Study Protocol Official Title:

A Single-Center, Open Label, Phase 4 Study of the Safety and Efficacy of Fixed combination Phenylephrine 2.5%-Tropicamide 1% Ophthalmic Solution (MydCombi®) Administered with the MydCombi Dispenser for Pupil Dilation (The MIST 2.1 Study)

NCT Number 06217796

Date of Document: 23 October 2023

PROTOCOL EYN-MYD-TP-41
VERSION A

A SINGLE-CENTER, OPEN LABEL, PHASE 4 STUDY OF THE SAFETY AND EFFICACY OF FIXED COMBINATION PHENYLEPHRINE 2.5%-TROPICAMIDE 1% OPHTHALMIC SOLUTION (MYDCOMBI®) ADMINISTERED WITH THE MYDCOMBI DISPENSER FOR PUPIL DILATION (THE MIST-2.1 STUDY)

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LIST OF ABBREVIATIONS

Abbreviation	Term
AC	Anterior chamber
AE	Adverse event
ADR	Adverse drug reaction
AT	Artificial tears
CF	Count fingers
CFR	Code of Federal Regulations
DVA	Distance Visual Acuity
eCRF	Electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study (Chart)
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HM	Hand motion
IB	Investigator brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOL	Intraocular lens
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
LP	Light perception
NLP	No light perception
OU	Both eyes (within this protocol, OU does not connote simultaneous treatment/evaluation)
PETG	Polyethylene terephthalate glycol
PP	Per-protocol
SAE	Serious adverse event
SD	Standard deviation
SLE	Slit lamp examination
TEAE	Treatment-emergent adverse event
TLR	Total letters read
UCDVA	Uncorrected distance visual acuity
US	United States
VA	Visual acuity
WMA	World Medical Association
µD	Microdose
µL	Microliter

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

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1. PERSONNEL AND FACILITIES

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2. STUDY SYNOPSIS

2.1. Study Objective

The primary objective of this study is to evaluate the safety and efficacy of MydCombi® (phenylephrine 2.5%-tropicamide 1% ophthalmic solution) when dosed with 1 spray per eye with the MydCombi dispenser for pupil dilation.

2.2. Study Drugs

- **Product, Dosage and Mode of Administration:** Commercially available MydCombi (Fixed combination ophthalmic solution - phenylephrine 2.5%-tropicamide 1%) administered as one spray per eye with the MydCombi dispenser.

2.3. Study Population

Up to 30 volunteer participants will be enrolled at a single study site in the United States (US) and a minimum of 25 subjects will receive study drug administration at the Treatment Visit in order to complete follow-up on 25 subjects.

2.4. Study Design

This trial is a single-center, open label study evaluating 1 spray per eye with the MydCombi dispenser, to provide adequate dilation to allow visualization of the back of the eye during a routine eye examination.

Volunteer participants will be screened for study eligibility during a Screening Visit and enrolled after signing the study-specific informed consent form (ICF). Subjects meeting all eligibility criteria may proceed to the Treatment Visit on the same day (Day 0) and screening values will be used for baseline. If the treatment visit is scheduled on a separate date, baseline measurements will be taken, then a single spray of MydCombi will be administered to each eye (OU). Afterwards, efficacy and safety assessments will be performed.

2.5. Inclusion Criteria

Subjects eligible for study participation must meet each criterion listed below. Ocular criteria must be met for both eyes.

1. Male or female ≥ 18 years of age
2. Female subjects must be either 1-year postmenopausal, surgically sterilized, or, if of childbearing potential, have a negative urine pregnancy test during the Screening Visit and agree to use an acceptable form of contraception throughout the study. *Acceptable methods include the use of at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.*
3. Ability to provide signed written consent prior to participation in any study-related procedures.
4. Ability to return for the study treatment visit.
5. Photopic screening pupil diameter ≤ 3.5 mm in each eye.

2.6. Exclusion Criteria

Subjects with any of the following diseases, surgeries or conditions are ineligible for study participation. Subjects may not participate if either eye meets any of the ocular exclusion criteria.

1. Pregnancy or lactation.
2. Allergy to phenylephrine hydrochloride.
3. Allergy to tropicamide.
4. Allergy to benzalkonium chloride.
5. History of benign prostatic hyperplasia.
6. Participation in any study of an investigational drug or device within 30 days prior to the Screening Visit, or at any time during the study period.
7. History of closed-angle glaucoma.
8. Anatomically narrow anterior chamber angles (Van Herrick grade ≤ 2 in either eye).
9. Ocular surgery or laser treatment of any kind prior to the Screening Visit.
10. History of chronic or acute uveitis.
11. History of traumatic iritis or hyphema.
12. History of traumatic mydriasis or angle recession.
13. History of heterochromia.
14. Irregularly shaped pupil secondary to ocular trauma or congenital defect.
15. History of neurogenic pupil disorder (e.g., Horner's syndrome, third cranial nerve palsy, Adie's pupil, Argyl Robertson syndrome, etc.).
16. History of anterior chamber intraocular lens (IOL) or iris-fixated IOL.
17. History of iris surgery of any kind (e.g., iridotomy, iridectomy, coreoplasty).
18. History of iris atrophy.
19. History of iris – cornea apposition/touch.
20. Unwilling or unable to discontinue use of contact lenses at the treatment visit.
21. Use of cholinergic agonists (varenicline, cevimeline, pilocarpine), ophthalmic cholinesterase inhibitors (isoflurophate, demecarium, physostigmine) and or any agent that may exaggerate the pressor effects of atropine-like drugs (phenylephrine, atropine).
22. Current active eye disease for which topical or systemic ophthalmic medication is necessary, except for dry eye disease managed using artificial tears (AT). *AT's must be discontinued on the day of the treatment visit.*
23. Presence of a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment and/or follow-up.

2.7. Primary Performance Endpoint

The primary performance endpoint is the mean change in pupil diameter at 30 minutes from the time of drug dose versus baseline, as measured by digital pupillometry in highly photopic conditions. The highly photopic condition will be established using a fully-charged transilluminator (muscle light) at the brightest setting.

2.8. Exploratory Outcomes

- Proportion of eyes achieving pupil diameter of 6.0 mm or greater at 30 minutes
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater at 30 minutes
- Mean change in pupil diameter at other timepoints (15, 60, 90, 150, 210 and 360 minutes)
- Distribution of pupil diameters at 15, 30, 60, 90, 150, 210 and 360 minutes
- Time from baseline to maximal pupil dilation
- Time from treatment time 0 to pupil size ≤ baseline

These exploratory outcomes will also be measured using digital pupillometry in highly photopic conditions.

2.9. Safety Outcomes

- Slit-lamp examination findings
- Occurrence of AEs
- Visual acuity changes

2.10. Schedule of Visits, Procedures and Evaluations

The study includes a Screening Visit, which must occur between 0 and 7 days prior to treatment; followed by the Treatment Visit. The Treatment Visit must occur between Day 0 (Screening Visit) and 7 days following the Screening Visit. The study visit schedule is presented in flow chart form in Figure 1.

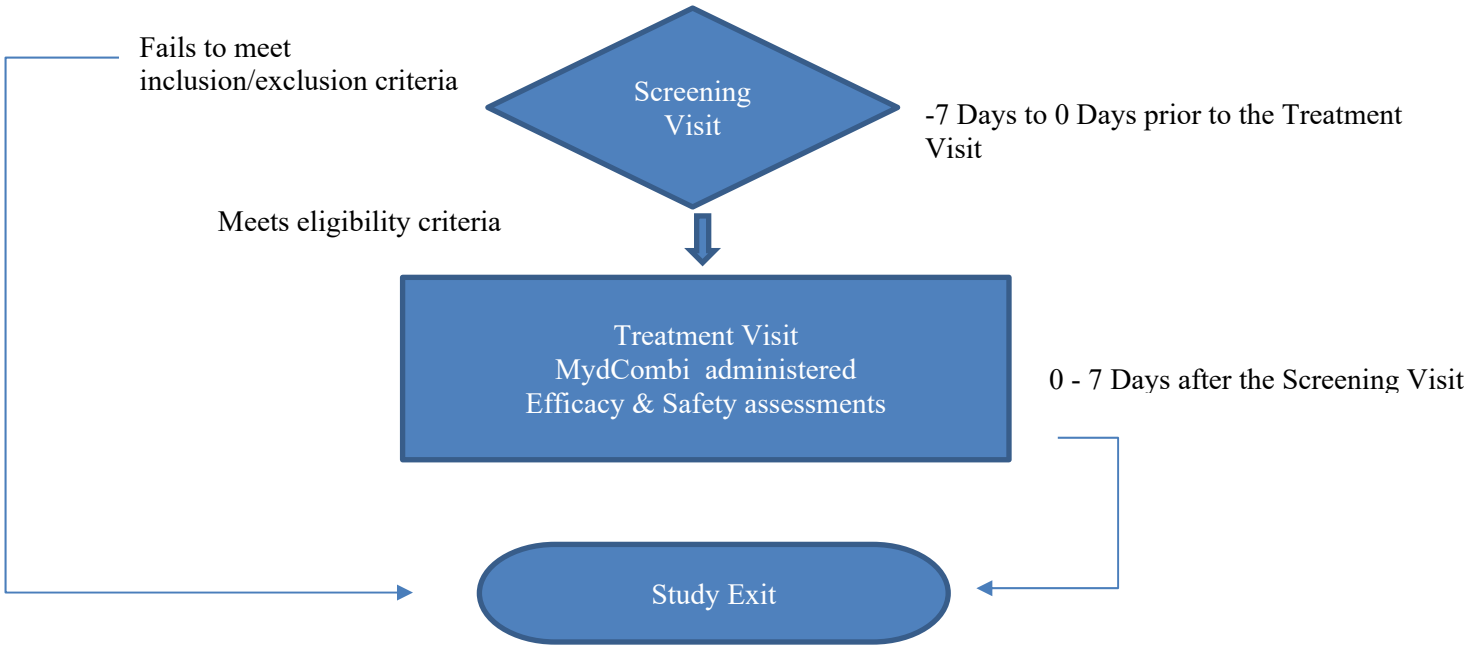

Figure 1: Study Visit Flow Chart

2.10.1. Study Medication Administration and Clinical Assessments

Study medication administration and clinical assessments will be performed at study visits as shown in **APPENDIX 1: SCHEDULE OF MEDICATION ADMINISTRATION AND EXAMS.**

