CONFIDENTIAL

Clinical Study Phase 2 Protocol
OPI-NYXRM-201
MIRA-1

Randomized, Cross-Over, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution to Reverse Pharmacologically Induced Mydriasis in Normal Healthy Subjects

Ocuphire Pharma, Inc.

[redacted]

Version: **02**

Original: **June 30th, 2019**

Amendment 1: **July 24, 2019**

SPONSOR SIGNATURE & CONTACTS

Study Title:	Randomized, Cross-Over, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution to Reverse Pharmacologically Induced Mydriasis in Normal Healthy Subjects
Study Number:	OPI-NYXRM-201
Original Protocol:	June 30th, 2019
Amendment 1:	July 24th, 2019

[redacted]

Medical Monitor

[redacted]

INVESTIGATOR'S AGREEMENT

OPI-NYXRM-201

MIRA-1

Randomized, Cross-Over, Double-Masked Placebo-Controlled Study of the Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution to Reverse Pharmacologically Induced Mydriasis in Normal Healthy Subjects

Version: **02**

Original: **June 30, 2019**

Amendment 1: **July 24, 2019**

Investigator Agreement:

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

Signature: _____ Date: _____

Printed Name: _____

PROCEDURES IN CASE OF EMERGENCY

EMERGENCY CONTACT INFORMATION

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

ABBREVIATIONS AND TERMS

Abbreviation	*Full term*
AE	Adverse Event
ANCOVA	Analysis of Covariance
ARP	All Randomized Population
BCDVA	Best Corrected Distance Visual Acuity
BP	Blood Pressure
°C	Degree Centigrade
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
°F	Degree Fahrenheit
DB	Database
DCNVA	Distance Corrected Near Visual Acuity
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart Rate
IB	Investigators' Brochure
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
IOP	Intra-Ocular Pressure
IRB	Institutional Review Board

ITT	Intent-To-Treat
IUD	Intra-Uterine Device
LSM	Least Squares Mean
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Nyxol	Phentolamine Mesylate Ophthalmic Solution 1% (Nyxol®)
OR	Odds Ratio
OTC	Over The Counter
OU	Oculus Uterque (both eyes)
PD	Pupil Diameter
SAE	Serious Adverse Event
SE	Standard Error
SOC	System Organ Class
SP	Safety Population
TEAE	Treatment Emergent Adverse Event
US	United States
VA	Visual Acuity

1. STUDY SUMMARY

Study Number	**OPI-NYXRM-201**
Clinical Phase	Phase 2b
Type of Study	Randomized, cross-over, double-masked, placebo-controlled study of the safety and efficacy of phentolamine mesylate ophthalmic solution to reverse pharmacologically induced mydriasis in normal healthy subjects
Name of Investigational Product	Nyxol® Eye Drops - 1% Phentolamine Mesylate ophthalmic solution (Nyxol)
Duration of Study	Up to 10 days, including screening and treatment
Rationale	Phentolamine mesylate is a non-selective alpha-1 and alpha-2 adrenergic antagonist that acts on the adrenergic receptors and inhibits contraction of the smooth muscle. Phentolamine mesylate inhibits contraction of the iris dilator muscle, resulting in a smaller pupil size. Pharmacologically induced mydriasis is achieved either by stimulating the iris dilator muscle with the use of alpha-1 agonists (e.g. phenylephrine), or by blocking the iris sphincter muscle with the use of muscarinic antagonists (e.g., tropicamide). Nyxol, either by directly antagonizing the alpha-1 agonist or by indirectly antagonizing the pupil dilation effect of muscarinic blocking, can expedite the reversal of mydriasis prior to natural reversal.
Study Objectives	The objectives of this study are: • To evaluate the efficacy of Nyxol to expedite the reversal of pharmacologic mydriasis • To evaluate the safety of Nyxol • To evaluate the effect of Lumify® to suppress conjunctival hyperemia (redness) potentially associated with administration of Nyxol
Design	Placebo-controlled, randomized, double-masked, 2-arm cross-over, Phase 2b study in 32 randomized subjects, evaluating safety and efficacy of Nyxol in subjects with pharmacologically induced mydriasis.

