

**PROTOCOL EYN-MYD-TP-32  
VERSION C**

**A MULTI-CENTER, DOUBLE-MASKED, PLACEBO-CONTROLLED, PHASE 3 STUDY OF  
THE SAFETY AND EFFICACY OF FIXED COMBINATION PHENYLEPHRINE 2.5%-  
TROPICAMIDE 1% OPHTHALMIC SOLUTION ADMINISTERED WITH A MICRODOSE  
DISPENSER FOR DILATION OF THE PUPIL  
(THE MIST-2 STUDY)**

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**LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Term</b>
AC	Anterior chamber
AE	Adverse event
ADR	Adverse drug reaction
AT	Artificial tears
BCDVA	Best-corrected distance visual acuity
CF	Count fingers
CFR	Code of Federal Regulations
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
MiDD	Eyenovia MicroDose Dispenser
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 Eyenovia's fixed combination of phenylephrine 2.5%-tropicamide 1% ophthalmic solution administered with Eyenovia's microdose dispenser (MiDD) for dilation of the pupil as compared a placebo.

### **2.2. Study Drugs**

- **Investigational Product, Dosage and Mode of Administration:** Fixed combination ophthalmic solution (phenylephrine 2.5%-tropicamide 1%) administered by Eyenovia's MiDD.
- **Placebo, Dosage and Mode of Administration:** Eyewash solution administered by Eyenovia's MiDD.

### **2.3. Study Population**

Up to 90 volunteer participants will be enrolled at 2 – 3 study sites in the United States (US) and a minimum of 65 subjects will be randomized to study drug administration at Treatment Visit 1 in order to complete follow-up on 54 subjects.

### **2.4. Study Design**

This trial is a multicenter, double-masked, placebo-controlled, cross-over superiority study evaluating Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution versus placebo.

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 inclusion/exclusion criteria will be scheduled for 3 treatment visits, which must occur at least 2 days, but no more than 7 days apart. A 2 sequence, 3 period crossover design will be used. At each of the three treatment visits, baseline measurements will be taken, then either the investigational drug or the placebo will be administered to both eyes (OU) in two separate instances, approximately 5 minutes apart. Only 1 drug will be administered per treatment visit, and drug administration will occur in a randomized order using one of two sequences - ABB and BAA, where A is the Eyenovia fixed combination and B is the placebo control. Afterwards, efficacy and safety assessments will be performed.

This study will be double-masked. There will be no differences in the presentation of the investigational drug or placebo administered and all study personnel conducting ophthalmic assessments will be masked to study drug assignment. Study drug administration will be performed by at least 3 different trained personnel during the study. Personnel who administer study drug on a given day will not be allowed to perform post-study drug administration ophthalmic assessments on that day.

## **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 of any age.
2. Female subjects must be either pre-menarche, 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. Subjects under the age required for informed consent must have the ability to provide additional written assent and/or parental consent, as required by the reviewing Institutional Review Board (IRB).
4. Ability to return for all study treatment visits.
5. Photopic screening pupil diameter  $\leq 3.5$  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. Use of benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressants, anticonvulsants, cholinergic drug at screening or anticipated during the study period.
7. 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.
8. History of closed-angle glaucoma.
9. Anatomically narrow anterior chamber angles (Van Herrick grade  $\leq 2$  in either eye).
10. Ocular surgery or laser treatment of any kind prior to the Screening Visit.
11. History of chronic or acute uveitis.
12. History of traumatic iritis or hyphema.
13. History of traumatic mydriasis or angle recession.
14. History of heterochromia.
15. Irregularly-shaped pupil secondary to ocular trauma or congenital defect.
16. History of neurogenic pupil disorder (e.g., Horner's syndrome, third cranial nerve palsy, Adie's pupil, Argyl Robertson syndrome, etc.).
17. History of anterior chamber intraocular lens (IOL) or iris-fixated IOL.
18. History of iris surgery of any kind (e.g., iridotomy, iridectomy, coreoplasty).

19. History of iris atrophy.
20. History of iris – cornea apposition/touch.
21. Unwilling or unable to discontinue use of contact lenses at treatment visits.
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 each 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 mean change in pupil diameter at 35 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.

### **2.8. Exploratory Outcomes**

- Proportion of eyes achieving pupil diameter of 6.0 mm or greater at 35 minutes
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater at 35 minutes
- Mean change in pupil diameter at other timepoints (20, 50, 65, 80, 120, and 180 minutes)
- Distribution of pupil diameters at 20, 35, 50, 65, 80, 120, and 180 minutes
- Time from baseline to maximal pupil dilation

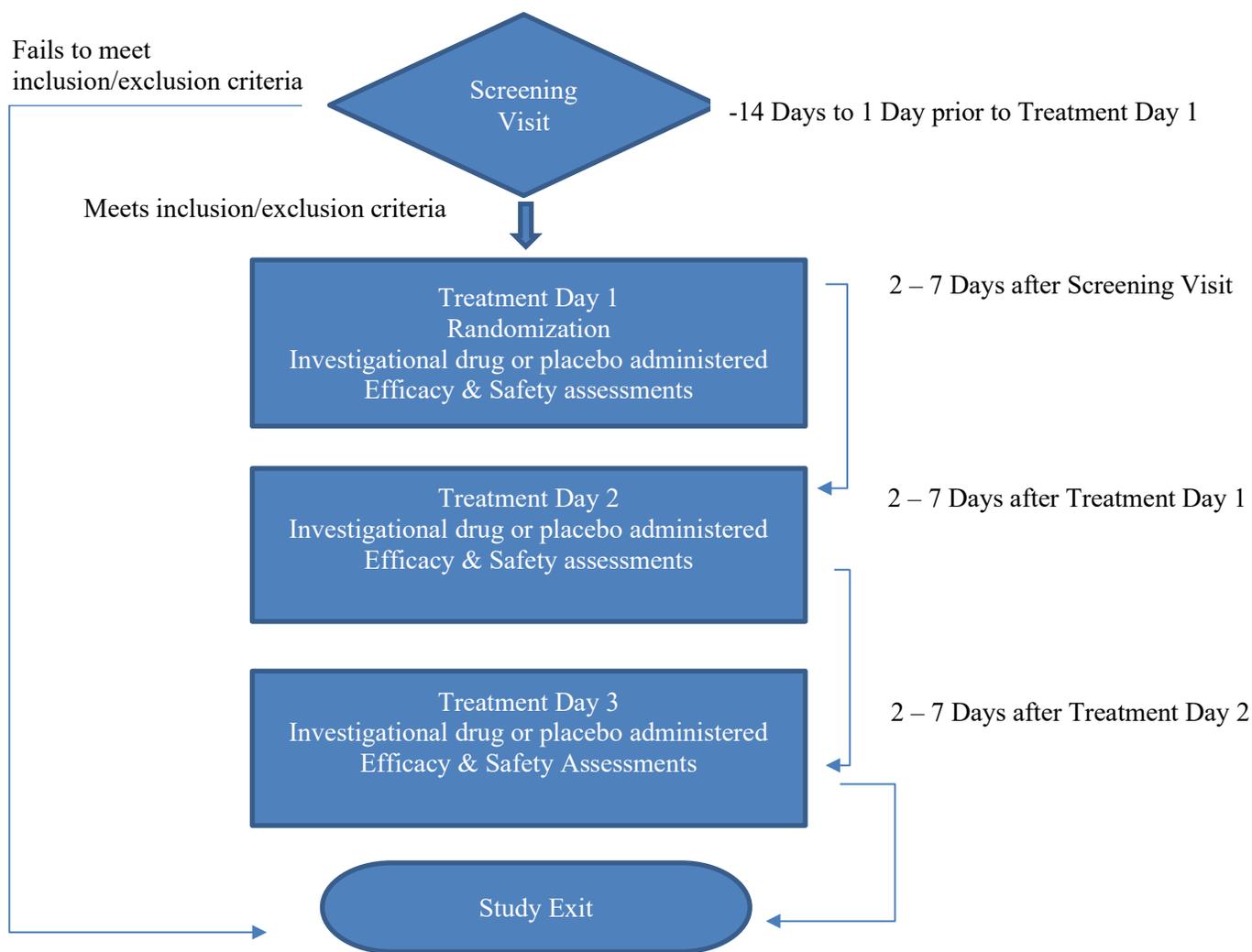
These exploratory outcomes will also be measured using digital pupillometry in highly photopic conditions.

### **2.9. Safety Outcomes**

- Slit-lamp examination findings
- Occurrence of AEs
- Intraocular pressure (IOP) measured at 65 minutes post-administration
- Visual acuity changes

### **2.10. Schedule of Visits, Procedures and Evaluations**

Study visits include a Screening Visit, which must occur between 1 and 14 days prior to treatment; followed by Treatment Day 1, Treatment Day 2, and Treatment Day 3. Treatment visits must occur at least 2 days and not more than 7 days apart. 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 EXAMINATIONS.**

### **3. INTRODUCTION AND RATIONALE**

#### **3.1. Introduction**

Eyenovia, the Sponsor of this study, is a specialty pharmaceutical company pursuing development of a variety of ocular topical medications, including a pupil dilation medication with a fixed combination formulation of phenylephrine 2.5% and tropicamide 1%, for microdose delivery. Eyenovia's drug formulations are administered using a proprietary system called the Microdose Delivery Dispenser (MiDD), which is designed to accurately deliver precise low-volume doses of topical ocular pharmaceuticals.

