be used to analyze efficacy endpoints.

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

Safety Population (SP): The SP will include all randomized subjects who have received at least 1 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). The p-values for the analysis of secondary efficacy endpoints will be considered descriptive.

9.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, race, and sex will be summarized by treatment group using the mITT, PP population, ARP, and the SP. 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 ARP. 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 SP.

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 World Health Organization Drug Dictionary and will both be summarized by treatment group using the SP.

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 mITT and PP population with subjects included in the treatment arm in which they were randomized. For the analysis of the primary efficacy endpoint, appropriate imputation techniques will be performed for missing observations if applicable; details will be provided in the study Statistical Analysis Plan. If the analysis using the PP population shows a positive effect for Nyxol at the 0.05 level of significance, the primary endpoint will be considered met. Confirmatory analyses may be performed using the ARP, 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 ARP with imputation for missing data will also be performed for the secondary efficacy endpoints.

For all efficacy endpoints, Baseline values are defined as the screening assessment values on Visit 1 (Day 1).

[redacted]

Secondary efficacy endpoints are indicated in Section 4.1.

Each of the continuous secondary efficacy endpoints will be analyzed using analysis of covariance (ANCOVA) with change from baseline as the dependent variable, treatment, [redacted], and the respective baseline value included as the covariate. Each ANCOVA will be performed using the mITT and PP population, with subjects included in their randomized treatment regardless of the treatment they actually received. The output from each ANCOVA will include the least squares mean (LSM) and standard error for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

For each of the secondary endpoints related to percent of subjects achieving certain criteria, the analysis will be performed using a logistic regression model with treatment, light/dark irides, and the respective baseline as a covariate. For each analysis, the percentage of subjects in each treatment group meeting the criteria, the OR with 95% CI and p-value will be provided. For these endpoints, the mITT and PP population will be used with subjects included in their randomized treatment regardless of the treatment they actually received.

In addition, each secondary efficacy endpoint will be analyzed[redacted] using the same model and sensitivity analysis indicated above, as appropriate. Other subgroups, such as age, sex, and race, may be analyzed as well.

9.3.6 Analysis of Safety

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. A statistical analysis of conjunctival hyperemia will be conducted as described below; otherwise, no statistical analysis of safety data will be performed.

For HR and BP, baseline value is defined as the screening value. HR and BP values and change from baseline in the values will be summarized by treatment group and timepoint (Day 1, Day 8, and Day 15).

Observed values and change from baseline (Day 1) in conjunctival hyperemia at each visit (Day 8 and Day 15), will be summarized for the study eye, the non-study eye, and the best of either eye. Treatments will be compared using the same ANCOVA model proposed for the continuous secondary efficacy endpoints.

For IOP, baseline is defined as the baseline value of Visit 1 (Day 1). Observed values and change from baseline in IOP at Day 8 and Day 15 will be summarized for the study eye, the non-study eye, and the best of either eye.

Subject questionnaire values will be summarized by treatment group and timepoint (Day 1, Day 8, and Day 15).

Verbatim descriptions of AEs will be coded using MedDRA. Only 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 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 AEs.

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. As appropriate, confirmatory efficacy analyses will be performed using imputation for missing data; details of the imputation, if performed, 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.

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 onsite, written, and telephone communications between personnel at the Investigator's site and the Medical Monitor. Should the COVID-19 pandemic restrict monitors from traveling to a site, remote review will be conducted to the extent possible, while still ensuring the study is monitored appropriately per applicable regulations and guidelines. The Investigator will allow Ocuphire, the Study Monitor, and the Medical Monitor to inspect all eCRFs, subject records (source documents), signed consent/assent 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 IRBs, the Helsinki Declaration, US FDA Law, International Council for Harmonisation (ICH) GCP guidelines, obtaining prospective informed consent, monitoring of the conduct of the study and the completeness of the eCRFs by Ocuphire or its designee(s), and appropriate record retention by the Investigator.