	TREATMENTS WILL BE ADMINISTERED TO BOTH EYES (OU). Following the successful completion of screening each subject will be randomized 1:1 to one of two treatment sequences. Treatment sequence 1: Placebo (Visit 1): Nyxol (Visit 2) Treatment sequence 2: Nyxol (Visit 1): Placebo (Visit 2) Randomization will be stratified by mydriatic agent (phenylephrine 2.5% or tropicamide 1%), with randomization into each stratum capped at 16 subjects; that is, approximately half of the randomized subjects will receive phenylephrine 1 hour before treatment and approximately half will receive tropicamide 1 hour before treatment. Each subject will receive the same mydriatic agent throughout the study. Photopic lighting conditions will remain the same during the two treatment visits. Two hours post treatment, subjects may request the administration of Lumify® (to be provided) in the non-study eye as needed (site shall record such usage).
Patient Population	Thirty-two (32) normal healthy subjects
Inclusion Criteria	1. Males or females ≥ 18 and ≤ 45 years of age with brown irides only (See Appendix 2). 2. Otherwise healthy and well controlled subjects. 3. Ability to comply with all protocol-mandated procedures and to attend all scheduled office visits. 4. Willing to give written informed consent to participate in this study.
Exclusion Criteria	**Ophthalmic (in either eye):** 1. Clinically significant ocular disease as deemed by the Investigator (e.g., cataract, glaucoma, corneal edema, uveitis, severe keratoconjunctivitis sicca) that might interfere with the study. 2. Unwilling or unable to discontinue use of contact lenses during treatment visits. 3. Ocular trauma, ocular surgery or non-refractive laser treatment within the 6 months prior to screening.

4. Ocular medication of any kind within 30 days of screening, with the exception of a) lid scrubs (which may have been used prior to, but not after screening) or lubricating drops for dry eye (preservative free artificial tears), which may be used in between the study treatment days.
5. Recent or current evidence of ocular infection or inflammation. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at screening.
6. History of diabetic retinopathy.
7. Closed or very narrow angles that in the Investigator's opinion are potentially occludable if the subject's pupil is dilated.
8. 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).
9. Known allergy or contraindication to any component of the mydriatic agents or the vehicle formulation.

Systemic:

1. [redacted]
2. [redacted]
3. Initiation of treatment with or any changes to the current dosage, drug or regimen of any topical or systemic adrenergic or cholinergic drugs up to 7 days prior to screening, or during the study [redacted]
4. Participation in any investigational study within 30 days prior to screening.
5. Women 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. An adult woman is considered to be of

	childbearing potential unless she is 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at Visit 1/Screening and Visit 2 examinations and must intend to not become pregnant during the study. 6. Resting HR outside the normal range (50-110 beats per minute) at the Screening Visit. HR may be repeated **only once** if outside the normal 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 the Screening Visit. BP may be repeated **only once** if outside the specified range following at least a 5-minute rest period in the sitting position.
Visit Schedule	At the first visit subjects will be screened for study eligibility. After screening, eligible subjects will be randomized 1:1 to one of the two treatment sequences. The first treatment sequence will entail subjects receiving placebo on the first treatment day (Visit 1/Day 1) and receiving active drug on the second treatment day (Visit 2/Day 8+2 days). The second treatment sequence will entail subjects receiving active drug on the first treatment day (Visit 1/Day 1) and receiving placebo on the second treatment day (Visit 2/Day 8+2 days). At Visit 1, subjects completing screening will receive one of two approved mydriatic agents, 1% tropicamide or 2.5% phenylephrine, approximately 1 hour prior to receiving study treatment. Randomization will be stratified on mydriatic agent, with randomization into each stratum capped at approximately 16 subjects (one half of the randomized subjects will receive phenylephrine, one half will receive tropicamide). Each subject will receive the same mydriatic agent throughout the study. Each subject will receive 1 drop of mydriatic agent in each eye. If the drop is missed, the Investigator should give the drop again. The study eye is defined as the eye with the largest pupil diameter at maximum (1 hour after instillation of the mydriatic agent) at Visit 1. If both eyes have the same pupil diameter at maximum, then the study eye will be the right eye. This is the study eye for both Visit 1 and Visit 2 assessments. **ALL TREATMENTS WILL BE ADMINISTERED TO BOTH EYES (OU).**