Phenylephrine is an  $\alpha_1$ -adrenergic receptor sympathetic agonist that has been used for more than 70 years to dilate the pupil for diagnostic, therapeutic, and surgical procedures. Systemically, phenylephrine, when administered topically to the eye at higher doses, is known to cause serious cardiovascular reactions including ventricular arrhythmias, myocardial infarction, and elevated blood pressure in some patients<sup>1,2</sup>. These risks are especially relevant when more mydriasis is required, and phenylephrine 10% is used, rather than the lower 2.5% concentration. Tropicamide is a synthetic derivative of tropic acid that became available for ocular use in 1959<sup>3</sup>. It is an anticholinergic mydriatic agent that acts by blocking the iris sphincter muscle and the ciliary muscle responses to acetylcholine. As an anticholinergic related to atropine and scopolamine, systemically absorbed tropicamide in higher doses has the potential to cause rare but potentially serious adverse events, particularly in the pediatric population.

Eyenovia's formulation (fixed combination phenylephrine 2.5%-tropicamide 1%) is a proprietary investigational product that utilizes microdosing technology 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.

#### **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.

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<sup>1</sup> Vaajanan A, Vapaatalo H. A single drop in the eye - Effects on the whole body? *Open Ophthalmol J.* 2017;11:305–314. doi: 10.2174/1874364101711010305

<sup>2</sup> Farkouh A, Frigo P, Czejka M. Systemic side effects of eye drops: a pharmacokinetic perspective. *Clin Ophthalmol.* 2016;10:2433–2441.

<sup>3</sup> Merrill D L, Goldber, B, Zavell S. bis-Tropamide, A new parasympatholytic. *Curr Ther Res.* 1960;12:43–50.

### **3.3. Existing Mydriatic Options**

Dilation of the pupil is currently produced with parasympathetic anticholinergics such as tropicamide, cyclopentolate, homatropine, and atropine; or with sympathetic agonists (sympathomimetics) such as phenylephrine<sup>4</sup>.

Parasympathetic antagonists block acetylcholine activation of muscarinic receptors, thereby paralyzing the iris sphincter muscle. The result is an enlarged pupil; however, at the same time, the ciliary muscle that regulates visual accommodation can be paralyzed, resulting in blurry vision that can persist for hours. Additionally, rare but serious systemic side effects have been observed after ocular administration of anticholinergics such as tropicamide, particularly in infants and children<sup>5,6</sup>.

Sympathetic agonists produce dilation by stimulating the iris dilator muscle and constricting ophthalmic blood vessels. Although phenylephrine does not induce blurry vision, at lower concentrations; e.g., 2.5%, it generally does not dilate the pupil as well as parasympathetic agonists. Where full mydriasis is required, higher concentrations of phenylephrine; e.g., 10%, are required. Higher concentration phenylephrine, however, has been known to cause cardiovascular effects after systemic absorption, which include hypertension, tachycardia, and more rarely, arrhythmia and stroke, especially in patients with pre-existing heart conditions<sup>7</sup>.

To maximize dilation efficacy and minimize side effects, most ophthalmologists employ a combination of both classes of mydriatic agents.

### **3.4. Phenylephrine and Tropicamide Ophthalmic Microdosing Solutions for Pupil Dilation**

Eyenovia's MiDD is designed to deliver precise microvolumes of topical ophthalmic medications using a piezo-generated microdroplet spray. When the dispenser is actuated, a precisely calibrated single microdose is delivered. It is anticipated that microdosing of ophthalmic drugs will enhance drug bioavailability and efficacy while minimizing systemic absorption and any associated side effects.

Phenylephrine ophthalmic solution is currently marketed with 2.5% and 10% concentrations (Paragon BioTeck; Akorn, Inc.) for dilation of the pupil. Tropicamide ophthalmic solution is also approved for eyedrop delivery at 0.5% and 1.0% concentrations (Alcon Laboratories; Bausch & Lomb; Akorn, Inc.). Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution formulation uses US Food and Drug Administration (FDA)-approved formulations of phenylephrine 2.5% and tropicamide 1.0%. The drug is administered in approximately 8 µL microdoses using the MiDD. Eyedrops

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<sup>4</sup> Grob SR, Gonzalez LA, Daly MK. Management of mydriasis and pain in cataract and intraocular lens surgery: review of current medications and future directions. *Clin Ophthalmol*. 2014;8:1281–1289. doi: 10.2147/OPHT.S47569

<sup>5</sup> Vaajanen A, Vapaatalo H. A single drop in the eye - Effects on the whole body? *Open Ophthalmol J*. 2017;11:305–314. doi: 10.2174/1874364101711010305

<sup>6</sup> Farkouh A, Frigo P, Czejka M. Systemic side effects of eye drops: a pharmacokinetic perspective. *Clin Ophthalmol*. 2016;10:2433–2441.

<sup>7</sup> Ibid.

containing a combination of phenylephrine and tropicamide are only available outside of the US (Mydrin-P, Japan; Phenyltrope, Canada); no similar drugs are formulated for microdosing.

Ocular microdosing with the MiDD has been evaluated in humans using phenylephrine 2.5%, phenylephrine 10%, and tropicamide 1.0% solutions, individually.

### **3.5. Ophthalmic Microdosing**

The rationale for Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution development is the desire to optimize mydriasis while reducing systemic side effects, improving local tolerability, and decreasing the amount of medication lost to drainage from increased tear turnover rate.

The average tear volume of an adult eye is 6–7  $\mu\text{L}$ <sup>8,9</sup>. The estimated maximum volume of eyedrops that the cul de sac can contain, albeit momentarily, is approximately 30  $\mu\text{L}$ ; this is reduced to 10  $\mu\text{L}$  with normal blinking<sup>10</sup>. The typical eyedropper (either unit dose or multidose), however, provides drops that range from 25  $\mu\text{L}$  to > 50  $\mu\text{L}$ . Even among bottles of the same size and shape, eyedrop sizes vary significantly depending on the angle of the bottle, the amount of ophthalmic solution remaining, and even among manufacturers<sup>11</sup>.

Much of the eyedrop volume overflows into the nasolacrimal canal where the active drug product becomes available systemically. Ocular drugs that are absorbed by the nasolacrimal mucosa mimic intravenous injection delivery insofar as they are not susceptible to first-pass hepatic metabolism. Additionally, ocular medication in swallowed nasolacrimal secretions is theoretically available for absorption in the gastrointestinal tract. Taken together, only a small fraction of the applied medication is absorbed directly into the eye, while there remain multiple opportunities for systemic absorption<sup>12</sup>. This can result in significant safety concerns, especially with drugs like phenylephrine and tropicamide that are known to produce dose-dependent systemic side effects<sup>13,14</sup>. Additionally, excess drug in the eye may cause ocular surface toxicity and tolerability issues.

Instillation of eyedrops stimulates lacrimation and can increase the tear turnover rate more than 4-fold, which additionally dilutes the drug product administered<sup>15</sup>. If the eyedrop causes discomfort, the loss rate

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<sup>8</sup> Mishima S, Gasset A, Klyce SD Jr, Baum JL. Determination of tear volume and tear flow. *Invest. Ophthalmol.* 5(3), 264–276 (1966).

<sup>9</sup> Scherz W, Doane MG, Dohlman CH. Tear volume in normal eyes and keratoconjunctivitis sicca. *Albrecht Von Graefes Arch. Klin. Exp. Ophthalmol.* 1974;192(2):141–150.

<sup>10</sup> Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. *Surv Ophthalmol.* 1982;26(4):207-18.

<sup>11</sup> Mammo ZN, Flanagan JG, James DF, Trope GE. Generic versus brand-name North American topical glaucoma drops. *Can J Ophthalmol.* 2012;47(1):55–61. doi: 10.1016/j.jcjo.2011.12.004.

<sup>12</sup> Urtti A, Salminen L. Minimizing systemic absorption of topically administered ophthalmic drugs. *Surv. Ophthalmol.* 37(6), 435–456 (1993).

<sup>13</sup> Vaajanen A, Vapaatalo H. A single drop in the eye - Effects on the whole body? *Open Ophthalmol J.* 2017;11:305–314. doi: 10.2174/1874364101711010305

<sup>14</sup> Farkouh A, Frigo P, Czejka M. Systemic side effects of eye drops: a pharmacokinetic perspective. *Clin Ophthalmol.* 2016;10:2433–2441.