3. INTRODUCTION AND RATIONALE

3.1. Introduction

MydCombi (fixed combination phenylephrine 2.5%-tropicamide 1%) is a proprietary product administered via the MydCombi dispenser to facilitate accurate topical ocular delivery of a controlled quantity of mydriatic agents in a precise manner to maximize therapeutic control and minimize systemic absorption and loss to washout. In the Phase 3 studies, the dose tested was 2 administrations given 5 minutes apart.

Eyenovia, the Sponsor of this study, received approval for MydCombi in May 2023. This approval was based upon Eyenovia studies EYN-MYD-TP-31 and EYN-MYD-TP-32. This approval included the labeling requirement that 2 sprays were required for dilation.

3.2. Pupil Dilation

A variety of ophthalmic evaluations require pupil dilation to provide an unobstructed view of the lens, retina, and optic nerve. The degree of pupil dilation required depends on the procedure being performed. For routine diagnostic procedures, and in conditions where short term pupil dilation is desired, the goal is to achieve adequate mydriasis for visualization with minimal cycloplegic effect. MydCombi was approved in May 2023 for this use.

As shown in Figure 2, the Eyenovia MydCombi dispenser is designed to deliver a finely controlled microdroplet spray of phenylephrine 2.5%-tropicamide 1% ophthalmic solution with precisely defined volume, velocity, and geometry.[1] These characteristics facilitate high-precision, piezo-generated medication delivery that gently coats the ocular surface.

[1] Ianchulev T, Chayet A, Kahook M, Packer M, Pasquale L, Weinreb RN. Pharmacodynamic profile of mydriatic agents delivered by ocular piezo-ejection microdosing compared with conventional eyedropper. Ther Deliv. 2016;7(11):751-760.

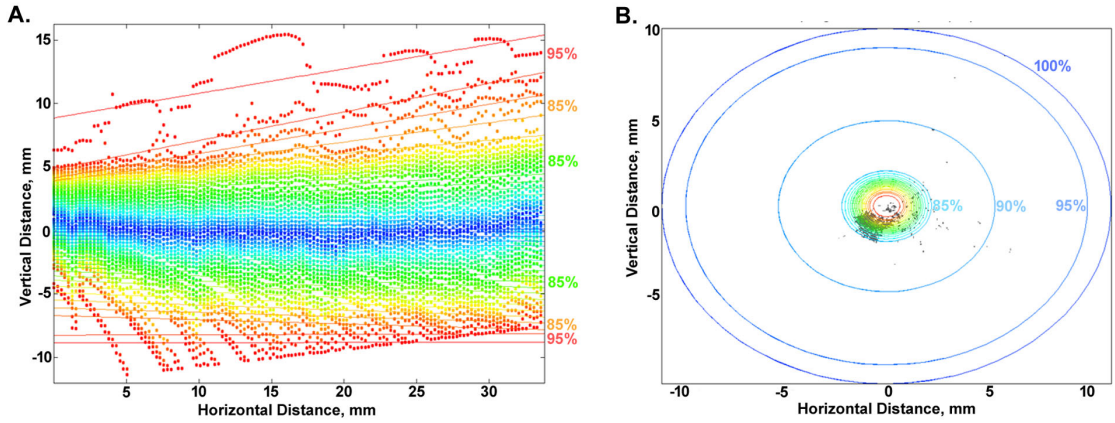

Figure 2: Microdroplet Distribution Pattern from the Mydcombi Dispenser

Image analysis of high-speed photographs of the microdroplet plume quantitatively confirms precise medication microdroplet delivery. Shown are representative side (A) and cross-sectional (B) views of the droplet dispersal pattern. Color-coding indicates the percentage of the total medication dose present at different distances from the nozzle-to-target dead- center axis. The cross-sectional pattern on the right was captured 3 cm from the Mydcombi dispenser nozzle.

4. INVESTIGATIONAL PRODUCT DESCRIPTION

This study will evaluate the safety and efficacy of MydCombi (phenylephrine 2.5%-tropicamide 1% ophthalmic solution) dosed as 1 spray per eye for mydriasis in routine diagnostic procedures and in conditions where short-term pupil dilation is desired.

4.1. Findings from Non-Clinical and Clinical Studies

The approved labeling is included as Appendix 2.

4.2. How Provided

Commercially available MydCombi will be provided in the MydCombi dispenser. Details are included in the approved label provided as Appendix 2.

4.3. Route of Administration, Dosage, Regimen, Treatment Period(s)

The study medication will be administered in accordance with FDA approved labeling with the exception that a single spray will be administered as opposed to the currently approved 2 sprays.

5. STUDY OBJECTIVE

The primary objective of this study is to evaluate the safety and efficacy of one spray of Eyenovia's fixed combination of phenylephrine 2.5%-tropicamide 1% ophthalmic solution (MydCombi®) for pupil dilation.

6. STUDY DESIGN

This trial is a single-center, open label study evaluating 1 spray of MydCombi, for mydriasis in routine diagnostic procedures and in conditions where short-term pupil dilation is desired.

Volunteer participants will be screened for study eligibility during a Screening Visit and enrolled after signing the study-specific informed consent form (ICF). Subjects meeting all eligibility criteria may proceed to the Treatment Visit on the same day (Day 0) and screening values will be used for baseline. If the treatment visit is scheduled on a separate date baseline measurements will be taken, then a single spray of MydCombi will be administered to both eyes (OU). Afterwards, efficacy and safety assessments will be performed.

7. STUDY OUTCOMES

7.1. Effectiveness Outcomes

The primary performance endpoint is mean change in pupil diameter at 30 minutes from the time of first drug dose versus baseline, as measured by digital pupillometry in highly photopic conditions. The highly photopic condition will be established using a fully-charged transilluminator (muscle light) at the brightest setting.

The curve of the mean change in pupil diameter will be defined for a single spray of MydCombi, Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1%.

The study's sample size will provide data to generate descriptive statistics for the dilation curve for 1 spray of MydCombi. No other formal analyses are planned.

Additional exploratory outcomes (also to be measured in highly photopic conditions) include:

- Proportion of eyes achieving pupil diameter of 6.0 mm or greater at 30 minutes
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater at 30 minutes
- Mean change in pupil diameter at other timepoints (15, 30, 60, 90, 150, 210 and 360 minutes)
- Distribution of pupil diameters at 15, 30, 60, 90, 150, 210 and 360 minutes
- Time from baseline to maximal pupil dilation
- Time from treatment time 0 to pupil size ≤ baseline

7.2. Safety Outcomes

All safety information will be collected and summarized for a single spray of MydCombi (fixed combination of phenylephrine 2.5%-tropicamide 1%) for the following outcomes:

- Slit-lamp examination (SLE) findings
- Occurrence of AEs
- Visual acuity changes

8. STUDY POPULATION

Up to 30 volunteer participants will be enrolled at a single study site in the United States (US) and a minimum of 25 subjects will be receive study drug administration at the Treatment Visit in order to complete follow-up on 25 subjects.

8.1. Inclusion Criteria

Subjects eligible for study participation must meet each criterion listed below. Ocular criteria must be met for both eyes.

1. Male or female ≥ 18 years of age.
2. Female subjects must be either 1-year postmenopausal, surgically sterilized, or, if of childbearing potential, have a negative urine pregnancy test during the Screening Visit and agree to use an acceptable form of contraception throughout the study. *Acceptable methods include the use of at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.*
3. Ability to provide signed written consent prior to participation in any study-related procedures.
4. Ability to return for the study treatment visit.
5. Photopic screening pupil diameter ≤ 3.5 mm in each eye.

8.2. Exclusion Criteria

Subjects with any of the following diseases, surgeries or conditions are ineligible for study participation. Subjects may not participate if either eye meets any of the ocular exclusion criteria.