	At each visit, pupil diameter, accommodation, near and distance visual acuity (VA) and redness in each eye will be measured before (-1 hour /baseline) and 1 hour after (maximum/0 minutes) the mydriatic agent instillation in each eye (i.e. right before the study treatment is administered), and at 30 minutes, 1 hour, 2 hours, 4 hours and 6 hours after treatment dosing. As needed, two hours post treatment, subjects may request the administration of Lumify® (to be provided) in the non-study eye (site shall record such usage).
Number of Investigational Sites	Up to 4 sites
Estimated Total Sample Size	Approximately 32 randomized normal healthy subjects, with approximately 28 completed subjects
Sample Size Justification	A sample size of 28 completed subjects is needed for the study. [redacted]
Primary Efficacy Endpoint	Change in pharmacologically induced mydriatic (max) pupil diameter (0 minutes) at 2 hours post treatment in the study eye
Secondary Efficacy Endpoints	Secondary efficacy endpoints (for the study eye, the non-study eye, and both eyes) will include: • Change (in mm) from max pupil diameter (0 minutes) at each remaining timepoint (30 min, 1 hour, 4 hours, 6 hours)

	• [redacted] • Percentage of subjects achieving pupil diameter of no more than 0.5 mm above baseline (-1 hour) at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours) • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • Change from baseline (-1 hour) in conjunctival hyperemia at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours), for study eye and non-study eye; in all subjects, in subjects taking Lumify®, and in subjects not taking Lumify

	Measurements:  The photopic lighting conditions will be kept the same during the 2 treatment visits. Every effort will be made to have the same person perform the measurements at all timepoints and at all visits. All of the efficacy endpoints will be analyzed overall and by mydriatic agent.
Primary Safety Endpoints	The primary safety measures are conjunctival hyperemia, subjective ocular tolerability and adverse events (AEs). Other safety measures are systemic safety as measured by HR and BP and intraocular pressure (IOP). Urine pregnancy tests for females of childbearing potential will be conducted. Please see Table 1 for details on measurements expected at each visit.
Study Medications, Dose and Mode of Administration	Nyxol® Eye Drops: One drop of Nyxol in each eye (1-hour post mydriatic drug instillation) Placebo (Nyxol vehicle): One drop of placebo in each eye (1-hour post mydriatic drug instillation) Lumify® (commercially available product): As needed, two hours post treatment, subjects may request administration of Lumify® (to be provided) in the non-study eye (site shall record such usage).

Duration of Subject Participation and Study	The total length of subject participation is approximately 10 days with 2 clinic visits, as summarized below: • Screening/Treatment-study Visit 1 Day 1 (1 week) • Treatment-study Visit 2 Day 8+2 days (1 day) The execution of the entire study (first subject screen through last randomized subject completed) is expected to be approximately 1 to 2 months.

TABLE OF CONTENTS

SPONSOR SIGNATURE & CONTACTS **2**

INVESTIGATOR'S AGREEMENT **3**

ABBREVIATIONS AND TERMS **5**

1. STUDY SUMMARY **7**

2. INTRODUCTION **17**
2.1. Investigational products **17**
2.2. Findings from nonclinical and clinical studies **17**
2.3. Route of administration, dosage regimen, and treatment period **19**
2.4. Compliance **19**
2.5. Study Population **19**

3. OBJECTIVES AND PURPOSE **20**

4. STUDY DESIGN **21**
4.1. Primary and secondary endpoints **21**
4.2. Description and schedule of visits and procedures **22**
4.3. Measures taken to minimize/avoid bias **24**
4.4. Study medications **24**
4.4.1. Packaging and labeling 24
4.4.2. Storage of study medication 24
4.4.3. Study medication accountability 24
4.4.3.1. Receipt and disposition of study medication 24
4.4.3.2. Return of study medication 24
4.5. Expected duration of subject participation **24**
4.6. Randomization and procedure for breaking the code **25**
4.7. Collection of data **25**
4.8. Completed subject **25**
4.9. Non-completing subject **25**
4.9.1. Study medication discontinuation 25
4.9.2. Reasons for Withdrawal from Study 26
4.9.3. Entire study terminated 26
4.9.4. Actions after discontinuation 26
4.10. Completed study **26**
4.11. Procedure after the completion of the study **26**

5. SUBJECT INCLUSION AND EXCLUSION CRITERIA **27**
5.1 Subject inclusion criteria **27**
5.2 Subject exclusion criteria **27**

6. TREATMENT OF SUBJECTS **29**
6.1. Treatment adherence **29**
6.2. Concomitant medications **29**

7. ASSESSMENT OF EFFICACY **31**
7.1. Specification of the efficacy parameters **31**
7.2. Assessing, recording, and analyzing of efficacy parameters **31**
7.2.1. Screening/Day 1 32
7.2.2. Treatment Visit 1/Day 1 32
7.2.3. Treatment Visit 2/Day 8 + 2 Days 33
7.2.4. Unscheduled Visits 34
7.2.5. Visit variation 34