12.2 Institutional Review Board

This protocol, materials used to recruit subjects, and materials used to document consent/assent must be approved by the IRB prior to initiation of the study. Written IRB approval must adequately identify the protocol and informed consent/assent. In addition to approving the protocol, the IRB must also approve the Subject Information and Consent/Assent/Parental Consent Form, as well as any advertising tools that will be used for the study. 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

The Investigator should not deviate from the requirements of this protocol without prior written approval of the Medical Monitor or Sponsor except in the event of a medical emergency.

A reportable protocol deviation is defined as nonadherence to the protocol that involves inclusion/exclusion criteria, affects subject safety, rights or welfare, or has the potential to affect the integrity of the data. Examples of major protocol deviations include study enrollment by ineligible subject, loss of key data such as equipment malfunction (e.g., pupillometer), and/or use of a prohibited medication during the study.

All protocol deviations will be reported by entering the event in the appropriate eCRF page. Protocol deviations should be reported to the IRB in accordance with IRB-specific guidelines. If there is any question as to whether the deviation is reportable, Ocuphire or designee and the IRB should be contacted.

All changes to the protocol will be made by the Sponsor or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation.

Changes implemented without prior approval will be considered protocol violations.

12.4 Informed Consent and Assent Requirements

Written informed consent will be obtained from each adult subject. A copy of the signed and dated consent/assent document will be given to each subject or parent guardian. The

original signed and dated informed consent/assent 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/assent. The subject must give written consent/assent 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/assent 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/assent may not be included or continued in this study, but this will not impact 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/assent document will be given to each subject. The original signed and dated informed consent/assent document must be maintained in the study files at the Investigator's site. Signed informed consent/assent 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 US FDA guidelines for the handling and analysis of data for clinical trials.

13.1 Data Entry

Study-specific data that have been outlined in the protocol will be entered into the clinical database by individual(s) designated by the Investigator.

13.2 Data Quality Control and Reporting

Data are verified electronically using a series of programmed edit checks that have been created by the Clinical Data Manager and programmed by the Clinical Data Programmer or designee. Data discrepancies will be brought to the attention of the clinical team and investigated by the clinical research associate (CRA) and site staff. CRAs will review and verify a targeted subset of data collected in the eCRF against source documentation during remote review or scheduled monitoring visits. The specific data selected for source data verification will be detailed in Clinical Monitoring Plan. The CRA will work closely with the site staff to address any discrepancies that have been found so that proper resolutions can be made and documented in the clinical database. An audit trail within the system will track all changes made to the data.

13.3 Archiving of Data

Archived versions of the database will be saved by Ocuphire consistent with ICH GCP 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 GCP 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, change of telephone number).

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

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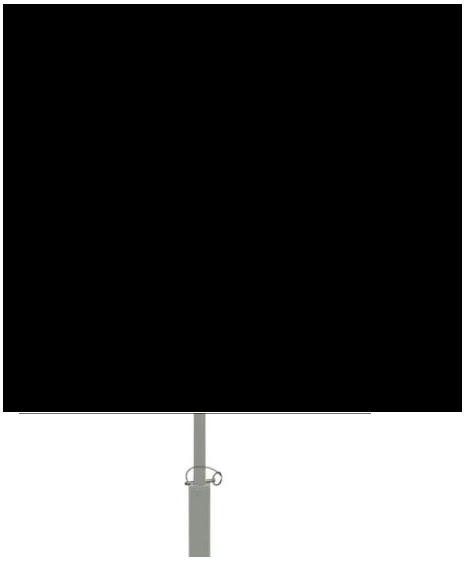
APPENDIX 1: IRIS COLOR CHART

Study enrollment includes both light and dark-colored eyes**.** Examples of [redacted]) and [redacted] for the purposes of this study are detailed in the chart below.

[redacted]

APPENDIX 2: VISUAL ACUITY CHARTS

BCDVA (distance) will be measured with a Standard [redacted]



Distance High-Contrast Chart

[redacted]

[redacted]

[redacted]

Distance Low-Contrast Chart

DCNVA will be measured under [redacted] (letters recorded, later converted to logMAR and number of lines).