1. Pregnancy or lactation.
2. Allergy to phenylephrine hydrochloride.
3. Allergy to tropicamide.
4. Allergy to benzalkonium chloride.
5. History of benign prostatic hyperplasia.
6. Participation in any study of an investigational drug or device within 30 days prior to the Screening Visit, or at any time during the study period.
7. History of closed-angle glaucoma.
8. Anatomically narrow anterior chamber angles (Van Herrick grade ≤ 2 in either eye).
9. Ocular surgery or laser treatment of any kind prior to the Screening Visit.
10. History of chronic or acute uveitis.
11. History of traumatic iritis or hyphema.
12. History of traumatic mydriasis or angle recession.
13. History of heterochromia.
14. Irregularly-shaped pupil secondary to ocular trauma or congenital defect.
15. History of neurogenic pupil disorder (e.g., Horner's syndrome, third cranial nerve palsy, Adie's pupil, Argyl Robertson syndrome, etc.).
16. History of anterior chamber intraocular lens (IOL) or iris-fixated IOL.
17. History of iris surgery of any kind (e.g., iridotomy, iridectomy, coreoplasty).

18. History of iris atrophy.
19. History of iris – cornea apposition/touch.
20. Unwilling or unable to discontinue use of contact lenses at treatment visits.
21. Use of cholinergic agonists (varenicline, cevimeline, pilocarpine), ophthalmic cholinesterase inhibitors (isoflurophate, demecarium, physostigmine) and or any agent that may exaggerate the pressor effects of atropine-like drugs (phenylephrine, atropine).
22. Current active eye disease for which topical or systemic ophthalmic medication is necessary, except for dry eye disease managed using artificial tears (AT). *AT's must be discontinued on the day of the treatment visit.*
23. Presence of a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment and/or follow-up.

9. STUDY METHODS

9.1. Subject Informed Consent

The IRB-approved study ICF must be used for administration of informed consent.

The investigator or designee will explain the study purpose, procedures and responsibilities to the potential participant and provide sufficient opportunity to ask questions, while allowing adequate time for consideration of the information provided. Written consent for study participation must be present prior to initiation of any study-specific procedure; subjects will be considered enrolled in the study upon their signature on the consent form(s). It is the responsibility of the Investigator to complete the informed consent process, maintain a copy of the signed consent form in the subject's medical records, and provide each subject with a copy of their fully-executed consent documents.

9.2. Subject Selection and Screening Procedures

Study participants will be recruited from the Investigator's patient population, referrals, or other outreach methods. Written recruitment materials directed to potential study participants must be approved by the IRB.

Where possible, candidate participants may be pre-screened via review of their medical charts to evaluate potential eligibility based on study inclusion/exclusion criteria. During the informed consent discussion, the potential participant's willingness and ability to meet the follow-up requirements will be evaluated. Those who elect to sign the study consent form(s) will be considered enrolled in the study and given a study identification code. At/after the time of enrollment, the subject will be evaluated at the Screening Visit for study eligibility based on eligibility requirements established in **Sections 8.1** and **8.2**. Subjects who fail to qualify for the study will be considered "screen failures" and exited from the study. Subjects who successfully complete the Screening Visit will continue to the Treatment portion of the visit or be scheduled for their Treatment Visit at which the study medication will be administered.

9.3. Randomization to Study Drug Administration Sequence

As the study is open label, this section is not applicable.

9.4. Study Drug Packaging, Labeling and Storage

Commercial MydCombi product will be provided for use in the study.

9.5. Study Drug Administration

Site personnel designated to administer study medication will be trained by the Sponsor on proper use of the MydCombi dispenser prior to study initiation. Commercial MydCombi will be used for drug administration for all subjects. Subjects will be administered 1 spray of study drug in each eye.
Study drug administration procedures are further detailed in APPENDIX 2: Mydcombi Approved label

Site personnel should confirm the spray was felt on the cornea. If the subject cannot confirm feeling the spray or the spray is visible on the lid of the eye, a second spray may be administered. The number of sprays will be recorded for each eye.

9.6. Study Visits and Clinical Assessments

Study participants will be evaluated at a Screening Visit. Subjects who qualify for further study participation will continue to the treatment portion of the visit or be scheduled for the Treatment Visit at which the study drug is administered, and examinations are performed. Data collected will be documented in the source records and recorded on study electronic Case Report Forms (eCRF).

The timing and frequency of assessments/procedures to be performed is outlined in **APPENDIX 1: SCHEDULE OF MEDICATION ADMINISTRATION AND EXAMS.** Methodology for study examinations is presented in **APPENDIX 3: EXAMINATION PROCEDURES**.APPENDIX **3: EXAMINATION PROCEDURES.**

9.6.1. Screening Visit (-7 Days to Day 0)

The Screening Visit must occur no more than 7 days prior and no less than 0 days prior to the Treatment Visit. At the Screening Visit, the following activities will be performed:

- Documentation of study informed consent using IRB-approved consent form(s)
- Collection of demographic data (gender, age, ocular comorbidities)
- Collection of medical/ocular history and medication use data
- Administration of urine pregnancy test, if applicable
- DVA using habitual correction – OU
- Pupil diameter measurement – OU
- Slit lamp biomicroscopy – OU
- IOP measurement - OU
- Pupillary light reflex - OU
- Iris Color
- Determination of study eligibility

9.6.2. Treatment Visit (Day 0)

Subjects may be screened and treated on the same day, however screening may occur no more than 7 days prior to treatment. If screening is not on the same day as treatment, the subject will be queried regarding the occurrence of any adverse events since the time of the Screening Visit. If the screening and Treatment visit are conducted on the same day, the screening values may be used for the baseline values. The subject will be treated after the following baseline measurements will be taken prior to study drug administration. (For subjects whose Screening and Treatment Day are on the same day, these tests do not need to be repeated.)

- Pupil diameter measurement – OU
- Pupillary light reflex - OU
- DVA using habitual correction– OU
- Slit lamp biomicroscopy – OU
- IOP measurement - OU
- AE assessment

The study drug will be administered as a single spray OU. The completion of the administration of medication in the subject's second eye will be considered Time 0 (T0). The following assessments will be done at the timepoints specified below:

Timepoint	**Clinical Assessment (to be performed in the specified order)**
Time 1: T0 + 15 minutes (+/- 2 minutes)	• Pupil diameter measurement – OU
Time 2: T0 + 30 minutes (+/- 5 minutes)	• Pupil diameter measurement – OU • Pupillary light reflex - OU
Time 3: T0 + 60 minutes (+/- 5 minutes)	• Pupil diameter measurement – OU
Time 4: T0 + 90 minutes (+/- 5 minutes)	• Pupil diameter measurement – OU • Pupillary light reflex - OU • IOP measurement – OU
Time 5: T0 + 150 minutes (+/-10 minutes)	• Pupil diameter measurement – OU
Time 6: T0 + 210 minutes (+/-10 minutes)	• Pupil diameter measurement – OU
Time 7: T0 + 360 minutes (+/-30 minutes)	• Pupil diameter measurement – OU • Pupillary light reflex - OU • DVA using habitual correction – OU • Slit lamp biomicroscopy – OU • AE assessment

9.6.3. Unscheduled Visits

Unscheduled visits are those which are not required by the study protocol, but which occur due to an ocular intervention or a subject complaint regarding their eye. No specific testing is required at unscheduled visits; rather, the investigator and/or qualified study staff will perform the procedures necessary to treat/evaluate the subject at these visits. Clinical data from these visits will be recorded on the relevant Unscheduled Visit eCRF.

9.6.4. Missed Visits

Subjects who miss a scheduled visit should be contacted by site personnel to encourage the subject to return to clinic as soon as possible after the missed visit. In the event a subject does not return for multiple consecutive examinations, site personnel must make a minimum of 3 documented attempts via telephone, email, or regular mail to contact the subject. If the subject does not reply to any of these attempts, site personnel must send a letter by certified mail (with request for notification of delivery receipt) to the subject. If a subject is non-responsive to each of these follow-up attempts, he/she will be terminated from the study and considered lost to follow-up.

9.7. Study Exit

9.7.1. Subject Termination

Subjects may be terminated from the study due to:

- Failure to meet protocol eligibility criteria
- Investigator decision that termination is medically indicated
- Voluntary withdrawal from the study
- Lost to follow-up
- Other administrative reasons (e.g., study terminated by Sponsor, technical problems, non-compliance with study medication administration or other study requirements, etc.)

Subjects who terminate due to the occurrence of an AE will be followed until resolution or stabilization of the event.

Subjects who exit the study due to failure to meet eligibility criteria may be replaced. Subjects who exit the study prematurely for other reasons will not be replaced. The Sponsor (or designee) should be promptly notified of a subject's early termination, and information regarding the termination (e.g., date and reason) should be documented in the source records and on the Study Exit eCRF.

9.7.2. Subject Completion

Subjects will be considered to have completed the study if they did not terminate study participation prior to completion of primary endpoint assessment at the Treatment Visit.

10. ADVERSE EVENTS

Throughout the course of the study, all efforts must be made by the investigator to remain alert to possible AEs or untoward findings. All AEs must be assessed for severity and relationship to the study drug, and the investigator must take all appropriate and necessary therapeutic measures required for AE resolution. Adverse events must be evaluated until resolution or, if the AE is assessed as chronic, until stable.