8. ASSESSMENT OF SAFETY **35**
8.1. Specification of safety parameters **35**
8.2. Assessing, recording, and analyzing safety parameters **35**
8.3. Adverse events and Serious Adverse Events **35**
8.3.1. Adverse event definitions 36

8.3.2. Follow-up of subjects after adverse events 39

9. STATISTICS 40
9.1. Sample Size 40
9.2. Analysis Populations 40
9.3. Statistical Methods 40
9.3.1. General Considerations 40
9.3.2. Demographic and Baseline Characteristics 40
9.3.3. Subject Disposition 40
9.3.4. Medical History and Prior/Concomitant Medications 41
9.3.5. Analysis of Efficacy 41
9.3.6. Analysis of Safety 42
9.4. Procedure for accounting for missing, unused, or spurious data 42
9.5. Procedure for reporting deviations from the statistical plan 43

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS 44

11. QUALITY CONTROL AND QUALITY ASSURANCE 45

12. ETHICAL CONSIDERATIONS AND GCP COMPLIANCE 46
12.1. GCP compliance 46
12.2. Institutional Review Board (IRB) 46
12.3. Protocol Deviations/Violations 46
12.4. Informed consent requirements 46

13. DATA HANDLING AND RECORD KEEPING 48
13.1. Data Entry 48
13.2. Data quality control and reporting 48
13.3. Archiving of data 48
13.4. Records retention 48
13.5. Amendments to the protocol 48

APPENDIX 1: ADRENERGIC AND CHOLINERGIC DRUGS 49

APPENDIX 2: IRIS COLOR CHART 50

APPENDIX 3: ORIGINAL SERIES SLOAN LETTER ETDRS CARD 51

2. INTRODUCTION

2.1. Investigational products

The test product is Nyxol® Eye Drops - 1% phentolamine mesylate ophthalmic solution (Nyxol), a non-selective alpha-1 and alpha-2 adrenergic antagonist. Placebo control is Nyxol vehicle alone.

2.2. Findings from nonclinical and clinical studies

Detailed findings from nonclinical and clinical studies and potential risk are provided in the Investigators' Brochure (IB) (version 2 March 2019).

[redacted]

(systolic and diastolic), with all vital sign parameters remaining within normal limits at assessed [redacted]

[redacted]

Design justification

Pupil size is under the control of two opposing sets of muscles – the circular constrictor muscles controlled by the cholinergic nervous system[3,4] and the radial dilator muscles, controlled by the adrenergic nervous system. The radial dilator muscles contain predominantly α-1 adrenergic receptors that can be inhibited by α-1 antagonists[5]; therefore it is possible to inhibit dilation of the pupil through blockade of the radial dilator muscles.

Pharmacologically induced mydriasis is achieved either by stimulating the iris dilator muscle with the use of alpha-1 agonists (e.g., phenylephrine), or by blocking the iris sphincter muscle with the use of muscarinic antagonists (e.g., tropicamide). A typical induced mydriasis dilates the pupil to 6-8mm, a size suitable for ophthalmic examination of the retina and other structures of the interior of the eye.

Such pharmacologically induced mydriasis can last from a few hours (typically 6 hours) to days, depending on the pigmentation of the iris, the age of the subject, and other unknown-to-date factors. The side effects of such dilation are sensitivity to light and blurred vision. Also, many drops cause cycloplegia (loss of accommodation), the temporary paralysis of the muscle which allows the eye to focus on near objects. Accelerating mydriatic reversal after an eye exam may be beneficial for many subjects.

Phentolamine mesylate is a non-selective alpha-1 and alpha-2 adrenergic antagonist acting on adrenergic receptors. Nyxol is known to inhibit contraction of the iris dilator muscle, resulting in a smaller pupil size. To counteract mydriatic agents (alpha-1 agonists and muscarinic antagonists), Nyxol is proposed to be instilled in the eyes allowing a rapid reversal, thereby minimizing the side effects and discomfort post eye exam.