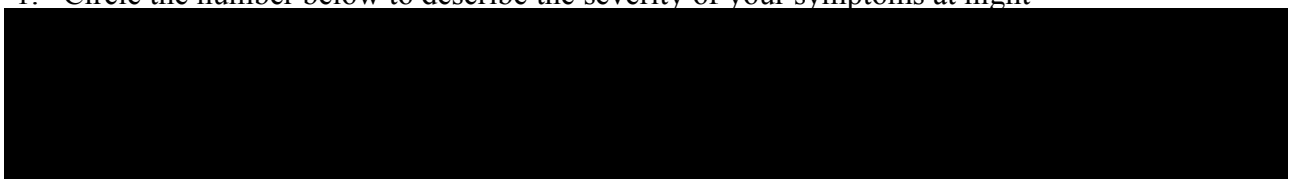
Near High-Contrast Chart

APPENDIX 3: SUBJECT QUESTIONNAIRE

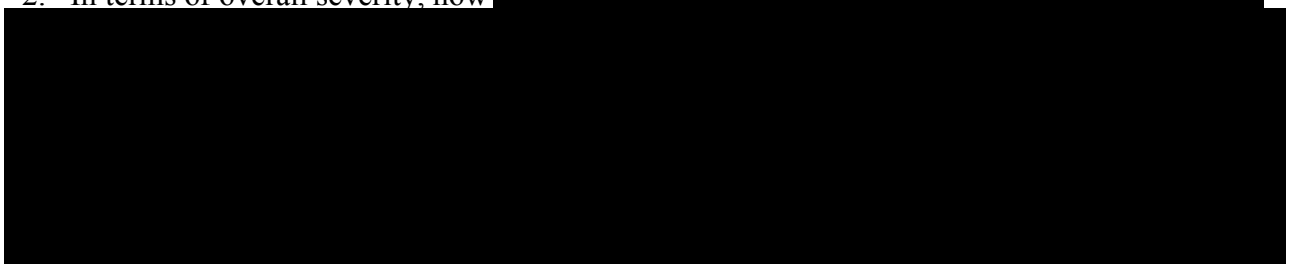
Please use the pictures below to answer the questions in the following table.

Representative Images of Dim Light Disturbances

1. Circle the number below to describe the severity of your symptoms at night



2. In terms of overall severity, how



3. Please circle all of the statements below that apply to your level of avoiding driving at night due to dim light vision disturbances?

D. I only drive at night when I know the exact routes
E. Occasionally I miss a social outing because it would require me to drive at night
F. I have no problems when I drive at night

4. For the following statements, **circle the number to indicate to what extent does dim light vision disturbance impact your day-to-day life.**

[redacted]

5. **I am satisfied with my night vision at the moment.**

[redacted]

6. **My night vision has improved.** [redacted]

7. **My night vision is 100% back to normal.**

[redacted]