10.1. Adverse Event Definitions

Most of the AE definitions provided are published in either **CFR 314.80 Post Marketing Reporting of Adverse Drug Experiences, CFR 312.32 – IND Safety Reporting** or **ICH E6 – Good Clinical Practice: Consolidated Guidance.** Because of the differing sources for these definitions, some terminology; e.g., "adverse event", "adverse reaction", and "adverse experience", differs. For this study, these terms should be considered equivalent.

10.1.1. Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.[2]

10.1.2. Adverse Drug Reaction (ADR)

Any noxious and unintended response to a medicinal product administered at any dose. A reasonable possibility must exist that the adverse reaction is related to the medicinal product administered.[3]

10.1.3. Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Package Insert (Appendix 2) or is not listed at the specificity or severity that has been observed; or, since an IB is not required, 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.[4]

10.1.4. Suspected Adverse Reaction

Any AE for which there is a reasonable possibility that the drug caused the event. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest

[2] CFR 312.23 – IND Safety Reporting, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32
[3] ICH E6 – Good Clinical Practice: Consolidated Guidance, Glossary, p 1.
[4] [4] CFR 312.23 – IND Safety Reporting, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

a causal relationship between the study 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.[5]

10.1.5. 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 Sponsor, its occurrence places the subject at immediate risk of death. Life-threatening AEs do not include AEs or suspected adverse reactions that, had they occurred in a more severe form, might have caused death.[6]

10.1.6. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction that, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death
- Is life-threatening[7]
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity, meaning there is a substantial disruption of the subject's ability to conduct normal life functions
- A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.[8]

10.1.7. Treatment-Emergent Adverse Event (TEAE)

An AE not present prior to initiation of therapy, or an already present event that worsens either in intensity or frequency following initiation of therapy will be considered Treatment-Emergent.

[5] CFR 312.23 – IND Safety Reporting, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32
[6] CFR 312.23 – IND Safety Reporting, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32
[7] A life-threatening SAE is any AE or adverse reaction that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred (*i.e.,* it does not include a reaction that, had it occurred in a more severe form, might have caused death).
[8] CFR 312.23 – IND Safety Reporting, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

10.2. Adverse Event Assessment and Documentation

All AEs that occur from the time the subject receives the first dose of study drug[9] until study participation has been completed (e.g., TEAEs) must be documented. Any medical condition present prior to the first study drug dose that remains unchanged or improves will not be recorded as an AE; however, a worsening of the condition after dosing with the study drug, will be considered an AE.

Adverse events may be determined by evaluating the following in relation to the study subject:

- Observed or volunteered problems
- Complaints
- Physical signs and symptoms
- The occurrence of a medical condition during the study, which was absent at baseline
- The worsening of a baseline medical condition during the study

Treatment-emergent AEs, regardless of causal relationship, must be assessed by the investigator and recorded in the source documentation and the appropriate eCRF. Each AE must be described as ocular or non-ocular along with the following information: date of onset, date of resolution, severity, frequency of the event (single episode, intermittent, continuous), action taken (none, medical and/or surgical), relationship to study drug, and seriousness criteria. Any medication necessary for the treatment of an AE must be recorded on the Concomitant Medication eCRF and any surgical intervention necessary for AE treatment must be recorded on the Concomitant Procedure eCRF. If more than one distinct AE occurs, each event should be recorded separately.

Adverse events will be documented beginning at the time of onset, and documentation must continue until recovery is noted. Events that are ongoing at the time of study exit must be followed until resolution or stabilization.

10.2.1. Adverse Event Severity

Adverse event severity will be assessed by the investigator using the following definitions:

Mild	Subject is aware of sign or symptom, but it is easily tolerated
Moderate	Subject experiences discomfort enough to cause interference with usual activity
Severe	AE is incapacitating to subject, causing inability to work or do usual activity

[9] *Events that occur between the Screening Visit and initial administration of study drug should be recorded as Medical History, and not as an AE.*

10.2.2. Adverse Event Relationship to Study Drug

The relationship of the AE to study drug will be assessed by the investigator using the following definitions:

Not Related	Evidence exists that the AE has a cause other than the study drug (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
Possibly Related	A temporal relationship exists between event onset and administration of study drug. Although the AE may appear unlikely to be related to the study drug, it cannot be ruled out with certainty; and/or the event cannot be readily explained by the patient's clinical state or concomitant therapies.
Probably Related	A temporal relationship exists between the event onset and administration of study drug; it appears with some degree of certainty to be related based on known therapeutic and pharmacologic actions of the study drug. It cannot be readily explained by the patient's clinical state or concomitant therapies.
Definitely Related	Strong evidence exists that the study drug caused the AE. There is a temporal relationship between the event onset and administration of the study drug. There is strong therapeutic and pharmacologic evidence that the event was caused by the study drug. The patient's clinical state and concomitant therapies have been ruled out as a cause.

10.3. Adverse Event Reporting

Any treatment-emergent AE occurring in the study must be reported on the AE eCRF. Expedited reporting of an AE is required if the event is considered "serious", regardless of relationship to the study drug or whether the event is expected or unexpected.

10.3.1. Expedited Adverse Event Reporting

Any SAE that occurs during the study, regardless of relationship to the study drug, or whether the event is expected or unexpected, ***must be reported to the Sponsor, or the Sponsor's designee, within 24 hours*** of the investigator's becoming aware of the event.

Reports should be made by completing the SAE eCRF. Information provided on the SAE eCRF should be supplemented with hospitalization records, death certificate, clinic notes from specialists evaluating the subject's condition, etc. as applicable for the event. The urgency for reporting SAEs is 3-fold:

- to facilitate discussion [and implementation, if necessary] by the Sponsor and the Investigator of appropriate follow-up measures;
- To facilitate Investigator reporting of unanticipated problems involving risk to human subjects to the IRB/EC; and
- To enable the Sponsor to fulfill the reporting requirements to the appropriate regulatory authority.

10.4. Device Deficiency Reporting

Any adverse event directly related to the use of the MydCombi dispenser must be documented and reported per the requirements listed in CFR Part A Section 803.10. Reporting to the sponsor withing 24 hours of learning of the event as follows:

- Reports of death
- Reports of serious injury

Device malfunction not related to an individual subject or that do not result in an adverse event should be report to the sponsor as soon as possible and include a description of the issue.

11. STATISTICAL METHODS

The primary objective of this study is to evaluate the safety and efficacy of one administration of MydCombi, Eyenovia's fixed combination of phenylephrine 2.5%-tropicamide 1% ophthalmic solution administered with MydCombi dispenser for dilation of the pupil. Descriptive statistics will be employed to define the dilation curve for a single spray.

11.1. Efficacy Endpoints

Primary Efficacy Endpoint: An efficacy analysis will be conducted to characterize a single spray of MydCombi:

The primary performance endpoint is mean change per visit in pupil diameter at 30 minutes versus baseline, as measured by digital pupillometry in highly photopic conditions. The highly photopic condition will be established using a fully-charged transilluminator (muscle light) at the brightest setting.

Additional Efficacy Analyses:

- Proportion of eyes achieving pupil diameter of 6.0 mm or greater at 30 minutes
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater at 30 minutes
- Mean change in pupil diameter at other timepoints (15, 60, 90, 150, 210 and 360 minutes)
- Distribution of pupil diameters at 15, 30, 60, 90, 150, 210 and 360 minutes
- Time from baseline to maximal pupil dilation

No other formal analyses are planned.

These additional efficacy readings will also be measured using digital pupillometry in highly photopic conditions.

11.2. Sample Size

Up to 30 subjects who have provided informed consent for study participation will be enrolled in the study and a minimum of 25 subjects will be receive study drug administration at Treatment Visit with the goal of having 25 subjects evaluable for the primary efficacy endpoint. The study's sample size will provide data to generate descriptive statistics for the dilation curve for 1 spray of MydCombi.

11.3. Safety Outcomes

A safety analysis will be conducted to summarize the effects of a single spray of phenylephrine 2.5%-tropicamide 1% ophthalmic solution for the following outcomes:

- Slit-lamp examination findings
- Occurrence of AEs
- IOP measured at 90 minutes post-administration*
- Visual acuity changes

11.4. Analysis Populations

Subjects who are missing efficacy assessments at any of the time points or are otherwise unevaluable for efficacy considerations will not be replaced.

11.4.1. Intent to Treat Population

The intent to treat (ITT) population will consist of all subjects who received a dose of study drug.

11.4.2. Per Protocol Population

The per protocol (PP) population will consist of all ITT subjects who completed all planned assessments without major protocol violations.

11.4.3. Safety Population

The safety population will consist of all ITT subjects.

11.5. General Statistical Considerations

Primary efficacy analyses will be conducted on the PP population. Safety analyses will be performed using the safety analysis set. All primary analyses will be performed in both eyes. The pupil diameter measurement at each corresponding time point after administration will be characterized. Descriptive statistics will be used to summarize continuous outcomes (number of subjects [N], mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables, i.e. race, sex, iris color (frequency and percentage) at each assessment time point.