Previous clinical studies of Nyxol conducted in normal healthy subjects or subjects with severe night vision complaints have shown that single doses and treatments for up to 30 days have resulted in statistically significant reductions of mean pupil diameter (15 to 20% or 1 mm to 2 mm change in diameter), in subjects without pharmacologically induced pupil dilation, with no significant local or systemic AEs[1,2] Further, some patients experienced mild conjunctival hyperemia which is transient and may last several hours. For this reason, Lumify® is available for those who may experience redness at 2 hours post treatment in the non-study eye to inform the use of Nyxol in this setting.

Alpha-1 adrenergic antagonists have been shown to be safe and effective for the pharmacological reversal of mydriasis. In 1990, the FDA approved Dapiprazole Hydrochloride Ophthalmic Solution 0.5% (Rev-Eyes) for this indication, however, the product was withdrawn and discontinued by the manufacturer for reasons not related to safety or efficacy. Many people who undergo pupil dilation for an annual ophthalmic examination or other ophthalmic procedure requiring pupil dilation continue to request an option for rapid reversal of the mydriasis.

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

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

The single dose selected for this study, 1%, was selected 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[6].

2.4. Compliance

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

2.5. Study Population

A sample size of approximately 32 subjects between 18 years of age and 45 years of age inclusive will be randomized in a 1:1 ratio to one of the two treatment sequences (placebo at Visit 1, followed by active treatment/Nyxol 1% at Visit 2; active treatment/Nyxol 1% at Visit 1, followed by placebo at Visit 2), with the expectation that approximately 28 subjects will complete the study. [redacted] Subjects will receive their mydriatic agent 1 hour before treatment. Each subject will receive the same mydriatic agent throughout the study.

3. OBJECTIVES AND PURPOSE

The objectives of this study are:

- To evaluate the efficacy of Nyxol to expedite the reversal of pharmacologic mydriasis
- To evaluate the safety of Nyxol
- To evaluate the effect of Lumify® to suppress conjunctival hyperemia (redness) potentially associated with administration of Nyxol

4. STUDY DESIGN

4.1. Primary and secondary endpoints

Efficacy:

The primary efficacy endpoint is the change in pharmacologically induced mydriatic (max) pupil diameter (0 minutes) at 2 hours post-treatment in the study eye.

The study eye is defined as the eye with the largest pupil diameter at maximum (1 hour after instillation of the mydriatic agent) at Visit 1. If both eyes have the same pupil diameter at maximum, then the study eye will be the right eye. This is the study eye for both Visit 1 and Visit 2 assessments.

Secondary efficacy endpoints (for the study eye; for the non-study eye; and for both eyes) will include:

- Change (in mm) from max pupil diameter (0 minutes) at each remaining timepoint (30 min, 1 hour, 4 hours, 6 hours)
- [redacted]
- Percentage of subjects achieving pupil diameter of no more than 0.5mm above baseline (-1 hour) at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours)
- [redacted]
- Change from baseline (-1 hour) in conjunctival hyperemia at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours), for study eye and non-study eye; in all subjects, in subjects taking Lumify®, and in subjects not taking Lumify®

The photopic lighting conditions will be kept the same during the 2 treatment visits. Every effort will be made to have the same person perform the measurements at all timepoints and at all visits

All of the efficacy endpoints will be analyzed overall and by mydriatic agent.

Safety:

The primary safety measures are conjunctival hyperemia, subjective ocular tolerability, and AEs. Redness will be assessed visually with the CCLRU bulbar redness scale.

Other safety measures are systemic safety as measured by HR, BP, and IOP. Urine pregnancy tests for females of childbearing potential will be conducted.

4.2. Description and schedule of visits and procedures

Approximately 32 subjects will be randomized, for a target of 28 completed subjects. Subjects will be randomized in a 1:1 ratio to one of two treatment sequences (placebo at Visit 1, followed by Nyxol 1%/active treatment at Visit 2; Nyxol 1%/active treatment at Visit 1, followed by placebo at Visit 2). [redacted] Subjects will receive their mydriatic agent 1 hour before treatment. Each subject will receive the same mydriatic agent throughout the study.

Study procedures are shown in detail in Table 1:

Table 1: Screening and Mydriatic/Treatment Schedule

4.3. Measures taken to minimize/avoid bias

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

4.4. Study medications

Nyxol (1%) is a sterile, non-preserved, isotonic, buffered aqueous solution containing phentolamine mesylate (1.0%), [redacted]. Placebo is Nyxol vehicle, consisting of non-preserved, [redacted] aqueous solution [redacted]

4.4.1. Packaging and labeling

[redacted]

4.4.2. Storage of study medication

[redacted]

4.4.3. Study medication accountability

4.4.3.1. Receipt and disposition of study medication

The Investigator or designee (e.g., study coordinator or pharmacist) will maintain a full accountability record for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study medication using the inventories supplied by Ocuphire. The Investigator or designee will account for all study medication. The monitor will review dispensing and study medication accountability records during site visits and at the completion of the study and note any discrepancies. All investigational study medication must be stored in a secure facility, with access limited to the Investigator and authorized staff.

