# MEDICAL OFFICER, CROSS DISCIPLINE TEAM LEADER, and DIVISION DIRECTOR REVIEW OF NDA 215352

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|---|---|
| Application Type | NDA |
| Application Number(s) | 215352 |
| Review Type | Class 2 Resubmission |
| Priority or Standard | Standard |
| Submit Date(s) | 11/8/2022 |
| Received Date(s) | 11/8/2022 |
| PDUFA Goal Date | 05/8/2023 |
| Division/Office | Division of Ophthalmology/Office of Specialty Medicine |
| Reviewer Name(s) | David B. Summer, MD, Rhea A. Lloyd, MD, Wiley A. Chambers., MD |
| Review Completion Date | See DARRTS stamp date |
| Established/Proper Name | tropicamide and phenylephrine hydrochloride ophthalmic spray, 1%/2.5% |
| (Proposed) Trade Name | MYDCOMBI |
| Applicant | Eyenovia, Inc. |
| Dosage Form(s) | Ophthalmic solution administered via ophthalmic spray |
| Proposed Dosing Regimen(s) | Administer one metered spray to the cornea of each eye to be dilated. Repeat after 5 minutes. |
| Applicant Proposed Indication(s)/Population(s) | Indicated to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired |
| Recommendation on Regulatory Action | Approval |

| Material Reviewed/Consulted<br>OND Action Package, including: | Names of discipline reviewers |
|---|---|
| Regulatory Project Manager | Michael Puglisi |
| Medical Officer Review | David Summer |
| Statistical Review | Yan Zhou |
| Pharmacology Toxicology Review | Maria Rivera |
| OPQ Review | Chunchun Zhang, Shazma Aftab, Elise Luong, Daniel Jansen, Catherine Gilbert, Jin Fang |
| Clinical Pharmacology Review | N/A |
| OPDP | Carrie Newcomer, |
| OSI | Ling Yang |
| CDTL Review | Rhea Lloyd |
| OSE/DMEPA | Oyinlola Fashina |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

## Glossary

| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |

| | |
|---|---|
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Phenylephrine is an α-adrenergic receptor agonist that has been used clinically since the 1930s to induce pupil dilation. Phenylephrine is commercially available for eyedrop administration in either 2.5% or 10% concentrations. Tropicamide is a rapid-acting anticholinergic agent that causes pupil dilation by blocking muscarinic acetylcholine receptor-mediated responses of, and thereby paralyzing, the iris sphincter muscle. Tropicamide ophthalmic solution is commonly used in either 0.5% or 1% concentrations; tropicamide 0.5% produces mydriasis with only slight cycloplegia, while 1% eyedrops results in a temporarily decrease accommodation. The ocular safety of tropicamide and phenylephrine is well established, with a long history of co-administration as the standard of care for mydriasis in the U.S. Eyenovia's Optejet Dispenser is intended to deliver ophthalmic solutions to the ocular surface with a controlled microdroplet spray. Eyenovia's fixed combination MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% is intended to achieve mydriasis in routine diagnostic procedures and in conditions where short term pupil dilation is desired.

The original NDA was submitted on December 28, 2020. On October 22, 2021, a Complete Response letter was issued for the application due to Product Quality and Device deficiencies. The safety and effectiveness of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% for dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired was demonstrated in the original submission. This is a Class 2 Resubmission of the application which the applicant has addressed the outstanding deficiencies from the Complete Response letter.

See the combined, original Medical Officer, CDTL, and Division Director Review in DARRTS dated 10/20/21.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 21352 is recommended for approval with the labeling revisions found in this review. The application supports the safety and effectiveness of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% for the dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. The regulatory action for this application will be APPROVAL.

## 1.3. Benefit-Risk Assessment

## Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% by demonstrating that it is effective in the dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. Transient blurred vision, reduced visual acuity, moderate photophobia, superficial punctate keratitis, and mild eye discomfort associated with drug administration may occur. Increased intraocular pressure has been reported following the use of mydriatics.

The potential benefits of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% for dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired outweigh the identified risks as demonstrated in the clinical studies submitted with this application.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Short-term pupil dilation is commonly used by clinicians to facilitate evaluation and treatment of disorders that are detectible through examination of intraocular structures. | Pharmacologic pupil dilation can be achieved by either stimulating the iris dilator muscle with a sympathomimetic agent (e.g., phenylephrine) and/or by inhibiting the sphincter muscle with an antimuscarinic (anticholinergic) eye drop (e.g., tropicamide). |
| Current Treatment Options | • Tropicamide ophthalmic solution available in 0.5% and 1%, and Phenylephrine ophthalmic solution, available in 2.5% and 10% are the most commonly used, marketed topical agents used for short term mydriasis (pupil dilation) | This product, if approved, would provide an alternative method of delivery of tropicamide and phenylephrine ophthalmic solutions intended for dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. |
| Benefit | • The MydCombi dispenser allows delivery of a metered spray of a lesser drug volume of ophthalmic solution than is delivered by standard eye dropper bottles. | EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) demonstrated that MYDCOMBI was effective in dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Risk and Risk Management | • The treatment emergent adverse events for MydCombi were consistent with the labeled adverse events for the individual tropicamide and phenylephrine components. | The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of this product could be monitored. The observed events rates with the use of this product were consistent with rates expected for a tropicamide and phenylephrine combination. |

## 1.4. Patient Experience Data

Clinical Trials EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) were reviewed during the first review cycle. This submission contains no new clinical studies.