<sup>15</sup> Jordan A, Baum J. Basic tear flow. Does it exist? *Ophthalmology.* 1980 Sep;87(9):920–930.

can be even higher<sup>16</sup>. Approximately 80% of a medication instilled as an eyedrop is lost to drainage during the first 15–30 seconds<sup>17</sup>.

Microdosed mydriatic medications have been demonstrated to provide similar or superior efficacy compared to traditional eyedropper systems. Microdosing can also reduce systemic absorption and side effects, improve patient comfort, and minimize drug dilution and spillage. Studies comparing microdosed phenylephrine and cyclopentolate to traditional eyedrops (26 – 30  $\mu$ L drop size) in premature babies<sup>18</sup> and in full-term infants<sup>19</sup> have shown equivalent pupil dilation with drop sizes ranging from 5 – 8  $\mu$ L<sup>20,21</sup> while reducing systemic levels by more than 50%<sup>22</sup>.

Tropicamide 1.0% spray application caused similar pupil dilation as the same solution delivered as an eyedrop, but with less discomfort<sup>23</sup>. The main reason microdosing has not become the accepted method for topical ocular dosing of ophthalmic medication is that no system has been developed that can consistently deliver accurate microdoses of these medications.

As shown in Figure 1, the Eyenovia MiDD is designed to deliver a finely controlled microdroplet spray of phenylephrine 2.5%-tropicamide 1% ophthalmic solution with precisely defined volume, velocity, and geometry.<sup>24</sup> These characteristics facilitate high-precision, piezo-generated medication delivery that gently coats the ocular surface.

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<sup>16</sup> Farris RL, Stuchell RN, Mandell ID. Basal and reflex human tear analysis. I Physical measurements: osmolarity, basal volumes, and reflex flow rate. *Am Acad Ophthalmol* 1981;88:852.

<sup>17</sup> Lallemand F, Daull P, Benita S, Buggage R, Garrigue JS. Successfully improving ocular drug delivery using the cationic nanoemulsion, novasorb. *J Drug Deliv*. 2012;2012:604204.

<sup>18</sup> Wheatcroft S, Sharma A, McAllister J. Reduction in mydriatic drop size in premature infants. *Br J Ophthalmol*. 1993;77(6):364-5.

<sup>19</sup> Lynch MG, Brown RH, Goode SM, Schoenwald RD, Chien DS. Reduction of phenylephrine drop size in infants achieves equal dilation with decreased systemic absorption. *Arch Ophthalmol*. 1987;105(10):1364-5.

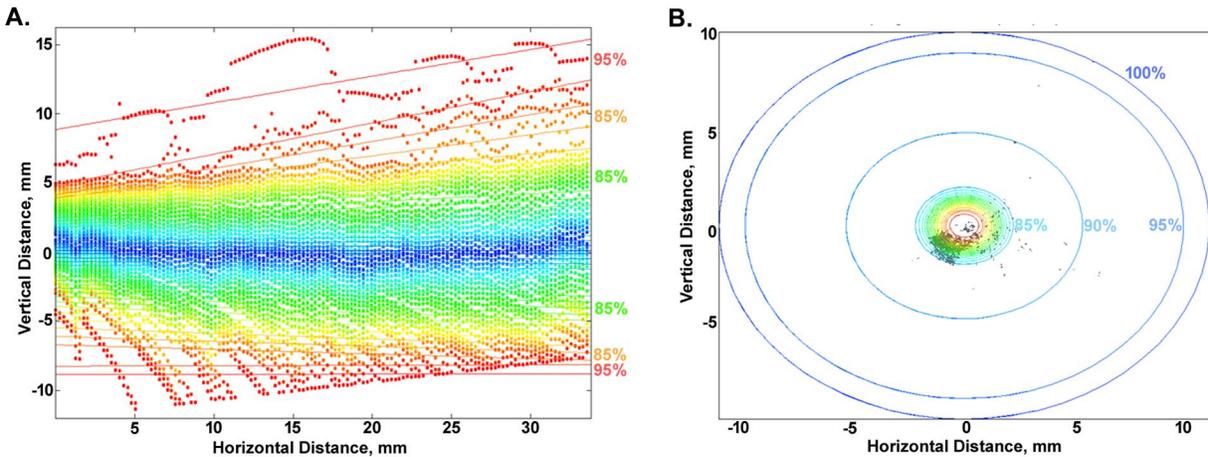
<sup>20</sup> Wheatcroft S, Sharma A, McAllister J. Reduction in mydriatic drop size in premature infants. *Br J Ophthalmol*. 1993;77(6):364-5.

<sup>21</sup> Lynch MG, Brown RH, Goode SM, Schoenwald RD, Chien DS. Reduction of phenylephrine drop size in infants achieves equal dilation with decreased systemic absorption. *Arch Ophthalmol*. 1987;105(10):1364-5.

<sup>22</sup> *Ibid*.

<sup>23</sup> Akman A, Aydin P. Comparison of mydriatic efficacy of spray application and drop instillation of tropicamide 1%. *Eye (Lond)*. 1999;13(5):653–655.

<sup>24</sup> 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 1: Microdroplet Distribution Pattern from the MiDD**

*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 MiDD nozzle.*

#### **4. INVESTIGATIONAL PRODUCT DESCRIPTION**

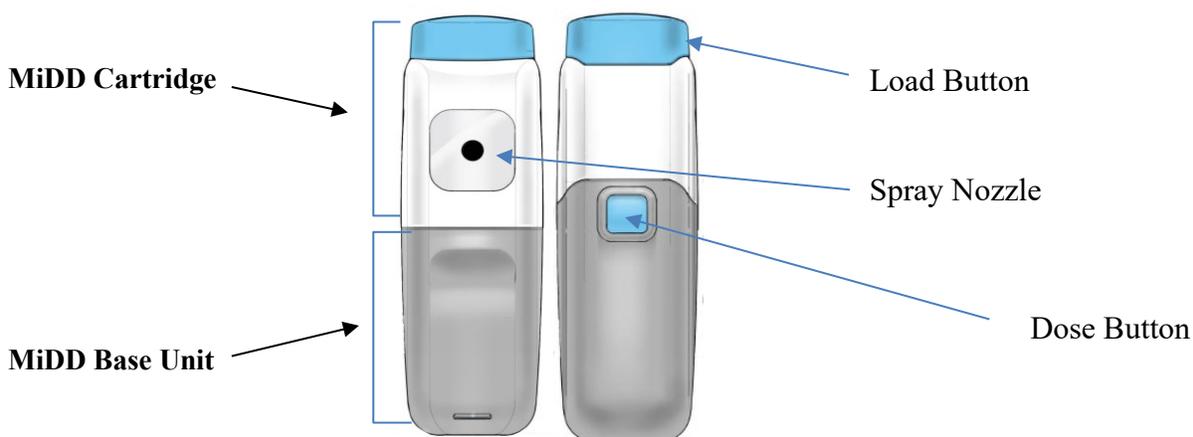
This study will evaluate the safety and efficacy of topical ocular microdose administration of a fixed combination of phenylephrine 2.5%-tropicamide 1% ophthalmic solution for mydriasis in routine diagnostic procedures and in conditions where short-term pupil dilation is desired.

##### **4.1. Findings from Non-Clinical and Clinical Studies**

Detailed information on nonclinical and clinical studies of fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution is provided in the Investigator Brochure (EYN-MYD-TP-3-1/32).

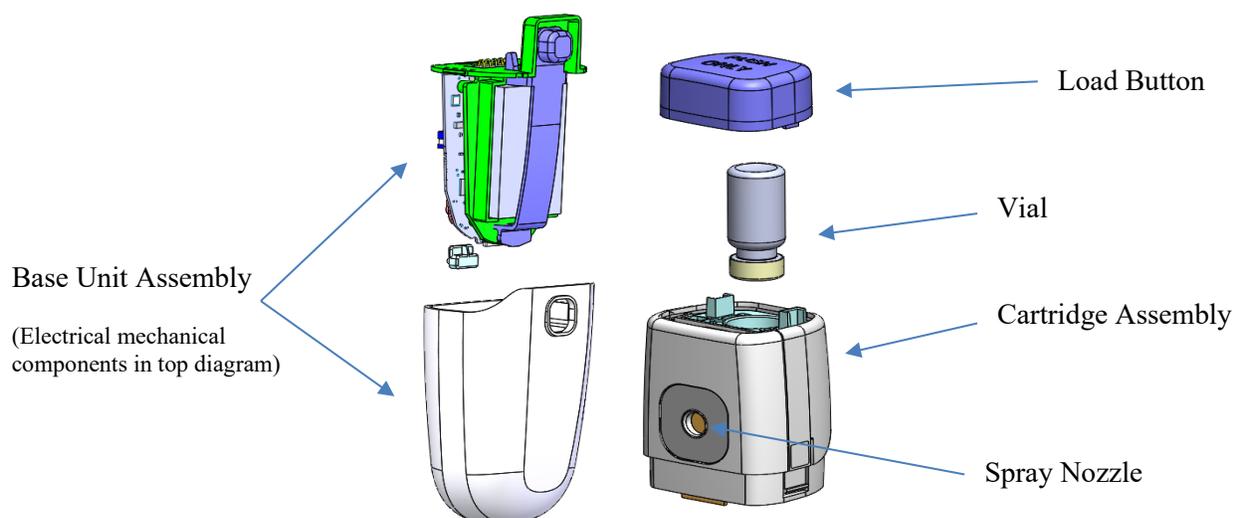
##### **4.2. How Provided**

Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution is contained sterile in the Eyenovia MiDD, which is designed to accurately deliver precise low-volume doses of topical ocular pharmaceutical ingredients. As shown in Figure 2, the MiDD is composed of a "cartridge assembly" (shown in white in the image below) and the base unit (shown in gray in the image below).