11.5.1. Analysis of Primary Efficacy

All time points for pupil diameter will be analyzed separately; however, only the 30-minute time point will support the primary efficacy analysis. Success is defined as drug effect resulting in ability to visualize the back of the eye. A pupil size of 6 mm is considered adequate to visualize the back of the eye.

11.5.2. Additional Efficacy Analyses

The proportion of eyes achieving pupil size of 6.0 mm or greater and 7.0 mm or greater at 30 minutes post-dose will be summarized by eye with descriptive statistics.

The distribution of time to maximum pupil diameter will be described by Kaplan-Meier plots.

Descriptive statistics will be employed to define the dilation curve for a single spray of MydCombi.

11.5.3. Interim Analyses

No interim analyses are planned for this study.

11.5.4. Analysis of Baseline Data

No separate analyses of baseline data are planned for this study.

12. QUALITY ASSURANCE AND QUALITY CONTROL

The Sponsor or designee will perform quality control and quality assurance checks for this study. Before initiation of study enrollment, the following documents will be reviewed with the investigator, site study staff, and pharmacy, as applicable:

- Study protocol
- MydCombi preparation procedures
- MydCombi administration procedures
- Electronic Case Report Forms (eCRF) and procedures for completion
- Informed consent process
- Adverse event (AE) reporting procedures

12.1. Study Monitoring

During the study, the Sponsor or designee will perform periodic visits to study sites. During these visits, information recorded on the study eCRFs will be verified against source documents to confirm data capture completeness, accuracy and logical consistency. Study documents will be reviewed to confirm protocol compliance and adherence to IRB and Sponsor-specified reporting requirements, and product accountability will be checked.

12.2. Study Product Accountability

Commercially available MydCombi will be used for this study. Accurate records of each MydCombi dispenser and medication administered must be maintained by the Sponsor, or designee, and each study investigator. Site personnel must review the shipper at the time of kit receipt and notify the Sponsor, or designee, of any discrepancies. The Sponsor, or designee, will provide an accountability log for the study medication.

The study investigator is responsible for documenting each MydCombi dispenser used, the date of use, the identifiers for subjects who received study drug, and the number of sprays administered to each subject eye.

MydCombi product accountability will be performed by reconciling all dispensers provided to the pharmacy with dispensers used for study drug administration, subjects for whom the dispenser was used, and dispensers returned to the Sponsor or designee.

13. ETHICAL AND REGULATORY CONSIDERATIONS

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP)[10]. Sponsor and Investigator responsibilities associated with adherence to GCP and CFR 312 are specified in **APPENDIX 4: SPONSOR AND INVESTIGATOR OBLIGATIONS**. The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later amendments (see **APPENDIX 5: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**).

13.1. Institutional Review

Before enrollment of study subjects, this protocol and the study-specific consent form must be reviewed and approved by an IRB operating in accordance with 21 CFR Part 50. Any changes to the study protocol or consent forms must be approved by the IRB prior to implementation. Materials for study patient recruitment and study-specific written materials provided to the subject must also be approved by the IRB prior to use.

Ongoing study progress reports will be submitted to the IRB at least annually, and more frequently if specified by the IRB. Reports of safety events and any protocol deviations that affect the safety and welfare of a study subject will be submitted to the IRB in accordance with FDA and IRB requirements.

13.2. Informed Consent

The study consent form has been developed in compliance with 21 CFR Part 50.25. Study consent form(s) must be submitted to and approved by the IRB prior to implementation. Any IRB-requested modifications to the consent form must remain in compliance with 21 CFR Part 50.25.

As discussed in **Section 9.1**, each participant must be provided with a copy of the IRB-approved consent form(s) for their review, and the participants written approval(s) must be provided prior to initiation of study procedures.

13.3. Subject Confidentiality

The Investigator will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in the study records. The records will be made available as required for review by FDA and a reviewing IRB; however, to the extent possible, the subject's identity will not be disclosed.

[10] Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry, March 2018.

14. DATA HANDLING AND RECORD KEEPING

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.

14.1. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be applied and written queries pertaining to data omissions and discrepancies will be forwarded to study sites for resolution. Study staff will update the database as appropriate to resolve queries generated. All changes to the study database will be documented.

14.2. Data Archiving

Archived versions of the database will be saved by the Sponsor or designee consistent with ICH GCP Guidelines, complying with whichever of the requirements is longer. The Sponsor will notify the investigator when documents should be returned.

14.3. Records Retention

The Investigator's site will retain all records related to the study in compliance with ICH GCP Guidelines.

14.4. Protocol Amendments

Modifications to the approved protocol are only possible using 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. This should be fully documented.

The investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by the Sponsor and prior review and documented approval/favorable opinion of the amendment from the relevant IRB, except where it is necessary to eliminate an immediate hazard to study patients, 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).

15. REFERENCES

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- CFR 314.80 Device deficiency reporting https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=803&showFR=1#:~:text=You%20must%20submit%20a%20report,or%20maintenance%20of%20one%20of
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APPENDIX 1: SCHEDULE OF MEDICATION ADMINISTRATION AND EXAMS

Assessment/Procedure	Screening Visit (Day -7 to Day 0)	Treatment Visit								
		Baseline[0]	Time 0[1]	Time 1 T0+15 min (± 2 min)	Time 2 T0+30 min (± 5 min)	Time 3 T0+60 min (± 5 min)	Time 4 T0+90 min (± 5 min)	Time 5 T0+150 min (± 10 min)	Time 6 T0+210 min (± 10 min)	Time 7 T0+360 min (± 10 min)
Informed consent	X									
Demographics	X									
Medical history	X									
Ocular history	X									
Urine pregnancy test[7]	X									
Prior/concomitant medication use	X									
DVA using habitual correction (OU)[2]	X	X								X
Study drug administration (OU)			X							
Slit lamp biomicroscopy (OU)	X	X								X
Angle Assessment[4]	X									
IOP (OU)[5]	X	X					X			
Pupil diameter assessment (OU)[3]	X	X		X	X	X	X	X	X	X
Pupillary light reflex (OU)	X	X			X		X			X
Study eligibility determination	X									
AE assessment	X	X								X

[0]Baseline refers to evaluations made at the Treatment Visit prior to study medication administration. If screening and baseline are completed on the same day, the screening values may be used for baseline.
[1] The completion of the administration of medication in the subject's second eye will be considered Time 0 (T0).
[2]DVA to be measured using subject's habitual correction according to office standard of practice.
[3]Performed using Neuroptics pupillometer – VIP 300.
[4] Performed as part of slit lamp examination using investigator's preferred method.
[5] IOP to be measured using noncontact tonometer.
[6] Performed using Neuroptics pupillometer – VIP 300.
[7]A urine pregnancy test will be conducted for females of childbearing potential

APPENDIX 2: MYDCOMBI APPROVED LABEL

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MYDCOMBI® safely and effectively. See full prescribing information for MYDCOMBI.

MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5%, for topical ophthalmic use
Initial U.S. Approval: 2023

---------- INDICATIONS AND USAGE ----------
MYDCOMBI is a combination of tropicamide, an anticholinergic, and phenylephrine hydrochloride, an alpha-1 adrenergic receptor agonist indicated to induce mydriasis for diagnostic procedures and in conditions where short term pupil dilation is desired (1)

----------DOSAGE AND ADMINISTRATION----------
Administer one metered spray to the cornea of each eye to be dilated. Repeat after 5 minutes. (2.1)
In pediatric patients younger than 1 year old, administer one metered spray to the cornea of each eye to be dilated, up to a maximum of 3 sprays per eye per day (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Ophthalmic spray containing tropicamide 1% and phenylephrine hydrochloride 2.5%. Each metered spray delivers 0.008 mL which contains 0.08 mg tropicamide and 0.2 mg phenylephrine HCl (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to any component of the formulation (4.1)

---------- WARNINGS AND PRECAUTIONS ----------
Not for Injection: Topical ophthalmic use (5.1)
Significant Elevations in Blood Pressure: Caution in pediatric patients less than 5 years of age, and in patients with cardiovascular disease or hyperthyroidism. In patients at high risk, monitor blood pressure post treatment (5.2)
Central Nervous System Disturbances: Caution in pediatric patients where rare incidences of central nervous system disturbances have been reported (5.3)
Intraocular Pressure: May produce a transient elevation (5.4)
Rebound Miosis: Reported 1 day after administration (5.5)

---------- ADVERSE REACTIONS ----------
Most common ocular adverse reactions include transient blurred vision, reduced visual acuity, photophobia, superficial punctate keratitis, and mild eye discomfort. Increased intraocular pressure has been reported following the use of mydriatics (6.1)
Systemic adverse reactions including dryness of the mouth, tachycardia, headache, allergic reactions, nausea, vomiting, pallor, central nervous system disturbances and muscle rigidity have been reported with the use of tropicamide (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Eyenovia, Inc. at 1-833-393-6684 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

---------- DRUG INTERACTIONS ----------
Atropine-like Drugs: May exaggerate the adrenergic pressor response (7.1)
Cholinergic Agonists and Ophthalmic Cholinesterase Inhibitors: May interfere with the antihypertensive action of carbachol, pilocarpine, or ophthalmic cholinesterase inhibitors (7.2)
Potent Inhalation Anesthetic Agents: May potentiate cardiovascular depressant effects of (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------
Pediatric Use: May rarely cause central nervous system disturbances which may be dangerous in pediatric patients (5.3, 8.4)

See 15 for PATIENT COUNSELING INFORMATION

Revised: 5/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1% / 2.5% is indicated to induce mydriasis for diagnostic procedures and in conditions where short term pupil dilation is desired.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Administer one metered spray to the cornea of each eye to be dilated. Repeat after 5 minutes.