Regarding Clinical Trials EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2)

Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| ☒ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | ☒ | Clinical outcome assessment (COA) data, such as | | See Section 6 |
| ✓ | | ☐ | Patient reported outcome (PRO) | |
| | | ☒ | Observer reported outcome (ObsRO) | |
| | | ☐ | Clinician reported outcome (ClinRO) | |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify) | | |
| ☐ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | ☐ | Input informed from participation in meetings with patient stakeholders | |
| | | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | | ☐ | Observational survey studies designed to capture patient experience data | |
| | | ☐ | Other: (Please specify) | |
| ☐ | Patient experience data was not submitted as part of this application. | | | |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

Pharmacologic pupil dilation can be achieved by either stimulating the iris dilator muscle with a sympathomimetic agent (e.g., phenylephrine) and/or by inhibiting the sphincter muscle with an antimuscarinic (anticholinergic) eye drop (e.g., tropicamide). Eyenovia's fixed combination MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% is intended to use be used to achieve mydriasis in routine diagnostic procedures and in conditions where short term pupil dilation is desired.

## 2.2. Analysis of Current Treatment Options

Table 1: Topical Pharmaceutical Ophthalmic Solutions Used for Pupil Dilation

| PRODUCT | DURATION | ACTION | APPROVED |
|---|---|---|---|
| Phenylephrine | ~3 to 8 hours | Mydriasis | Yes |
| Tropicamide | ~6 to 7 hours | Mydriasis & Cycloplegia | Yes |
| Cyclopentolate | ~12 hours | Mydriasis & Cycloplegia | Yes |
| Scopolamine | ~72 hours | Mydriasis & Cycloplegia | No |
| Homatropine | ~48 hours | Mydriasis & Cycloplegia | No |
| Atropine | ~12 days | Mydriasis & Cycloplegia, and Treatment of Amblyopia | Yes |

# 3. Regulatory Background

## 3.1. Summary of Presubmission/Submission Regulatory Activity

A Type A Meeting was held on January 14, 2022, to reach agreement on Eyenovia's proposed plan to address the Agency's comments and recommendations in the October 22, 2021, Complete Response Letter.

## 3.2. Foreign Regulatory Actions and Marketing History

MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% is not approved in any foreign market.

## 3.3. Office of Scientific Investigations (OSI)

OSI completed a Clinical Inspection Summary during the first review cycle on 9/17/2021. The clinical sites inspected were found to be compliant.

## 4. Product Quality

OPQ completed their integrated review of the original application on 05/01/2023. See the combined, original Medical Officer, CDTL, and Division Director Review in DARRTS dated 10/20/21.

**DRUG SUBSTANCE**

The drug substance, Tropicamide, was previously reviewed (see CMC review #1 dated 6/10/21) and was found adequate. No new drug substance information has been included in the resubmission. See the previous CMC review for all drug substance information.

**From the June 10, 2021, review: Drug Substance(s)**

**Table 2: Specifications for Tropicamide, USP**

| Test | Acceptance Criteria | | Analytical Method |
|---|---|---|---|
| | USP | (b) (4) | |
| Description /Appearance | Not performed | White or practically white, crystalline powder odorless or having not more than a slight odor | Visual Observation |
| Identification A: IR | The identification is positive if the sample exhibits maxima only at the same wavelengths as a similar preparation of Tropicamide WS | The identification is positive if the sample exhibits maxima only at the same wavelengths as a similar preparation of tropicamide WS | IR, USP <197> |
| Identification B: HPLC | The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay. | The retention time of the major peak of the sample solution corresponds to that of the standard solution as obtained in the assay | HPLC |
| Assay by HPLC | 98.0% to 102.0% on the dried basis | 98.0% to 102.0% on the dried basis | HPLC |
| Organic Impurities | Related compound A: NMT 0.15%<br>Related compound B: NMT 0.3%<br>Related compound C: NMT 0.15%<br>Related compound D: NMT 0.15%<br>Any individual unspecified impurity: NMT 0.10%<br>Total Impurities: NMT 0.5% | Related compound A: NMT 0.15%<br>Related compound B: NMT 0.3%<br>Related compound C: NMT 0.15%<br>Related compound D: NMT 0.15%<br>Any individual unspecified impurity: NMT 0.10%<br>Total Impurities: NMT 0.5% | HPLC |
| Residue on Ignition | NMT 0.1% | Not More Than 0.1% | USP <281> |
| Residual Solvents | Not performed | Not More Than (b) (4) ppm | USP<467> |
| | Not performed | Not More Than (b) (4) ppm | |
| Loss on drying | NMT 0.5% | Not More Than 0.5% | USP <731> |
| Heavy Metals | Not performed | Not More Than (b) (4) ppm | USP<231> |