**Figure 2: Eyenovia MiDD Front (L) and Back (R) View**

Figure 3 shows a diagram of the MiDD base unit and cartridge assembly. The cartridge assembly is the primary container closure system, which contains a vial filled with sterile fixed combination phenylephrine 2.5% - tropicamide 1% ophthalmic solution. At the time of initial MiDD actuation, the seal on the vial is punctured to allow the drug to flow to the MiDD delivery system. The cartridge assembly also contains a piezo-delivery system designed to drive delivery of the drug through the Spray Nozzle in discrete pulses repeated in a discrete cycle of duration  $\leq 100$  milliseconds, which is the average involuntary blink response time.



**Figure 3: Diagram of the MiDD Base Unit (L) and Cartridge Assemblies (R)**

Prior to initial MiDD use, fixed combination phenylephrine 2.5%-tropicamide 1% solution is aseptically transferred from the 2R vial in which it was received into the MiDD vial, the MiDD vial is inserted into the cartridge assembly, the cartridge and base are clipped together, and the seal on the vial containing the drug is punctured by depressing the MiDD Load Button. Puncture of this seal creates a fluid path for the drug. Depression and release of the Load Button 5 times primes the system for drug delivery. At the time of dosing, the Load Button is again pressed and released to activate the piezo element to create the aerosol containing the drug dose. When the Dose Button is pressed, approximately 8  $\mu\text{L}$  of the drug is delivered through the Spray Nozzle to the cornea.

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

The study medication will be administered in accordance with the treatment assignment schedule on a single day in the clinic by trained clinical study staff. Two sprays of fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution will be topically administered within a 5-minute period to both eyes. The concentration of the active ingredients selected for this study is based on the standard regimen used for mydriasis where short term pupil dilation is required. The single-use regimen and 1-day treatment period is selected based on the medication's intended use for in-office mydriasis.

## **5. STUDY OBJECTIVE**

The primary objective of this study is to evaluate the safety and efficacy of Eyenovia's fixed combination of phenylephrine 2.5%-tropicamide 1% ophthalmic solution administered with the MiDD for dilation of the pupil as compared to placebo.

## **6. STUDY DESIGN**

This trial is a multicenter, double-masked, placebo-controlled, cross-over superiority study evaluating Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution versus placebo.

Volunteer participants from 2 – 3 US-based investigational sites will be screened for study eligibility during a Screening Visit and enrolled after signing the study-specific informed consent form (ICF). Subjects meeting all inclusion/exclusion criteria will be scheduled for 3 treatment visits, which must occur at least 2 days, but no more than 7 days apart. A 2 sequence, 3 period crossover design will be used. At each of the three treatment visits, baseline measurements will be taken, then either the investigational drug or the placebo will be administered to both eyes (OU) in two separate instances, approximately 5 minutes apart. Only 1 investigational product will be administered per treatment visit, and product administration will occur in a randomized order using one of two sequences - ABB and BAA, where A is the Eyenovia fixed combination and B is the placebo control. Afterwards, efficacy and safety assessments will be performed at specific time intervals.

This study will be double-masked. There will be no differences in the presentation of the investigational drug or placebo administered and all study personnel conducting ophthalmic assessments will be masked to study drug assignment. Study drug administration will be performed by at least 3 different trained personnel during the study. Personnel who administer study drug on a given day will not be allowed to perform post-study drug administration ophthalmic assessments on that day.

## **7. STUDY OUTCOMES**

### **7.1. Effectiveness Outcomes**

The primary performance endpoint is mean change in pupil diameter at 35 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 difference in mean change in pupil diameter will be compared between Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% and placebo.

The study's sample size will provide 95% power to detect a 0.5 mm difference between drugs assuming a standard deviation of 1.0 mm using a paired t-test with a two-sided significance level of 0.05.

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 35 minutes
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater at 35 minutes
- Mean change in pupil diameter at other timepoints (20, 50, 65, 80, 120, and 180 minutes)
- Distribution of pupil diameters at 20, 35, 50, 65, 80, 120, and 180 minutes
- Time from baseline to maximal pupil dilation

### **7.2. Safety Outcomes**

A safety analysis will be conducted to compare fixed combination of phenylephrine 2.5%-tropicamide 1%  $\mu$ D against the placebo control for the following outcomes:

- Slit-lamp examination (SLE) findings
- Occurrence of AEs
- IOP measured at 65 minutes post-administration
- Visual acuity changes

## **8. STUDY POPULATION**

Volunteer participants will be considered enrolled after signing the study-specific ICF(s) and screened for study eligibility during a Screening Visit. Subjects meeting all inclusion/exclusion criteria will be scheduled for 3 treatment visits. It is assumed that up to 20% of subjects (n = 10) will fail to complete the study visits; therefore, to have 54 subjects evaluable for the primary efficacy analysis, a minimum of 65 subjects will be randomized to study drug administration at Treatment Visit 1 (Day 1). To account for possible screen failures, the study will enroll up to 90 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 of any age.
2. Female subjects must be either pre-menarche, 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. Subjects under the age required for informed consent must have the ability to provide additional written assent and/or parental consent, as required by the reviewing IRB.
4. Ability to return for all study treatment visits.
5. Photopic screening pupil diameter  $\leq 3.5$  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. Use of benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressants, anticonvulsants at screening or anticipated during the study period.
7. 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.
8. History of closed-angle glaucoma.
9. Anatomically narrow anterior chamber angles (Van Herrick grade  $\leq 2$  in either eye).
10. Ocular surgery or laser treatment of any kind prior to the Screening Visit.
11. History of chronic or acute uveitis.

12. History of traumatic iritis or hyphema.
13. History of traumatic mydriasis or angle recession.
14. History of heterochromia.
15. Irregularly-shaped pupil secondary to ocular trauma or congenital defect.
16. History of neurogenic pupil disorder (e.g., Horner's syndrome, third cranial nerve palsy, Adie's pupil, Argyl Robertson syndrome, etc.).
17. History of anterior chamber intraocular lens (IOL) or iris-fixated IOL.
18. History of iris surgery of any kind (e.g., iridotomy, iridectomy, coreoplasty).
19. History of iris atrophy.
20. History of iris – cornea apposition/touch.
21. Unwilling or unable to discontinue use of contact lenses at treatment visits.
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 each 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. Dependent on IRB requirements for subjects under 18 years of age, an IRB-approved study assent form may be supplemental to the study ICF.

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 (and assent, if applicable) for study participation must be present prior to initiation of any study-specific procedure; subjects will be considered enrolled in the study upon their (and/or their parent's/guardian's, if applicable) 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/assent forms 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 inclusion/exclusion 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 be scheduled for their next visit at which the first study medication will be administered.

### **9.3. Randomization to Study Drug Administration Sequence**

Each eligible subject will be randomly assigned to receive one of 2 sequences (ABB or BAA) of study drug administration where either investigational drug or placebo will be administered in both eyes at each of the 3 treatment visits. After Treatment Visit 3, each study subject should have received either 2 treatments with the investigational product or 2 treatments with the placebo. The study drug administration schedule is equally distributed across the 2 randomization sequences. Subject drug administration assignments will be prepared using a computer-generated randomization scheme by an independent statistician who is not involved in the day-to-day conduct of the study. The drug assignment sequence (Study Drug ABB or BAA) will be provided in paper format contained in a sealed envelope for each subject who randomized to treatment.

The study drug administered will be masked to the study subject, the investigator, and study staff administering performing clinical assessments. The Sponsor (or designee) involved in day-to-day study management will also be masked to study drug assignments.

### **9.3.1. Procedure for Unmasking Study Drug Assignment Code**

Unmasking of study drug assignments can only occur in the event of a medical emergency or occurrence of an AE that, in the opinion of the investigator, warrants such action. In the absence of medical need, the study drug assignment code will not be available to the investigator, site staff, or Sponsor (or designee) representative involved in day-to-day study management until study completion and database lock.

In the event an investigator considers unmasking of a subject's study drug assignment to be necessary, he/she must first contact the study Medical Monitor (or designee) to discuss the case. Only after consultation with the study Medical Monitor will the decision be made regarding unmasking. Study drug assignments will be revealed only for the subjects approved for unmasking, thus leaving masking on remaining subjects intact.