Pediatric Patients Younger Than 1 Year Old

In pediatric patients younger than 1 year old, administer one metered spray to the cornea of each eye to be dilated, up to a maximum of 3 sprays per eye per day.

2.2 Administration Instructions

The following steps should be followed sequentially:

A. Load the MYDCOMBI dispenser by depressing the FILL BUTTON at the top of the dispenser once.

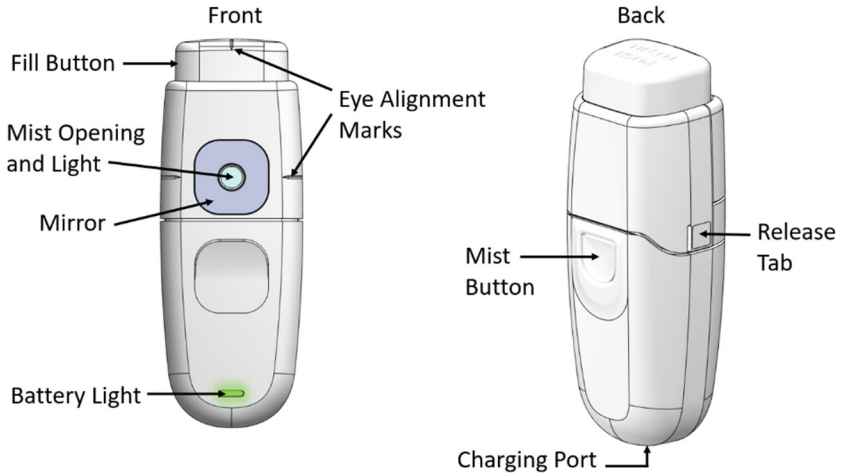


Figure 1: MYDCOMBI Dispenser Front (L) and Back (R) View

B. Hold MydCombi™ dispenser with thumb over Mist Button, wrapping other fingers around base.
C. Bring MydCombi™ dispenser to patient's eye with Mirror facing the eye.
   - The dispenser should be as close as patient's nose.

- To prevent blinking, use your other hand to gently pull lower eyelid down or ask patient to pull her/his lid down.

D. Aim Mist Opening toward the center of eye.
E. Confirm Alignment Marks (on the Fill Button and the cartridge side) align with the center of eye.
   - Ask patient to confirm when their eye is centered on the BLUE Mirror.

   If patient is having trouble centering their eye on the blue light, ask that they look up, then look at the BLUE Mirror.
F. Firmly press and release Mist Button.
   - The drug solution should gently wet the eye. Repeat steps A to F if needed.
G. Administer a second metered spray after 5 minutes to each dilated eye.
H. Repeat steps A to G for the contralateral eye if it is to be dilated.

3 DOSAGE FORMS AND STRENGTHS

MYDCOMBI is a sterile, clear, colorless, topical ophthalmic spray containing tropicamide 1% (w/w) and phenylephrine hydrochloride 2.5% (w/w). Each metered spray delivers 0.008 mL which contains 0.08 mg tropicamide and 0.2 mg phenylephrine hydrochloride.

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity

Contraindicated in persons showing known hypersensitivity to any component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use

MYDCOMBI is not indicated for injection.

5.2 Blood Pressure Elevation

Caution should be exercised with the use of MYDCOMBI in pediatric patients less than 5 years of age and patients with hyperthyroidism, or cardiovascular disease. The post-treatment blood pressure of patients with cardiac and endocrine diseases and any patients who develop symptoms should be carefully monitored.

5.3 Central Nervous System Disturbances

Tropicamide in MYDCOMBI may cause CNS disturbances which may be dangerous in pediatric patients. The possibility of psychotic reactions and behavioral disturbances due to hypersensitivity to anticholinergic drugs should be considered.

5.4 Intraocular Pressure

Mydriatics may produce a transient elevation of intraocular pressure.

5.5 Rebound Miosis

Rebound miosis has been reported one day after receiving phenylephrine hydrochloride ophthalmic solution, and re-administration of the drug produced a lesser mydriatic effect.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reactions (incidence < 2%) were transient blurred vision, reduced visual acuity, photophobia, and mild eye discomfort.

6.1 Ocular Adverse Reactions

Transient blurred vision, reduced visual acuity, photophobia, superficial punctate keratitis, and mild eye discomfort may occur. Increased intraocular pressure has been reported following the use of mydriatics.

6.2 Systemic Adverse Reactions

Dryness of the mouth, tachycardia, headache, allergic reactions, nausea, vomiting, pallor, central nervous system disturbances and muscle rigidity have been reported with the use of tropicamide. Psychotic reactions, behavioral disturbances, and vasomotor or cardiorespiratory collapse in children have been reported with the use of anticholinergic drugs.

A marked increase in blood pressure has been reported with the use of phenylephrine, particularly, but not limited to, low weight premature neonates, infants, and hypertensive patients.

7 DRUG INTERACTIONS

7.1 Agents That May Exaggerate Pressor Responses

Phenylephrine in MYDCOMBI may enhance the pressor effects of atropine-like drugs and induce tachycardia in some patients.

7.2 Cholinergic Agonists and Ophthalmic Cholinesterase Inhibitors

Tropicamide in MYDCOMBI may interfere with the antihypertensive action of carbachol, pilocarpine, or ophthalmic cholinesterase inhibitors.

7.3 Potent Inhalation Anesthetic Agents

Phenylephrine in MYDCOMBI may potentiate the cardiovascular depressant effects of some inhalation anesthetic agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on MYDCOMBI use in pregnant women or animals to inform any drug-associated risks. It is also not known whether tropicamide or phenylephrine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. MYDCOMBI should be given to a pregnant woman only if clearly needed.

8.2 Lactation

Risk Summary

There are no data on the presence of tropicamide or phenylephrine in human milk from the administration of MYDCOMBI, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MYDCOMBI and any potential adverse effects on the breastfed child from MYDCOMBI.

8.4 Pediatric Use

Tropicamide in MYDCOMBI may rarely cause CNS disturbances which may be dangerous in pediatric patients. Psychotic reactions, behavioral disturbances, and vasomotor or cardiorespiratory collapse in children have been reported with the use of anticholinergic drugs *[see Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

No overall differences in safety or effectiveness of MYDCOMBI have been observed between patients 65 years of age and older and younger adult patients.

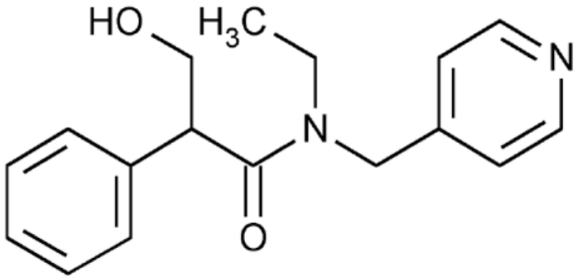
10 OVERDOSAGE

Overdosage of MYDCOMBI may cause a rapid rise in blood pressure. It may also cause headache, anxiety, nausea and vomiting, and ventricular arrhythmias. Prompt injection of a rapidly acting alpha-adrenergic blocking agent such as phentolamine has been recommended.

11 DESCRIPTION

MYDCOMBI is a sterile, clear, colorless fixed dose combination of an anticholinergic (tropicamide) and an alpha-adrenergic receptor agonist (phenylephrine hydrochloride) for topical ophthalmic use. The 2 active ingredients are represented by the chemical structures below.

Tropicamide:

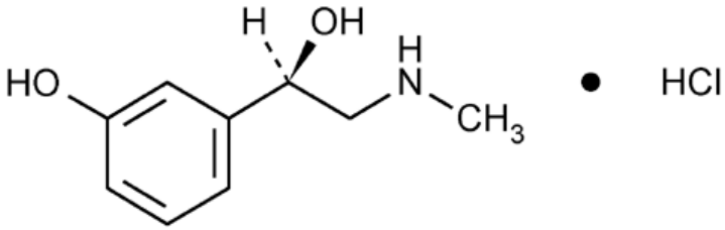


Chemical Name: Benzeneacetamide, N-ethyl-α-(hydroxymethyl)-N-(4-pyridinylmethyl)-

Molecular Formula: $C_{17}H_{20}N_2O_2$

Molecular Weight: 284.35 g/mol

Phenylephrine Hydrochloride:



Chemical Name: (R)-3-hydroxy-α[(methylamino)methyl]benzenemethanol hydrochloride

Molecular Formula: $C_9H_{13}NO_2 \bullet HCl$

Molecular Weight: 203.67 g/mol

Each mL of MYDCOMBI ophthalmic spray (sterile) contains: ACTIVES: Phenylephrine Hydrochloride 2.5% (25 mg) equivalent to 20.6 mg of phenylephrine base, Tropicamide 1% (10 mg); INACTIVE: Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust pH (pH 4.8–5.2), Water for Injection; PRESERVATIVE: Benzalkonium Chloride 0.01% (0.1 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tropicamide, the anticholinergic component of MYDCOMBI, blocks the responses of the sphincter muscle of the iris, dilating the pupil (mydriasis). Phenylephrine hydrochloride, the alpha-1 adrenergic agonist component of MYDCOMBI, acts as a mydriatic agent by contracting the dilator muscle of the iris.