HPLC = high-performance liquid chromatography; IR = infrared; NMT = not more than; USP = United States Pharmacopeia; **Source: Module 3.2.S.4.1**

**Table 3: Specifications for Phenylephrine Hydrochloride, USP**

| Test | Acceptance Criteria | | Method (b) (4) |
|---|---|---|---|
| | (b) (4) | USP | |
| Description | White or practically white, odorless crystals, having a bitter taste | Not Performed | (b) (4) |
| Solubility | Freely soluble in water and in alcohol | Not Performed | |
| Identification | A. Concordant with the IR spectrum of Phenylephrine Hydrochloride reference standard<br>B. Tests for chloride<br>C. The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in Assay | A. Concordant with the IR spectrum of Phenylephrine Hydrochloride reference standard<br>B. Tests for chloride<br>C. The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in Assay | |
| Specific rotation | Between -43.0° and -47.0° | Between -43.0° and -47.0° | |
| Loss on drying | Not more than 1.00% | Not more than 1.0% | |
| Residue on ignition | Not more than 0.20% | Not more than 0.20% | |
| Sulfate | Not more than 0.20% | Not more than 0.20% | |
| Organic impurities by HPLC | Norphenylephrine: not more than 0.10%<br><br>Phenylephrine related compound C: not more than 0.10%<br><br>Phenylephrine related compound D: not more than 0.10%<br><br>Phenylephrine related compound E: not more than 0.10%<br><br>Any individual unspecified impurity: not more than 0.10%<br><br>Total impurities: not more than 0.20% | Norphenylephrine: not more than 0.10%<br><br>Phenylephrine related compound C: not more than 0.10%<br><br>Phenylephrine related compound D: not more than 0.10%<br><br>Phenylephrine related compound E: not more than 0.10%<br><br>Any individual unspecified impurity: not more than 0.10%<br><br>Total impurities: not more than 0.20% | |
| Assay by HPLC | Between 98.0% and 102.0%, calculated on the dried basis | Between 98.0% and 102.0%, calculated on the dried basis | |
| | (b) (4) | Not Performed | |

| | | | |
|---|---|---|---|
| Residual solvents | (b) (4) | | (b) (4) |
| Enantiomeric excess | Not less than (b) (4)% | Not Performed | |
| Microbial contamination | Total Aerobic Microbial Count: NMT (b) (4) cfu/g<br>Total combined Yeast & Mold count: NMT (b) (4) cfu/g | Not Performed | USP |
| Endotoxin content | NM (b) (4) Eu/mg | Not Performed | USP |

HPLC = high-performance liquid chromatography; NMT = not more than; USP = United States Pharmacopeia
Source: Module 3.2.S.4.1

DRUG PRODUCT

*Assessment Summary during review cycle 2:* The updated 24 months long-term stability data for one registration batch manufactured at the commercial manufacturing site Alcami meet specifications. In addition, Eyenovia also provided 9 months long-term stability data for 3 process validation batches from Alcami, which also meet specifications. Thus, the data support a drug product shelf-life of 24 months when the drug product is stored between (b) (4) and 25°C (b) (4) and 77°F).

From the OPQ review finalized June 2021.
Drug Product Composition

Table 4: Composition of MYDCOMBI (tropicamide 1% and phenylephrine hydrochloride 2.5%, USP) Ophthalmic Solution

| Ingredient | Function of Components | Quality Standard | Concentration (w/w %) | Amount (mg/mL) |
|---|---|---|---|---|
| Phenylephrine HCl | Active | USP | 2.5 | 25 |
| Tropicamide | Active | USP | 1.0 | 10 |
| (b) (4)® Benzalkonium Chloride (b) (4) | Preservative | USP/NF | 0.01 | 0.1 |
| Hydrochloride Acid and/or Sodium Hydroxide | pH adjustment | USP/NF | As needed for pH adjustment to 5.0±0.2 | As needed for pH adjustment to 5.0±0.2 |
| Water for Injection | (b) (4) | USP | q. s | q. s |

q. s = quantum satis Source: Module 3.2.P.1

Drug Product Specifications

Table 5: Quality Control Specifications Tropicamide 1% and Phenylephrine Hydrochloride 2.5% Ophthalmic Solution