### **9.4. Study Drug Packaging, Labeling and Storage**

The investigational product and placebo, each delivered in microdose form using the Eyenovia MiDD, will be evaluated in this study. Each product must be aseptically transferred by a licensed pharmacist affiliated with the study site from the container in which they are received to the sterile vial provided with the MiDD cartridge. After aseptic transfer, the filled vial is re-inserted into the MiDD cartridge.

To maintain masking of the study drug assignments for staff administering investigational product and/or performing clinical evaluations, study inventory storage and management will be performed by a pharmacy associated with the study site. The Sponsor, or designee, will ship study drug kits to each site pharmacy. Each kit will be labeled with the study protocol number, study drug code, product storage requirements, and the Caution – New Drug – Limited by Federal (US) Law to Investigational Use label.

Instructions regarding study medication preparation are included in **APPENDIX 2: STUDY MEDICATION PREPARATION PROCEDURE**. Each designated site pharmacist will be trained and certified by the Sponsor, or designee, prior to study medication preparation.

Prior to use, study medication must be stored in a secure area. To maintain product stability, store at 20° to 25° C (68° to 77° F). Protect product from light and excessive heat.

New MiDDs must be prepared by the pharmacy for use by site personnel on each treatment day. To maintain masking of site personnel, the MiDD containing each study drug will be labeled with the appropriate study randomization code, pharmacy preparation date and "use by" date, then forwarded to site personnel for use. The date on which the MiDD is used will be added by site personnel. At the end of the treatment day, each MiDD provided will be returned to the pharmacy for storage. **Please note that each MiDD prepared must be used on the day of preparation; the MiDD may not be re-used on subsequent days.**

### **9.5. Study Drug Administration**

Site personnel designated to administer study medication will be trained by the Sponsor on proper use of the MiDD prior to study initiation. A single MiDD should be used for study drug administration to all subjects whose study drug assignment corresponds to the dispenser code on that treatment day. At each treatment visit, after collection of baseline BCDVA, IOP and SLE data, study medication will be administered by designated site personnel in accordance with the subject's assigned sequence. Subjects will be administered 2 doses of study drug in each eye. After the initial dosing of each eye, approximately 5 minutes should elapse before the second dose administration. Study drug administration procedures are further detailed in **APPENDIX 3: STUDY MEDICATION ADMINISTRATION PROCEDURE**.

### **9.6. Study Visits and Clinical Assessments**

Study participants will be evaluated at a Screening Visit. Subjects who qualify for further study participation will be scheduled for visits on Treatment Day 1, Treatment Day 2 and Treatment Day 3 at which the assigned study drug is administered and examinations are performed. Data collected from each visit 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 at each visit is outlined in **APPENDIX 1: SCHEDULE OF MEDICATION ADMINISTRATION AND EXAMINATIONS**. Methodology for study examinations is presented in **APPENDIX 4: EXAMINATION PROCEDURES**.

#### **9.6.1. Screening Visit (-14 Days to -1 Day)**

The Screening Visit must occur no more than 14 days prior and no less than 1 day prior to Treatment Visit 1. At the Screening Visit, the following activities will be performed:

- Documentation of study informed consent/assent 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
- BCDVA<sup>25</sup> – OU
- Pupil diameter measurement – OU
- Slit lamp biomicroscopy including Van Herrick angle assessment – OU
- Dilated Fundus Exam – OU
- IOP measurement - OU
- Determination of study eligibility

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<sup>25</sup> Pediatric subjects who are unable to perform ETDRS testing must have uncorrected visual acuity evaluated using an age-appropriate acuity testing method.

### **9.6.2. Treatment Visit 1 (Day 1)**

Subjects will return to the site at least 1 day and no more than 14 days after the Screening Visit. The subject will be queried regarding the occurrence of any adverse events since the time of the Screening Visit. The subject will be assigned to his/her study drug randomization schedule based on iris color cohort assignment (dark irises are either black or brown in color, while light irises are all other colors), and the following baseline measurements will be taken prior to study drug administration:

- Pupil diameter measurement – OU
- Pupillary light reflex - OU
- BCDVA<sup>26</sup> – OU
- Slit lamp biomicroscopy – OU
- IOP measurement - OU

The first study drug in the drug administration sequence will be administered OU, then administered again approximately 5 minutes later OU. The completion of the first administration of medications will be considered Time 0 (T0). The following assessments will be done at the timepoints specified below:

<b>Timepoint</b>	<b>Clinical Assessment (to be performed in the specified order)</b>
T0 + 20 minutes (+/- 2 minutes)	<ul style="list-style-type: none"><li>• Pupil diameter measurement – OU</li></ul>
T0 + 35 minutes (+/- 5 minutes)	<ul style="list-style-type: none"><li>• Pupil diameter measurement – OU</li><li>• Pupillary light reflex - OU</li><li>• AE assessment</li></ul>
T0 + 50 minutes (+/- 5 minutes)	<ul style="list-style-type: none"><li>• Pupil diameter measurement – OU</li></ul>
T0 + 65 minutes (+/- 5 minutes)	<ul style="list-style-type: none"><li>• Pupil diameter measurement – OU</li><li>• Pupillary light reflex - OU</li><li>• IOP measurement – OU</li></ul>
T0 + 80 minutes (+/-10 minutes)	<ul style="list-style-type: none"><li>• Pupil diameter measurement – OU</li></ul>
T0 + 120 minutes (+/-10 minutes)	<ul style="list-style-type: none"><li>• Pupil diameter measurement – OU</li></ul>
T0 + 180 minutes (+/-10 minutes)	<ul style="list-style-type: none"><li>• Pupil diameter measurement – OU</li><li>• Pupillary light reflex - OU</li><li>• BCDVA<sup>23</sup> – OU</li><li>• Slit lamp biomicroscopy – OU</li><li>• AE assessment</li></ul>

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<sup>26</sup> Pediatric subjects who are unable to perform ETDRS testing must have uncorrected visual acuity evaluated using an age-appropriate acuity testing method.

**9.6.3. Treatment Visit 2 (Day +3 to Day +8)**

Subjects will return to the site. Subjects will be queried regarding the occurrence of any adverse events since the previous visit and the following baseline measurements will be taken prior to study drug administration:

- Pupil diameter measurement – OU
- Pupillary light reflex - OU
- BCDVA<sup>27</sup> – OU
- Slit lamp biomicroscopy – OU
- IOP measurement - OU

The second study drug in the drug administration sequence will be administered OU, then administered again approximately 5 minutes later OU. The completion of the first administration of medications will be considered Time 0 (T0). The following assessments will be done at the timepoints specified below:

<b>Timepoint</b>	<b>Clinical Assessment (to be performed in the specified order)</b>
T0 + 20 minutes (+/- 2 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 35 minutes (+/- 5 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> <li>• Pupillary light reflex - OU</li> <li>• AE assessment</li> </ul>
T0 + 50 minutes (+/- 5 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 65 minutes (+/- 5 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> <li>• Pupillary light reflex - OU</li> <li>• IOP measurement – OU</li> </ul>
T0 + 80 minutes (+/-10 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 120 minutes (+/-10 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 180 minutes (+/-10 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> <li>• Pupillary light reflex - OU</li> <li>• BCDVA<sup>23</sup> – OU</li> <li>• Slit lamp biomicroscopy – OU</li> <li>• AE assessment</li> </ul>

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<sup>27</sup> Pediatric subjects who are unable to perform ETDRS testing must have uncorrected visual acuity evaluated using an age-appropriate acuity testing method.

**9.6.4. Treatment Visit 3 (Day +5 to Day +15)**

Subjects will return to the site. Subjects will be queried regarding the occurrence of any adverse events since the previous visit and the following baseline measurements will be taken prior to study drug administration:

- Pupil diameter measurement – OU
- Pupillary light reflex - OU
- BCDVA<sup>28</sup> – OU
- Slit lamp biomicroscopy – OU
- IOP measurement - OU

The third study drug in the drug administration sequence will be administered OU, then administered again approximately 5 minutes later OU. The completion of the first administration of medications will be considered T0. The following assessments will be done at the timepoints specified below:

<b>Timepoint</b>	<b>Clinical Assessment (to be performed in the specified order)</b>
T0 + 20 minutes (+/- 2 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 35 minutes (+/- 5 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> <li>• Pupillary light reflex - OU</li> <li>• AE assessment</li> </ul>
T0 + 50 minutes (+/- 5 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 65 minutes (+/- 5 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> <li>• Pupillary light reflex - OU</li> <li>• IOP measurement – OU</li> </ul>
T0 + 80 minutes (+/-10 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 120 minutes (+/-10 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> </ul>
T0 + 180 minutes (+/-10 minutes)	<ul style="list-style-type: none"> <li>• Pupil diameter measurement – OU</li> <li>• Pupillary light reflex - OU</li> <li>• BCDVA<sup>25</sup> – OU</li> <li>• Slit lamp biomicroscopy – OU</li> <li>• AE assessment</li> </ul>

If applicable, a urine pregnancy test will be administered at this visit and, upon completion of the T0 + 180-minute assessment, the subject will have completed the study.<sup>29</sup>

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<sup>28</sup> Pediatric subjects who are unable to perform ETDRS testing must have uncorrected visual acuity evaluated using an age-appropriate acuity testing method.