4.4.3.2. Return of study medication

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

4.5. Expected duration of subject participation

The total length of subject participation is approximately 8+2 days with 2 clinic visits, as summarized below:

- Screening Visit (1 day)

- Treatment Visit 1 Day 1 (1 day; same day/same clinic visit as Screening Day)
- Treatment Visit 2 Day 8+2 Days (1 day; 7+2 days after Treatment Visit 1)

The execution of the entire study (first subject screened through last randomized subject completed) is expected to be approximately 1 to 2 months.

4.6. Randomization and procedure for breaking the code

A randomization code for allocating subjects to treatment sequence will be prepared by a masked biostatistician not connected with the study. Randomization will be stratified by mydriatic agent.

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

The study medications will be masked to both Investigator and study subjects, as well as Ocuphire. Assignment to treatment sequence will be masked to the Investigator, Ocuphire, and the subjects. Only in case of medical emergency or occurrence of SAEs will the randomization code be unmasked by the study pharmacist and made available to the Investigator, Ocuphire, and/or other personnel involved in the monitoring or conduct of this study.

4.7. Collection of data

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

4.8. Completed subject

A completed subject is defined as one who completes all planned dosing and procedures through the end of Visit 2.

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 CRF
- **Death:** If a subject dies, the AE that caused the death should be documented on the CRF and be noted as serious and fatal.
- **Disallowed concurrent medication:** Any medication not allowed by the protocol would be a protocol violation.

- **Lack of efficacy:** A subject may elect to discontinue participation in the study for a perceived lack of efficacy.
- **Investigator decision:** A subject may be discontinued for reasons other than those bulleted previously if the Investigator thinks it is not in the best interest of the subject to continue.
- **Other:** If there is any other reason for subject discontinuation this should be noted on the CRF.

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

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 IRB and to regulatory authorities is also required.

4.9.4. Actions after discontinuation

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

For any subject who chooses to withdraw consent or who is non-compliant, every possible effort should be made by the Investigator to assure there is a final telephone call that includes assessments for AEs, concomitant medications and conjunctival redness.

4.10. Completed study

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

4.11. Procedure after the completion of the study

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

5. SUBJECT INCLUSION AND EXCLUSION CRITERIA

ALL TREATMENTS WILL BE ADMINISTERED TO BOTH EYES (OU).

5.1 Subject inclusion criteria

1. Males or females ≥ 18 and ≤ 45 years of age with brown irides only (see Appendix 2).
2. Otherwise healthy and well controlled subjects
3. Ability to comply with all protocol mandated procedures and to attend all scheduled office visits
4. Willing to give written informed consent to participate in this study

5.2 Subject exclusion criteria

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

Ophthalmic (in either eye):

1. Clinically significant ocular disease as deemed by the Investigator [redacted] that might interfere with the study
2. Unwilling or unable to discontinue use of contact lenses during treatment visits.
3. Ocular trauma, ocular surgery or non-refractive laser treatment within the 6 months prior to screening
4. Ocular medication of any kind within 30 days of screening, with the exception of a) lid scrubs [redacted]
5. Recent or current evidence of ocular infection or inflammation. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at Screening.
6. History of diabetic retinopathy.
7. Closed or very narrow angles that in the Investigator's opinion are potentially occludable if the subject's pupil is dilated.
8. 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).
9. Known allergy or contraindication to any component of the mydriatic agents or the vehicle formulation.