8. Please indicate the [redacted])

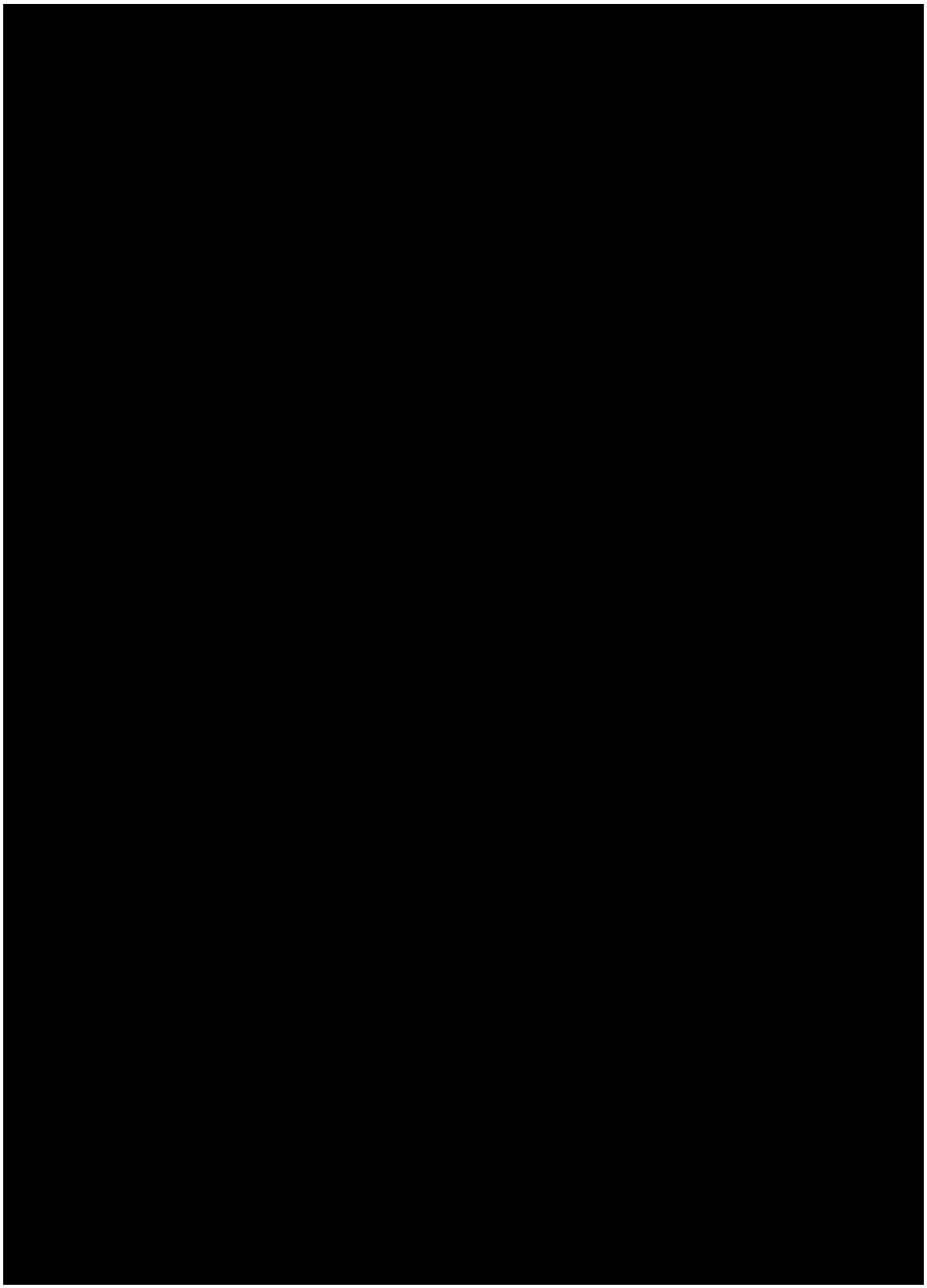
[redacted]

APPENDIX 4: ADRENERGIC AND CHOLINERGIC DRUGS

The following drugs are examples of drugs which cannot be used within 7 days prior to screening, or during the study unless the drug, dose and regimen has been consistent for the 7 days prior to screening. ***This list is not inclusive of all drugs in these classes. If there is any doubt, please consult with the Medical Monitor.***

Alpha-1-agonists Methyl norepinephrine Naphazoline Oxymetazoline Tetrahydrozoline Phenylephrine Xylometazoline ***Alpha-2-agonists*** Brimonidine Clonidine Guanfacine Guanabenz Guanoxabenz Guanethidine Xylazine Tizanidine Methyldopa	***Non-selective alpha-antagonists*** Phenoxybenzamine Tolazoline Labetalol Carvedilol ***Alpha-1-antagonists*** Alfuzosin Prazosin Doxazosin Tamsulosin Terazosin ***Alpha-2-antagonists*** Atipamezole Idazoxan Yohimbine	***Acetylcholine receptor agonists*** Pilocarpine (M_3 receptors) ***Acetylcholine receptor antagonists*** Scopolamine Dicycloverine Tolterodine Oxybutynin Ipratropium Mamba Toxin (MT_7) Pirenzepine Telenzepine ***Antivertigo*** meclizine Scopolamine	***Gastrointestinal*** atropine belladonna ***Parkinsonism*** amantadine benztropine biperiden trihexyphenidyl

APPENDIX 5: SCREENING PROCESS FOR INCLUSION/EXCLUSION CRITERIA



APPENDIX 6: CONJUNCTIVAL HYPEREMIA GRADING SCALE USING IMAGES FROM CCLRU