<sup>29</sup> Subjects whose pupil diameter is larger than baseline at the time of study exit may be followed at hourly intervals up to 6 hours after medication administration to gather additional data regarding the duration of study treatment effect.

#### **9.4.5. 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.

#### **9.4.6. 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
- Loss 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 Treatment Visit 3.

## **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 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.<sup>30</sup>

#### **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.<sup>31</sup>

#### **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 Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.<sup>32</sup>

#### **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

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<sup>30</sup> CFR 312.23 – IND Safety Reporting,  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

<sup>31</sup> ICH E6 – Good Clinical Practice: Consolidated Guidance, Glossary, p 1.

<sup>32</sup> <sup>32</sup> CFR 312.23 – IND Safety Reporting,  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

suggest 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.<sup>33</sup>

#### **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.<sup>34</sup>

#### **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<sup>35</sup>
- 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.<sup>36</sup>

#### **10.1.7. Serious Ocular Adverse Events**

Serious ocular AEs include, but are not limited to:

- A decrease in BCDVA of  $\geq 30$  total letters read (TLR) or an increase of  $\geq 0.6$  logMar from the most recent previous measurement of BCDVA
- A decrease in BCDVA to light perception (LP) or worse that lasts  $> 1$  hour
- An ocular event that, in the opinion of the investigator, requires medical or surgical intervention to prevent permanent loss of sight
- Severe intraocular inflammation; e.g., 4+ anterior chamber cell/flare or 4+ vitritis

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<sup>33</sup> CFR 312.23 – IND Safety Reporting,  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

<sup>34</sup> CFR 312.23 – IND Safety Reporting,  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

<sup>35</sup> 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).

<sup>36</sup> CFR 312.23 – IND Safety Reporting,  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

- Corneal decompensation
- Retinal tear or detachment
- Central or branch retinal vein occlusion

#### **10.1.8. 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.

### **10.2. Adverse Event Assessment and Documentation**

All AEs that occur from the time the subject receives the first dose of study drug<sup>37</sup> 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:

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<sup>37</sup> Events that occur between the Screening Visit and initial administration of study drug should be recorded as Medical History, and not as an AE.

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

### **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:

<b>Not Related</b>	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.
<b>Possibly Related</b>	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.
<b>Probably Related</b>	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.
<b>Definitely Related</b>	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.

## **11. STATISTICAL METHODS**

The primary objective of this study is to evaluate the safety and efficacy of Eyenovia's fixed combination of phenylephrine 2.5%-tropicamide 1% ophthalmic solution administered with the MiDD for dilation of the pupil as compared to the individual components.

### **11.1. Efficacy Endpoints**

**Primary Efficacy Endpoint:** An efficacy analysis will be conducted to compare fixed combination of phenylephrine 2.5%-tropicamide 1% microdose ophthalmic solution against placebo with the following endpoint:

*The primary performance endpoint is mean change per visit in pupil diameter at 35 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 35 minutes
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater at 35 minutes
- Mean change in pupil diameter at other timepoints (20, 50, 65, 80, 120, and 180 minutes)
- Distribution of pupil diameters at 20, 35, 50, 65, 80, 120, and 180 minutes
- Time from baseline to maximal pupil dilation

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

### **11.2. Sample Size**

Up to 90 subjects who have provided informed consent for study participation will be enrolled in the study and a minimum of 65 subjects will be randomized to study drug administration at Treatment Visit 1 with the goal of having 54 subjects evaluable for the primary efficacy endpoint. A sample size of 27 subjects per sequence, 54 total (the study has two sequences, ABB and BAA where A is the Eyenovia fixed combination drug, and B is the placebo control), will have 95% power to detect a difference in means of 0.5 mm, assuming a standard deviation of differences of 1.0 mm, using a paired t-test with a 0.05 two-sided significance level.

Power calculations are provided for additional exploratory outcomes below on an informational basis.

When the sample size is 54, a two-sided 95% exact confidence interval for a single proportion will have a half-width of 13.9% or less.

- For evaluation of the proportion of eyes achieving pupil size of 6.0 mm or greater at 35 minutes: if the observed proportion in the fixed combination treatment is 70.4% (38/54), then the exact 95% confidence interval for the proportion will be [56.4%, 82.0%], with a half-width of 12.8%.

- For evaluation of the proportion of eyes achieving pupil size of 7.0 mm or greater at 35 minutes: if the observed proportion in the fixed combination treatment is 40.7% (22/54), then the exact 95% confidence interval for the proportion will be [27.6% 55.0%], with a half-width of 13.7%.

### **11.3. Safety Outcomes**

A safety analysis will be conducted to compare fixed combination of phenylephrine 2.5%-tropicamide 1% microdose against placebo for the following outcomes:

- Slit-lamp examination findings
- Occurrence of AEs
- IOP measured at 65 minutes post-administration\*
- Visual acuity changes\*

*\*IOP and VA line listings will be provided for pediatric subjects because of the variable testing methods appropriate for this sub-group*

### **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 randomized subjects who received a dose of study drug. Subjects will be analyzed according to the planned sequence of drugs.

#### **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. Subjects to be excluded from the PP population will be selected prior to unmasking drug assignment. Subjects will be analyzed according to the sequence of study drugs received.

#### **11.4.3. Modified Per Protocol Population**

The modified per protocol (MPP) population is defined similarly to the PP population, except that classification will be made for each subject at the individual treatment visit level, rather than at the subject level. Unlike the PP population, subjects who only complete 1 or 2 of the 3 treatment visits may be included.

The MPP will consist of all ITT subjects who completed all planned assessments without major protocol violations for the given treatment visit. Subjects to be excluded from the MPP population will be selected prior to unmasking treatment

#### **11.4.4. Safety Population**

The safety population will consist of all ITT subjects. Subjects will be analyzed according to the sequence of study drugs received

#### **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 compared between study drugs.

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.

The ABB/BAA crossover design used in this study allows for within-subject (i.e. within-eye) estimates of both drug effects (A and B) and carryover (AA, AB, BA, BB). Thus, there is no need to include random effects for subject or eye in the analysis model, we will use fixed effects ANOVA to analyze these data (Jones and Kenward, 2015, section 5.2, 5.3.1) and tests will be based on within-eye variances. A SAS REPEATED statement will be used to adjust for correlation between fellow eyes.

This study has both a “pre-randomization” covariate (iris color) and a “period-dependent” covariate (baseline pupil measurement) as discussed in Jones and Kenward (2015, section 5.4.4). We are assuming that the time between visits is sufficiently long that the baseline pupil measurement at each visit is unaffected by carryover.

Unless explicitly stated otherwise, all statistical tests and confidence intervals will be two-sided,  $\alpha = 0.05$ .

##### **11.5.1. Analysis of Primary Efficacy**

All time points for pupil diameter will be analyzed separately; however, only the 35-minute time point will support statistical inference. Success is defined as a statistically significant drug effect, with the fixed combination better (greater deltaPD) than placebo.

The null and alternative hypotheses for comparison of Eyenovia’ s fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution with placebo, are defined as follows:

- $H_0$ : The mean change per visit in pupil diameter at 35 minutes versus baseline, as measured by digital pupillometry in highly photopic conditions, is not different between Eyenovia’ s fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution and placebo

- $H_A$ : The mean change per visit in pupil diameter at 35 minutes versus baseline, as measured by digital pupillometry in highly photopic conditions, is different between Eyenvia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution and placebo

Comparisons among drugs on mean pupil diameter will be based on a fixed-effects analysis of variance model. The model will contain an effect due to subject, eye, subject x eye, period (1, 2, or 3), direct effect of drug, first order carryover, baseline pupil diameter, and iris color (dark vs light). The SAS PROC MIXED procedure will be used to fit the ANOVA model. Hypothesis tests will be based on confidence intervals produced by the SAS LSMEANS option for the difference between treatment groups. Details are provided in the statistical analysis plan.

The SAS PROC MIXED procedure uses all available data to produce maximum likelihood parameter estimates, in such a setting the missing observations are ignorable if data are missing at random (MAR).

#### **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 35 minutes post-dose will be summarized by eye and by treatment group with descriptive statistics.

For each of these proportions, pairwise comparisons of the fixed combination of phenylephrine 2.5%-tropicamide 1% microdose ophthalmic solution administered against placebo will be conducted with a generalized estimating equation (GEE) model for binomial outcome, allowing for correlation between eyes.