Systemic:

1. Known hypersensitivity or contra-indication to α- and/or β-adrenoceptor antagonists (e.g. chronic obstructive pulmonary disease or bronchial asthma; abnormally low BP or HR; second or third-degree heart block or CHF; severe diabetes)

2. Clinically significant systemic disease (e.g., uncontrolled diabetes, 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 topical or systemic adrenergic or cholinergic drugs up to 7 days prior to Screening, or during the study
4. Participation in any investigational study within 30 days prior to screening
5. Women 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. An adult woman is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at Visit 1 Screening and Visit 2 examinations and must intend to not become pregnant during the study
6. Resting HR outside the normal range (50-110 beats per minute) at the Screening Visit. HR may be repeated **only once** if outside the normal 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 the Screening Visit. 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 32 subjects will be randomized, with a target completion of 28 subjects. Subjects will be randomized in a 1:1 ratio to one of two treatment sequences (the first treatment sequence will entail subjects receiving placebo on the first treatment day and receiving active drug on the second treatment day; the second treatment sequence will entail subjects receiving active drug on the first treatment day and receiving placebo on the second treatment day). [redacted] Subjects will receive their mydriatic agent 1 hour before treatment. Treatment Visit 1 will be on Day 1, with the subject receiving the first treatment in his/her treatment sequence. Treatment Visit 2 will be on Day 8+2 days, with the subject receiving the second treatment in his/her treatment sequence. Each subject will receive the same mydriatic agent throughout the study.

6.1. Treatment adherence

All subjects will be treated by the Investigator or designee, at the study clinic on both Visit 1 and Visit 2. As such, it is expected that all subjects will receive both doses of study treatment (one dose of placebo, one dose of active treatment/Nyxol 1%).

6.2. Concomitant medications

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

- Use of ocular medication within 30 days of the Screening Visit, or anticipated use during the study, with the exception of lubricating drops for dry eye (preservative-free artificial tears), which may be used throughout the study
- Initiation of treatment with or any changes to the dosage, drug or regimen of any topical or systemic adrenergic or cholinergic drugs up to 7 days prior to Screening, or during the study (Appendix 1). A large number of drugs, both prescription and over-the-counter (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 blood-pressure medications, many drugs used for migraines, and many other products. ***If there is any question about whether a medication is acceptable, Ocuphire or the Medical Monitor should be consulted before proceeding***

Intermittent use of OTC lubricating drops for dry eye (preservative free artificial tears is acceptable between treatment visits. However, no other ocular medications (OTC or prescription) are allowed within 30 days of the Screening Visit, or during the study.

Topical or systemic therapy with agents that could have an ophthalmic effect are to be consistent in dose, regimen and agent within the 7 days prior to Screening and throughout the study. For example, a subject can be treated with a systemic adrenoceptor antagonist as long as the particular agent and its dose and regimen had been consistent for the 7 days prior to Screening, and there was no reason to believe that alteration would be necessary at some point later during the study.

Use of all medications should be documented on the appropriate CRF. Investigators are encouraged to contact Ocuphire or the Medical Monitor for any questions regarding allowed medications. Judgment of continued study participation by the subject, and

inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by Ocuphire.

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

7. ASSESSMENT OF EFFICACY

7.1. Specification of the efficacy parameters

The primary efficacy endpoint is the change in pharmacologically induced mydriatic (max) pupil diameter (0 minutes) at 2 hours post-treatment in the study eye.

The study eye is defined as the eye with the largest pupil diameter at maximum (1 hour after instillation of the mydriatic agent) at Visit 1. If both eyes have the same pupil diameter at maximum, then the study eye will be the right eye. This is the study eye for both Visit 1 and Visit 2 assessments.

Secondary efficacy endpoints (for the study eye; for the non-study eye; and for both eyes) will include:

- Change (in mm) from max pupil diameter (0 minutes) at each remaining timepoint (30 min, 1 hour, 4 hours, 6 hours)
- [redacted]
- Percentage of subjects achieving pupil diameter of no more than 0.5mm above baseline (-1 hour) at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours)
- [redacted]
- Change from baseline (-1 hour) in conjunctival hyperemia at each timepoint (30 min, 1 hour, 2 hours, 4 hours, 6 hours), for study eye and non-study eye; in all subjects, in subjects taking Lumify®, and in subjects not taking Lumify®

Each efficacy endpoint will be analyzed overall and by mydriatic agent.

7.2. Assessing, recording, and analyzing of efficacy parameters

Pupil diameter, accommodation, near and distance visual acuity will be measured at the Screening Visit (which is also the same day as Treatment Visit 1) and Treatment Visit 2.

- [redacted]

All assessments will be conducted under photopic conditions. The photopic lighting conditions will be kept the same during the 2 treatment visits. Every effort will be made to have the same person perform the measurements at all timepoints and at all visits.

7.2.1. Screening/Day 1

[redacted]

7.2.2. Treatment Visit 1/Day 1

[redacted]

[redacted]

7.2.3. Treatment Visit 2/Day 8 + 2 Days

[redacted]

7.2.4. 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 CRF.