12.2 Pharmacodynamics

MYDCOMBI acts in 15 to 30 minutes with maximal mydriasis occurring in 20 to 90 minutes. Darker irides tend to dilate slower than lightly pigmented irides and to achieve maximal effect may require more doses than lighter irides.

Mydriasis will reverse spontaneously with time, with recovery after 3 to 8 hours. Complete recovery from mydriasis in some individuals may require 24 hours.

13 CLINICAL STUDIES

Two Phase 3 clinical trials were conducted to evaluate the efficacy of MYDCOMBI for achievement of mydriasis. The MIST-1 study was a prospective, double-masked, active-controlled, 3-period cross-over, superiority study to compare the pupil dilating effect of MYDCOMBI to tropicamide 1% and to phenylephrine 2.5%, with all solutions topically administered by the Optejet® Dispenser (N = 64 subjects; 128 eyes). The MIST-2 study was a prospective, multicenter, double-masked, placebo-controlled, 3-period crossover, superiority study to compare the pupil dilating effect of MYDCOMBI to placebo (eyewash solution), with both solutions topically administered by the Optejet Dispenser (N = 70 subjects; 140 eyes).

The primary efficacy endpoint for both studies was the mean change in 35-minute pupil diameter compared to baseline as measured by digital pupillometry in highly photopic conditions. Data from the 2 studies are presented in Table 1. At 35 minutes post-dose, the mean change in pupil diameter was 4.7 mm with MYDCOMBI, 4.1 mm with tropicamide, and 0.9 mm with phenylephrine in MIST-1, and was 4.8 mm with MYDCOMBI and 0.1 mm with placebo in MIST-2. MYDCOMBI was statistically superior to tropicamide administered alone and phenylephrine administered alone.

Table 1 Pupil Size and Change in Diameter from Baseline at 35 Minutes Post-Dose (MIST-1 and MIST-2) (Per-Protocol Population [1])

	MIST-1			MIST-2	
Visit	MYDCOMBI (N = 124)	Tropicamide Alone (N = 124)	Phenylephrine Alone (N = 124)	MYDCOMBI (N = 138)	Placebo (N = 138)
Mean Baseline (SD)	2.6 (0.05)	2.6 (0.05)	2.6 (0.05)	2.6 (0.04)	2.6 (0.04)
35-Minutes Post-Dose (SD)	7.3 (0.08)	6.7 (0.08)	3.5 (0.08)	7.3 (0.07)	2.7 (0.05)
Change from Baseline (SD)	4.7 (0.07)	4.1 (0.06)	0.9 (0.08)	4.8 (0.07)	0.1 (0.04)
Difference from MYDCOMBI (95% CI) [2]	--	0.6 (0.4, 0.8)	3.9 (3.7, 4.1)	--	4.7 (4.5, 4.8)

SD=Standard Deviation

[1] The per-protocol (PP) population included all randomized subjects who received at least one dose of study medication and completed all planned assessments (related to the primary endpoint) without major protocol violations. Two subjects in MIST-1 and one subject in MIST-2 who withdrew consent after their first treatment visit were not included in the PP populations which resulted in 62 completed subjects (124 eyes) in MIST-1 and 69 completed subjects (138 eyes) in MIST-2 comprised the PP populations. Sensitivity analysis performed on the intent-to-treat (ITT) population including all randomized subjects resulted in consistent efficacy results.

[2] Treatment differences and 95% confidence interval estimates were based on a mixed model including treatment, eye, baseline diameter, and carryover effect (for MIST-2 study only). In both studies, an unstructured covariance structure was used to account for within-subject correlation between eyes.

MYDCOMBI provided a clinically significant effect in the proportion of eyes achieving pupil diameter of ≥ 6 mm at 35-minute post-dose in 94% of eyes compared to 78% of eyes administered tropicamide alone and 1.6% of eyes administered phenylephrine alone, and 0% of eyes administered placebo. As shown in Figure 2, peak effect was measured at the 80-minute evaluation when the mean change from baseline was 5.2 mm. Treatment differences in mydriasis were observed as early as 20 minutes and still present at 180 minutes post-dose, the end of the protocol-specified observation period.

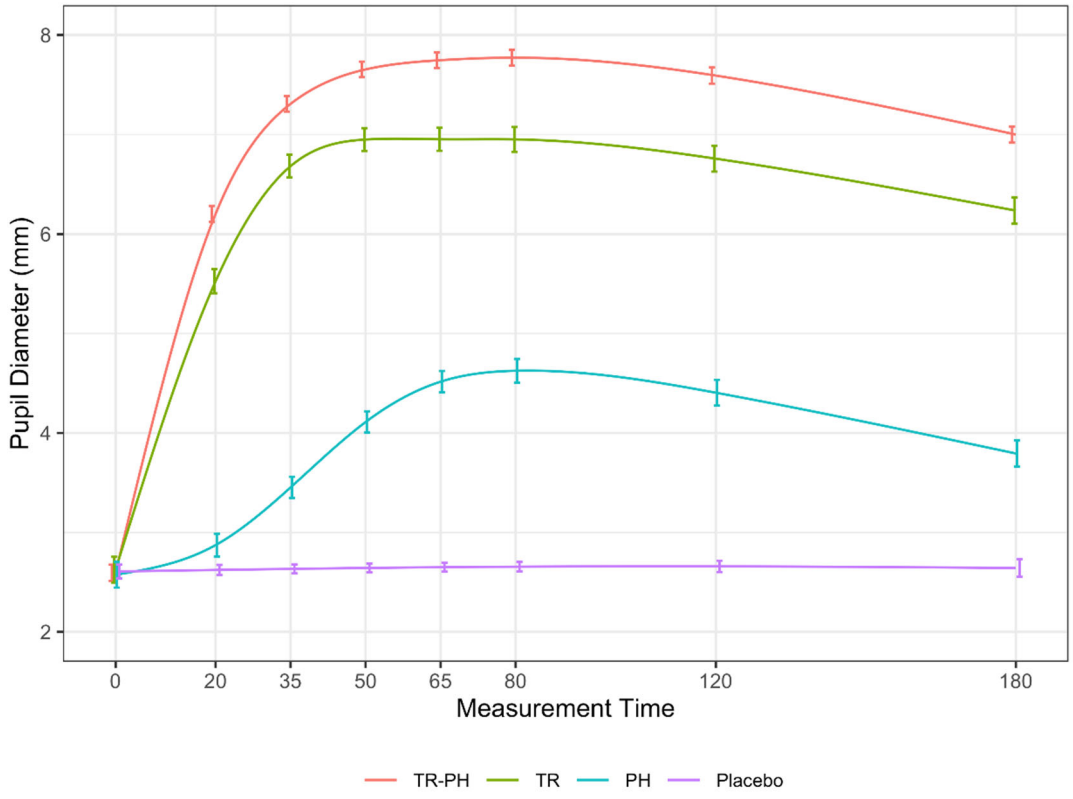


Figure 2: MIST-1 and MIST-2 pooled, mean pupil diameter vs measurement time, by treatment group. Vertical bars show 95% confidence interval for the mean at each point. Smooth curves are based on an 8 degrees of freedom (df) generalized additive model (GAM) smooth through time, adjusting for baseline pupil diameter. Confidence intervals are not adjusted for correlation.

14 HOW SUPPLIED/STORAGE AND HANDLING

MYDCOMBI is supplied as sterile, clear, colorless solution in a 2 mL vial enclosed in a dispenser cartridge. Each MYDCOMBI cartridge holds approximately 180 sprays.

Do not tamper with or attempt to open the MYDCOMBI cartridge. Such action may damage the dispenser causing an incorrect medication discharge volume; additionally, the dispenser base may not function properly.

Only use the MYDCOMBI cartridge with the MYDCOMBI Dispenser base which may be supplied separately. The MYDCOMBI base will not work with any other cartridges.

NDC 81046-0111-1. Carton containing one replacement sterile drug cartridge

NDC 81046-0111-2. Box containing one carton with one sterile drug cartridge, and one carton with one base unit

NDC 81046-0111-5. Box containing five cartons, each with one replacement sterile drug cartridge

The MYDCOMBI cartridge must be used prior to the expiration date on the cartridge.

Storage: Store at room temperature 15°C to 25°C (59°F to 77°F).

Manufactured for Eyenovia, Inc. by Alcami Corporation

15 PATIENT COUNSELING INFORMATION

Advise patients that they may experience sensitivity to light and blurred vision while their pupils are dilated.