The SAS PROC GENMOD procedure will be used to fit the model, using the same fixed effects as the primary analysis. Once again, comparisons between treatment groups will be based on SAS LSMEANS for the difference between drug and placebo. Details are provided in the statistical analysis plan.

In addition, a cumulative proportion of responders analysis (CPRA) will be created to graphically display the proportions of subjects with a pupil size at 35 minutes post-dose over the entire range of possible pupil size cut-offs (Farrar 2006), with separate lines for each treatment and eye combination.

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

#### **11.5.3. Sensitivity Analyses**

The primary efficacy analysis described above will be rerun using the MPP population as a sensitivity analysis.

As a further sensitivity analysis, multiple imputation based on reference-based multiple imputation will be used to impute missing data at the 35-minute time point based on a missing not at random (MNAR) assumption. Since the PP population contains only subjects with non-missing values, this analysis will be conducted using the ITT population, which may contain subjects who have only partially available information. Placebo treatment will serve as reference group for this approach. Each subject will be

included for all three treatment visits for this approach, regardless of how many treatment visits were actually completed. Details are provided in the statistical analysis plan.

**11.5.4. Interim Analyses**

No interim analyses are planned for this study.

**11.5.5. 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:

- Study protocol
- Study medication preparation procedures
- Study medication 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**

Accurate records of each MiDD base unit and cartridge shipped and medication administered must be maintained by the Sponsor, or designee, and each study investigator. Each of the 2 study medications will be provided to the site pharmacy in a kit labeled with the medication code. Study kits will be accompanied by a shipper listing the number of kits provided and the contents of each kit. Pharmacy 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 a study kit accountability log to the pharmacy for documentation of kits received, kits used for site product administration, and kits returned or discarded.

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

MiDD 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. Additionally, for the placebo product, each commercial bottle provided will be reconciled with vials prepared by the pharmacy, the associated dispensers used in study drug administration, subjects for whom the dispenser was used, and the dispenser 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)<sup>38</sup>. Sponsor and Investigator responsibilities associated with adherence to GCP and CFR 312 are specified in **APPENDIX 5: 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 18<sup>th</sup> World Medical Assembly, Helsinki, Finland, 1964 and later amendments (see **APPENDIX 6: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**).

#### **13.1. Institutional Review**

Before enrollment of study subjects, this protocol and the study-specific consent/assent form(s) 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.

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<sup>38</sup> 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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**PHENYLEPHRINE 2.5%-TROPICAMIDE 1% MICRODOSE OPTHALMIC SOLUTION  
EYENOVIA CLINICAL STUDY PROTOCOL EYN-MYD-TP-32 VERSION C**

**APPENDIX 1: SCHEDULE OF MEDICATION ADMINISTRATION AND EXAMINATIONS**

Assessment/Procedure	Screening Visit (Day -14 to Day -1)	Treatment Visit 1 (Day 1) <sup>1</sup> , Visit 2 <sup>1</sup> and Visit 3 <sup>1</sup>								
		Baseline <sup>0</sup>	Time 0 <sup>2</sup>	Time 1 T0+20 min (± 2 min)	Time 2 T0+35 min (± 5 min)	Time 3 T0+50 min (± 5 min)	Time 4 T0+65 min (± 5 min)	Time 5 T0+80 min (± 10 min)	Time 6 T0+120 min (± 10 min)	Time 7 T0+180 min (± 10 min)
Informed consent	X									
Demographics	X									
Medical history	X									
Ocular history	X									
Prior/concomitant medication use	X									
Urine pregnancy test <sup>3</sup>	X					X <sup>3</sup>				
Manifest refraction (OU)	X									
BCDVA (OU) <sup>4</sup>	X	X								X
Study drug administration sequence determination (OU)		X								
Study drug administration (OU)			X							
Slit lamp biomicroscopy (OU) <sup>5</sup>	X	X								X
Van Herrick Angle Assessment (OU) <sup>6</sup>	X									
IOP (OU) <sup>7</sup>	X	X					X			
Pupil diameter assessment (OU) <sup>8</sup>	X	X		X	X	X	X	X	X	X
Pupillary light reflex (OU)		X			X		X			X
Study eligibility determination	X									
Dilated fundus exam (OU)	X									
AE assessment		X			X					X

<sup>0</sup> Baseline refers to evaluations made at each Treatment Day prior to study medication administration.

<sup>1</sup> Treatment Visit 1, 2 and 3 must be separated by at least 2 days; but may be up to 7 days apart to allow for scheduling flexibility.

<sup>2</sup> Time 0 starts at the point the first of two study medication doses is administered in second eye of the study subject

<sup>3</sup> A urine pregnancy test will be conducted in females of childbearing potential at the Screening Visit and at the last visit (Treatment Visit 3). The test may be administered at any time during the Screening and Treatment Day 3 Visits. If the subject terminates study participation prior to Treatment Visit 3, this test must be administered promptly at the time of termination.

<sup>4</sup> BCDVA to be measured using ETDRS methods. For younger pediatric subjects, UCDVA may be measured using age-appropriate methods per investigator's usual practice.

<sup>5</sup> For younger pediatric subjects who cannot cooperate with a traditional SLE, a portable slit lamp model may be used, if necessary.

<sup>6</sup> Performed as part of slit lamp examination.

<sup>7</sup> IOP to be measured using Goldmann Applanation tonometry. For younger pediatric subjects, IOP may be measured using age-appropriate methods per investigator's usual practice.

<sup>8</sup> Performed using Neuroptics pupillometer – VIP 300. For younger pediatric subjects for whom the pupillometer cannot be successfully used, a ruler or pupil gauge may be used. At Treatment Visit 3 - Time 7, subjects whose pupil diameter is larger than baseline may be followed at hourly intervals up to 6 hours after medication administration to gather additional data regarding the duration of study treatment effect.

**APPENDIX 2: STUDY MEDICATION PREPARATION PROCEDURE**

To maintain masking of the drug assignments for study staff performing clinical evaluations, study medication preparation and inventory management will be performed by a pharmacy associated with the study site. The Sponsor, or designee, will ship the following study drug kits to each site's pharmacy:

<b>Kit Components</b>
<ul style="list-style-type: none"><li>• 2 x MiDD base units</li><li>• 2 x MiDD cartridges containing empty 2 mL vial (sterile) + loose adhesive label to be applied to cartridge</li><li>• 2 x Site transport boxes</li><li>• 2 x 10cc syringes (sterile)</li><li>• 2 x 21g needles (sterile)</li><li>• 2 x 2 mL injection vials of phenylephrine 2.5%-tropicamide 1% ophthalmic solution for sterile fill</li><li>• 1 x Micro USB charging cable/connector plug</li></ul>
<ul style="list-style-type: none"><li>• 2 x MiDD base units</li><li>• 2 x MiDD cartridges containing empty 2 mL vial (sterile) + loose adhesive label to be applied to cartridge</li><li>• 2 x Site transport boxes</li><li>• 2 x 10cc syringes (sterile)</li><li>• 2 x 21g needles (sterile)</li><li>• 2 x 4mL bottles of eyewash solution for sterile fill (commercial container)</li><li>• 1 x Micro USB charging cable/connector plug</li></ul>

Each kit will be labeled with the following information:

- Study protocol number
- Study drug code (A or B)
- Statement that kit contains either phenylephrine 2.5%-tropicamide 1% ophthalmic solution or eyewash solution
- Product storage requirement
- Caution – New Drug – Limited by Federal (US) Law to Investigational Use

The MiDD base unit and cartridge are supplied in separate boxes within each study drug kit. The MiDD base unit is contained in a polyethylene terephthalate glycol (PETG) plastic tray inside the box. The MiDD cartridge, which includes the empty vial into which the drug is transferred, is supplied sterile in a PETG plastic tray with a peel lid. Prior to initial MiDD use, the relevant study ophthalmic solution must be aseptically transferred from the container in which it is received into the MiDD vial.

The vial is then inserted into the MiDD cartridge assembly, the cartridge and base are clipped together, and the seal on the vial containing the drug is punctured by depressing the MiDD Load Button. Puncture of this seal creates a fluid path for the drug. Depression and release of the Load Button 5 times primes the system for drug delivery. At the time of dosing, the Load Button is again pressed and released to activate the piezo element to create the aerosol containing the dose. When the Dose Button is pressed, approximately 8  $\mu$ L of the ophthalmic solution is delivered through the Spray Nozzle to the cornea.