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 final telephone follow-up that includes assessments of AEs, concomitant medications and conjunctival redness.

7.2.5. Visit variation

[redacted]

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:

- [redacted]
- IOP
- HR and BP (As per the site's normal equipment and procedures)
- AEs

8.2. Assessing, recording, and analyzing safety parameters

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

8.3. Adverse events 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 (see Section 9.3.5).

All AEs/adverse reactions occurring during the study (i.e. once the subject has signed the informed consent) **must** be documented, regardless of the assumption of causal relationship, on the respective CRF. All treatment-emergent AEs/adverse reactions must be documented from the time the subject receives the **first dose** of study medication until the subject's participation in the study has been completed. If a subject has ongoing 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 abnormal laboratory findings 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 in a patient or clinical study subject administered a study medication (pharmacological/biological product) that does not necessarily have a causal relationship to this medication. 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 visit, study personnel should ask the following question: “Have you had any problems since your last visit?”. AEs also may be detected when they are volunteered by the subject during or between visits or through study assessments.

Life-threatening adverse event 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 or 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.

Serious adverse event 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 at any dose:

- Death
- Life threatening
- Initial or prolonged hospitalization
- Disability or permanent damage
- Congenital anomaly or birth defect
- Needs intervention to prevent impairment
- 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 or subject 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 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 Investigators' Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigators' Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigators' Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

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 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" Adverse Event, 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 adverse event.
- Not recovered/not resolved: One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated.
- Recovered/resolved: One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated.
- Recovered/Resolved with sequelae: One of the possible results of an adverse event 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 adverse event outcome that indicates that the event is improving
- Unknown: Not known, not observed, not recorded, or refused

[redacted]

Should a pregnancy occur, it must be reported and recorded on the pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The subject will be withdrawn from study medication and followed through conclusion of pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

Expedited reporting of Serious and Unexpected Adverse Events: All SAEs (related and unrelated) will be recorded following subject signature of the informed consent and until the final study visit (Visit 3). 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 Oculos within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to Oculos as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the site with a copy emailed [redacted] The Investigator must assess the SAE relationship and complete the SAE form. Oculos may request additional information. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy will be emailed to [redacted]. In addition, all SAEs should be recorded on the AE CRF page with the serious question marked "Yes".

It is the Investigator's responsibility to notify the approving IRB of any SAEs on a timely basis as instructed by 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 US Food and Drug Administration (FDA) on the appropriate schedule depending if the event is drug related or not drug related, expected, unexpected (based on the available information in the Investigators' Brochure).

Any death occurring during the study and follow-up period must be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to study medication, the SAE resulting in the death must be reported to Oculos. A death occurring after completion of the study including the Safety Follow-up Visits, that is not reasonably associated with study 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 28 completed subjects is needed for the study.

[redacted]).

9.2. Analysis Populations

Full Analysis Set (FAS): [redacted]

All Randomized Population (ARP): [redacted]

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

9.3. Statistical Methods

9.3.1. General Considerations

[redacted]

9.3.2. Demographic and Baseline Characteristics

[redacted]

9.3.3. Subject Disposition

[redacted]

9.3.4. Medical History and Prior/Concomitant Medications

[redacted]

9.3.5.Analysis of Efficacy

[redacted]

randomized treatment sequence regardless of the treatment they actually received.

[redacted]

[redacted]

9.3.6. Analysis of Safety

[redacted]

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

[redacted]

9.5. Procedure for reporting deviations from the statistical plan

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

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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

11. QUALITY CONTROL AND QUALITY ASSURANCE

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

12. ETHICAL CONSIDERATIONS AND GCP COMPLIANCE

12.1. GCP compliance

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

12.2. Institutional Review Board (IRB)

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

12.3. Protocol Deviations/Violations

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

12.4. Informed consent requirements

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

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

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

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

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

13. DATA HANDLING AND RECORD KEEPING

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

13.1. Data Entry

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

13.2. Data quality control and reporting

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

13.3. Archiving of data

Archived versions of the database will be saved by Ocuphire consistent with ICH Good Clinical Practices (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(s), change of telephone number(s)].

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

APPENDIX 1: ADRENERGIC AND CHOLINERGIC DRUGS

APPENDIX 2: IRIS COLOR CHART

APPENDIX 3: ORIGINAL SERIES [redacted] CARD

Bibliography

[redacted]