Advise patients not to drive, use machinery, or do any activity that requires clear vision until they are sure they can perform such activities safely.

APPENDIX 3: EXAMINATION PROCEDURES

1. Visual Acuity

The evaluation of VA will be determined using the subject's habitual refraction. Distance VA measurements should be obtained at a testing distance of 4 meters by an optometrist, physician, or trained technician and according to the office standard of practice.

2. Pupil Diameter Measurement

Pupil diameter should be measured prior to additional study-specified examinations using the Neuroptics VIP 300 pupillometer; the same pupillometer should be used for each evaluation on any study visit day for a given subject. The subject should be asked to focus straight ahead at a target placed at 3 meters to avoid accommodation. A fully-charged transilluminator, or muscle light, will be shone into one eye while the pupillometer is used to measure the pupil diameter in the fellow eye. After a brief rest period, the process will be repeated to measure pupil diameter in the other eye.

3. Pupillary Light Reflex

Pupillary light reflex will be evaluated using a fully-charged transillumator, or muscle light. The response will be recorded on a scale ranging from 0 (non-responsive) to 3 (brisk).

4. Intraocular Pressure Measurement

IOP should be taken after the slit lamp examination using a non-contact tonometer that does not require anesthetic. Recent tonometer calibration must be documented.

The same tonometer should be used throughout the study.

5. Slit Lamp Biomicroscopy

The eyelids, conjunctiva, sclera, cornea, anterior chamber, lens, iris and anterior vitreous of the eye will be examined with the aid of a table-mounted binocular microscope, called a slit lamp. The patient will be seated during this examination and fluorescein dye should be instilled into the ocular cul-de-sac to facilitate the examination. Grading will be assigned as follows:

LID

Erythema

None (0)	Normal, without any redness, or less than mild
Mild (+1)	A low grade flushed reddish color
Moderate (+2)	Diffused redness encompassing entire lid margin
Severe (+3)	Deep diffused reddish color of lid margins and superior or inferior eyelid

Edema

None (0)	Normal, no swelling of the lid tissue, or less than mild
Mild (+1)	Slight diffuse swelling above normal
Moderate (+2)	General swelling
Severe (+3)	Extensive swelling of the eyelid, with/without eversion of upper or lower lids

CONJUNCTIVA

Hyperemia

None (0)	Normal. Appears white with a small number of conjunctival blood vessels 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 conjunctival with evidence of subconjunctival hemorrhage

Edema

None (0)	Normal, no swelling of the conjunctiva or less than mild
Mild (+1)	Slight diffuse or regional swelling of the conjunctiva
Moderate (+2)	General swelling of the conjunctiva
Severe (+3)	Extensive swelling of the conjunctiva

SCLERA

Normal
Abnormal

CORNEA

Edema

None (0)	Transparent and clear, or less than mild
Mild (+1)	Dull glassy appearance
Moderate (+2)	Dull glassy appearance of epithelium with large number of vacuoles
Severe (+3)	Stromal edema, localized or diffuse, with stromal striae

Staining

None (0)	No fluorescein staining of epithelium, or less than mild
Mild (+1)	Slight punctate fluorescein staining
Moderate (+2)	Regionally dense coalescent fluorescein staining

Severe (+3)	Marked fluorescein staining with immediate stromal leakage as a result of epithelial loss

ANTERIOR CHAMBER

Cells

None (0)	No cells seen, or less than mild
Mild (+1)	+ cells
Moderate (+2)	++ cells
Severe (+3)	+++ cells
Hypopyon (+4)	++++ cells, hypopyon formation (indicate hypopyon size)

Flare

None (0)	No Tyndall effect, or less than mild
Mild (+1)	Tyndall beam in the AC has mild intensity
Moderate (+2)	Tyndall beam in the AC is of strong intensity
Severe (+3)	Tyndall beam is very intensive. Aqueous has a white, milky appearance

IRIS

Normal
Abnormal

LENS

Lens Status

Phakic*

*Indicate **Lens Opacity Grade**:

None (0)	None present, or less than mild
Mild (+1)	Subtle
Moderate (+2)	Moderate
Severe (+3)	Dense

Pseudophakic
Aphakic

ANTERIOR VITREOUS

Normal
Abnormal

.

APPENDIX 4: SPONSOR AND INVESTIGATOR OBLIGATIONS

SPONSOR OBLIGATIONS

The Sponsor is committed to:

1. Complying with all applicable health authority regulations governing the conduct of clinical research studies, including the US FDA.
2. Protecting the rights, health, safety and welfare of study subjects.
3. Informing clinical investigators of any new information about the study which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.
4. Providing clinical investigators with the study protocol, and CRFs on which to document the study evaluation variables for each subject entered into the study.
5. Providing the statistical analysis and study report writing resources necessary to complete reporting of study results.
6. Ensuring equity of consideration among all investigators in multicenter studies in all matters of publications, meeting presentations, etc.
7. Certifying that IRB/EC approval of the protocol and Investigator Agreement will be completed prior to treatment at an investigational site.

The Sponsor shall have the right to terminate the study at any time by written notice to the investigator. Without limiting this right, the Sponsor will normally only terminate the study under the following circumstances:

- If severe and/or SAEs associated with the study medication in human and/or animal studies indicate discontinuation of the study
- If the Sponsor wishes to discontinue the study for commercial reasons
- If the Sponsor has reasons to believe that the study cannot be satisfactorily completed due to insufficient patient enrollment, or an insufficient number of participating study sites identified within a reasonable time frame.

INVESTIGATOR OBLIGATIONS

Each Investigator must be either a licensed optometrist or licensed physician who has completed a residency or preceptorship in ophthalmology. The Investigators have the following responsibilities:

1. **Subject Selection**
   The Investigator is responsible for assuring that all subjects entering the study conform to the patient selection criteria.

2. **Informed Consent**
   The Investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with prospective patients prior to their enrollment in the study. The Investigator is responsible for obtaining written informed consent in compliance with 21 CFR 50 for each patient, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the patient's medical record.

3. **Institutional Review Board/Ethics Committee Approval**
   The Investigator must obtain approval for participation in this protocol from the IRB/EC for the institution at which the procedure will be performed prior to entering any patients in the study. The ICF to be used will also be submitted to the IRB/EC for approval prior to initiation of the study. Assurance that IRB/EC approval of the study protocol and ICF has been obtained will be provided to the Sponsor, or Sponsor designee, prior to initiation of the study.

4. **Subject Evaluations and Data Reporting**
   The Investigator is responsible for complying with the requirements of the study protocol and any amendment or clarification as published by the Sponsor, or Sponsor designee. Patient evaluations will be performed as described in the study protocol. All information generated by the patient evaluation will be recorded using eCRFs with access provided by the Sponsor or Sponsor designee.

   Investigator(s) will not deviate from the study protocol without prior approval of the Sponsor, or Sponsor designee, unless the protection of health, safety or welfare of study subjects requires prompt action.

5. **Record Retention**
   The Investigator shall maintain all patient records for whichever of the following periods is shortest:
   a. A period of 2 years after the date on which the FDA approves the marketing of the drug for the purpose that was the subject of the study.
   b. A period of 5 years after the date on which the results of the study are submitted to the FDA in support of the marketing of the drug for the purpose that was the subject of the study.

6. **Investigational Material Accountability**
   The Investigator must maintain accurate records of the receipt of all investigational material shipped by the Sponsor, or Sponsor designee, including the date, and identification numbers of the

product received. In addition, accurate records must be kept on the amount and date that investigational material was dispensed or returned to the Sponsor. The Investigator must assure that study supplies be dispensed only to subjects enrolled in the study per study inclusion / exclusion criteria and under the direct supervision of the Investigator or his/her Co-Investigators.

Records of all investigational supplies received, used and returned must be kept by the Investigator. All unused investigational supplies must be returned to the Sponsor, or Sponsor designee, as soon as practical upon completion of the trial. Investigational material accounting procedures must be completed before the study is considered terminated.

APPENDIX 5: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be

evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate

any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious AEs. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional

affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

PROTOCOL EYN-MYD-TP-41
VERSION A

A SINGLE-CENTER, OPEN LABEL, PHASE 4 STUDY OF THE SAFETY AND EFFICACY OF FIXED COMBINATION PHENYLEPHRINE 2.5%-TROPICAMIDE 1% OPHTHALMIC SOLUTION (MYDCOMBI®) ADMINISTERED WITH THE MYDCOMBI DISPENSER FOR PUPIL DILATION (THE MIST-2.1 STUDY)

SPONSOR:

EYENOVIA, INC.
295 MADISON AVENUE, SUITE 2400
NEW YORK NY 10017
USA
PHONE: 833-393-6684

I have read this protocol in its entirety. I agree to:

- Implement and conduct this study in compliance with this study protocol; conditions of approval imposed by FDA and my reviewing Institutional Review Board (IRB); Good Clinical Practice (GCP); and any other applicable laws and regulations.
- Maintain all study-related information supplied by Eyenovia in a confidential manner.

Protocol Amendment

Modification of the study protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the reviewing IRB prior to implementation at your site, except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

_____	_____	_____
Print Name of Investigator	Signature	Date