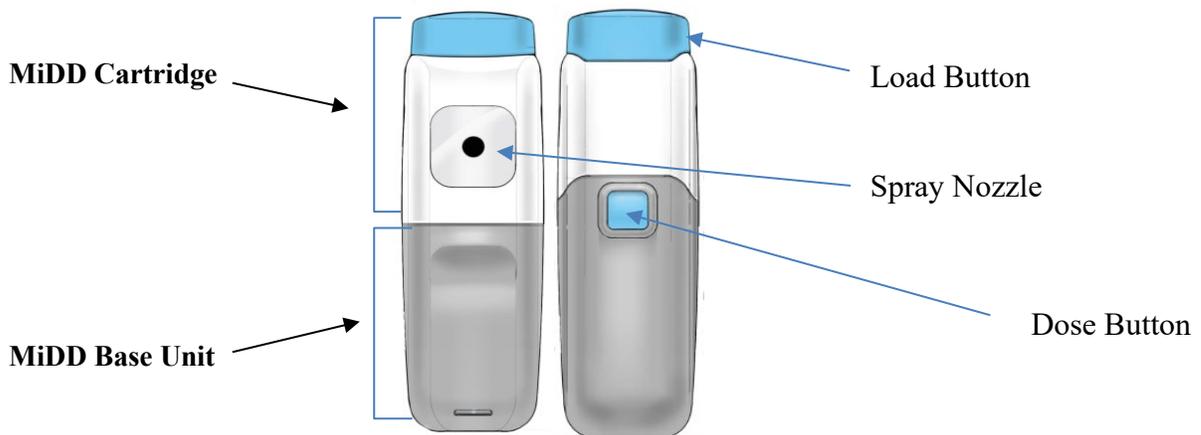
The site study pharmacist will be trained and certified by the Sponsor, or designee, regarding aseptic drug transfer and MiDD cartridge assembly processes prior to their performance.

New study drug MiDDs must be prepared for each treatment day. MiDD cartridges containing each of the 2 study drugs and labeled with the appropriate study drug code, pharmacy preparation date and “use by date” date will be forwarded with the accompanying base unit by the pharmacy to site personnel for use. Site personnel will assemble the cartridge and base unit for each study drug to be used that day and the “date used” for the MiDD will be added to the product preparation/use label by site personnel. At the end of the treatment day, each MiDD provided will be returned to the pharmacy for storage. **Please note that each MiDD prepared must be used on the day of preparation; the MiDD may not be re-used on subsequent days.**

**APPENDIX 3: STUDY MEDICATION ADMINISTRATION PROCEDURE**

This study will be double-masked so that there are no differences in presentation (Eyenovia’s fixed combination mydriasis agent is formulated as a multi-dose microdroplet spray and the placebo is also administered as a microdroplet spray). Site personnel designated to administer study medication will be trained by the Sponsor on proper use of the MiDD prior to study medication administration. In order to reduce the potential for operational bias, study personnel who administer study medication on a given day will not be allowed to perform post-study drug administration ophthalmic assessments on that day. Study drug must be administered in location unattended by examining staff so that examiners are not aware of which drug the subject received.

For each treatment day, one or more new MiDD base units and cartridges containing the study drug to be administered will be provided by the pharmacy for use. Each MiDD will appear the same except for a label indicating the study drug code. Study site personnel will assemble the cartridge and base unit, then add the study drug administration day to the MiDD label and prime the system for use by depressing and releasing the Load Button, then depressing and releasing the Dose Button. This sequence must be performed 5 times to complete the priming process.



**Figure 1: Eyenovia MiDD Front (L) and Back (R) View**

At the time of study medication administration, the following steps should be followed sequentially:

1. Load MiDD dose by depressing the **LOAD BUTTON** once.
2. Hold MiDD such that that the thumb and 3<sup>rd</sup> finger are positioned on each side of the cartridge and index finger is positioned on **DOSE BUTTON** at the back of the MiDD. *Note: Holding MiDD with fingers around the front of the device may affect dispenser alignment with the eye, resulting in spray administration outside of the targeted corneal area.*
3. Begin to position the MiDD over the patient’s eye such that the **SPRAY NOZZLE** is facing the cornea and the **DOSE BUTTON** is facing the medication administrator. While positioning, it is

- suggested to use the little finger of the hand holding the MiDD to open the lower lid and the thumb of the opposite hand to hold the upper lid open.
4. Lower the MiDD toward the eye such that it is almost touching the patient's brow and cheek. The MiDD may be rotated slightly to avoid interference that might affect stability during spray administration; however, it is important that the SPRAY NOZZLE be aligned directly toward the patient's cornea.
  5. Ask patient to first look up, then look at the blue light around the SPRAY NOZZLE
  6. When blue light is centered on the patient's iris, depress, then quickly release DOSE BUTTON to administer medication. Visually confirm medication delivery to the cornea.
  7. If medication delivery missed the cornea, withdraw MiDD from eye, then reload by depressing the LOAD BUTTON once and repeat Steps 1-6.
  8. Repeat steps 1-7 for the contralateral eye.

## **APPENDIX 4: EXAMINATION PROCEDURES**

All study personnel conducting ophthalmic assessments will be masked to the study drug administered.

### **1. Visual Acuity**

The evaluation of VA should be performed before the subject's pupils have been dilated. Distance VA measurements should be obtained at a testing distance of 4 meters by a physician or trained technician using ETDRS lighted charts. Chart background luminance must be between 80 cd/m<sup>2</sup> and 160 cd/m<sup>2</sup>, inclusive (85 cd/m<sup>2</sup> is recommended).

Adult subjects' BCDVA will be determined using subjective manifest refraction.

The subject should be seated so that the distance from the subject's eyes to the ETDRS chart (Chart 1 for right eye and Chart 2 for left eye) is 4 meters (157.5 inches). The middle line of letters to approximately one-third of the distance from the top line of letters should be at eye level for the subject. The subject should be asked to start reading letters at the top line of the chart. Document the number of letters correctly read the line. Move to the next line down if 4 or more letters are read correctly and document the number of letters correctly read on this line. Continue moving down the lines (documenting the number of letters read for each line) until the subject reads 2 or more letters incorrectly, then stop. *Note: If the total number of letters read (TLR) correctly is less than 20 letters, position the subject 1 meter from the chart and add +0.75 D sphere, then resume testing in the same manner.* If the subject is unable to read letters correctly at both 4.0 meters and 1.0 meters, then the subject should be tested to determine if vision is count fingers (CF), hand motion (HM), light perception (LP), or no light perception (NLP). All visual acuities will be expressed in logMar units.

For younger pediatric subjects, uncorrected distance visual acuity (UCDVA) should be measured using age-appropriate methods per the Investigator's usual 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.

For younger pediatric subjects in whom the Neuroptics pupillometer cannot be used to obtain a Time 0 measurement, the pupil diameter may be measured using a ruler or pupil gage using the instructions that follow. Only a single measurement method can be used on any study visit day for a given subject.

**a. Pupil Diameter Determination by Ruler or Pupil Gauge**

For younger pediatric subjects in whom the Neuroptics pupillometer cannot be used to obtain a Time 0 measurement, the pupil diameter may be measured using a ruler or pupil gage using the instructions that follow. A ruler or pupil gauge requires special care to ensure the measurement is accurate. Begin by placing the ruler as close as possible alongside the eye, making certain not to tilt or bend the device. 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 pupil diameter in the fellow eye is measured. For optimal accuracy, take the measurement at the patient's eye level and repeat each measurement 2-3 times to ensure the result is consistent. The pupil diameter recorded should be either the mean (if 2 measurements are taken) or the median (if 3 measurements are taken) values.

**3. Pupillary Light Reflex**

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

**4. Intraocular Pressure Measurement**

After completion of slit lamp biomicroscopy, local anesthetic will be applied to facilitate IOP measurements with the Goldmann Applanation Tonometer. Recent tonometer calibration must be documented.

Two consecutive IOP measurements of each eye must be obtained. If the 2 measurements differ by more than 2 mmHg, a third measurement must be obtained. IOP will be analyzed as the mean of these 2 measurements, or as the median of the 3 measurements.

For pediatric subjects, IOP should be measured using age-appropriate methods per the Investigator's usual practice.

**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. For pediatric subjects who cannot cooperate with a traditional SLE, a portable slit lamp model may be used according to the Investigator's usual practice. 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\*

<b>*Indicate Lens Opacity Grade:</b>	None (0)	None present, or less than mild
	Mild (+1)	Subtle
	Moderate (+2)	Moderate
	Severe (+3)	Dense

Pseudophakic  
Aphakic

**ANTERIOR VITREOUS**

Normal  
Abnormal

**6. Dilated Fundus Examination**

Using ophthalmoscopy, the fundus will be examined and evaluated by the Investigator to be either normal or abnormal at the Screening Visit.

## **APPENDIX 5: 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 a 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 6: 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-32  
VERSION C**

**A MULTI-CENTER, DOUBLE-MASKED, PLACEBO-CONTROLLED, PHASE 3 STUDY OF  
THE SAFETY AND EFFICACY OF FIXED COMBINATION PHENYLEPHRINE 2.5%-  
TROPICAMIDE 1%OPHTHALMIC SOLUTION ADMINISTERED WITH A MICRODOSE  
DISPENSER FOR DILATION OF THE PUPIL  
(THE MIST-2 STUDY)**

**SPONSOR:**

**EYENOVIA, INC.  
295 MADISON AVENUE, SUITE 2400  
NEW YORK NY 10017  
USA  
PHONE: 917-289-1117**

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