| Test | Method | Acceptance Criteria |
|---|---|---|
| Appearance | Visual | Clear, colorless solution free of visible particulates in a clear glass vial with stopper and open top seal. |
| Phenylephrine HCl Identification Retention Time | HPLC | (b) (4) |
| Phenylephrine HCl Identification | HPLC<br>UV Spectrum<br>PDA | |
| Tropicamide Identification | Retention Time<br>HPLC | |
| Tropicamide Identification | HPLC<br>UV Spectrum<br>PDA | |
| Phenylephrine HCl Assay | HPLC | |
| Phenylephrine HCl Related Substances | HPLC | |
| Tropicamide Assay | HPLC | |
| Tropicamide Related Substances | HPLC | |
| Benzalkonium Chloride Assay | HPLC | |
| pH | USP<791> | |
| Minimum Fill | USP<755> | |
| Osmolality | USP<785> | |
| Viscosity | cUSP<912> | |
| Particulate Matter | USP<788>,<br>USP<789> | |

| | | | |
|---|---|---|---|
| | | (b) (4) | |
| Sterility | USP<71> | | |

HPLC = high-performance liquid chromatography; NLT = not less than; NMT = not more than; PDA = Photodiode Array; USP = United States Pharmacopeia; UV = ultraviolet **Source: Module 3.2.P.5**

**MICROBIOLOGY:**

***Assessment Summary during review cycle 2:***

(b) (4)

**Container Closure Systems**

| Component | Packaging | Description (Gland material code) | Manufacturer |
|---|---|---|---|
| Vial | Primary | (b) (4) | |
| Stopper | Primary | | |
| Seal | Secondary | | |
| Cartridge | Primary | | |
| Cartridge tray | Secondary | | |
| Base | Secondary | | |

**Figure 2: Base Assembly and Cartridge Assembly**

(b) (4)

**Figure 1: Eyenovia Microdose Delivery (Optejet) Front (Left) and Back (Right) Views**

(b)

(b) (4)

The applicant has provided adequate information supporting the integrity of the proposed container/closure system.

Alcami sterility validation data were provided in DMF (b) (4). The DMF review conclusions were summarized and found adequate in the original NDA review. Validation data summarized included recent (2020) RQ studies for all validated processes. A 12/01/2021 submission to the DMF (b) (4) included (b) (4) (not proposed for this product) (b) (4). As no processes or equipment proposed for production have been changed and the previously reviewed data is recent, no additional validation data from the Alcami facility will be included in this review.

The applicant has provided adequate information to support (b) (4) production. The (b) (4) simulations adequately validate (b) (4) of the subject drug product.

MANUFACTURING
The proposed drug product is a Tropicamide and Phenylephrine fixed dose combination ophthalmic spray, where the attached dispenser enables precision dose delivery (spray). The spray is in micro-volumes, 8 µl of active can be delivered topically to the eye in micro droplets in less than (b) (4)

The applicant proposed to split the (b) (4) manufacturing steps among the (b) (4) different facilities:

(b) (4)

The applicant proposed one primary and one alternative facility for bulk drug product manufacturing (b) (4) They are Alcami Carolinas FEI (b) (4) and (b) (4) The residual risk in critical product quality attributes such as particulates and spray pattern has been evaluated by both DP and Microbiology reviewers.

Information request related to the consistency of (b) (4) process were issued. Upon IRs, the applicant adequately addressed process related issues.

The (b) (4) manufacturing operations in Alcami Carolinas is captured in DMF (b) (4), which has been referenced by multiple approved ANDA/NDA for (b) (4) drug product manufacturing. (b) (4) (b) (4). Therefore, PAI at (b) (4) concluded the facility failed to demonstrate readiness for commercial manufacturing before the action date for the first review cycle ended in 2022.

The Optejet dispenser cartridge includes (b) (4) delivery system that releases the ophthalmic formulation and dispenses the micro-dose are part of the primary packaging system. The suitability of the proposed facility (b) (4) is acceptable per CDRH e-mail communication dated 9/20/2021, via ATL Chunchun. PAI conducted at the facility found the facility is acceptable as a drug product packager.

Resubmission Review:

- Applicant withdrew the alternative drug product manufacturing facility (b) (4) ((b) (4) FEI# (b) (4) for commercial production as mentioned in cover letter dated 08Nov2022. Three new PPQ batches had been manufactured at Alcami Corporation FEI# (b) (4) the only bulk drug product facility for now, and new stability data on the new batches were submitted.
- Facility (b) (4) FEI# (b) (4) is now named as (b) (4) The proposed function of (b) (4) ((b) (4) FEI# (b) (4) has changed from Dispenser manufacturer and Primary packaging (original submission) to Primary container closure system assembly and packaging (resubmission).
- A new facility Eyenovia FEI# 3015097092 with two sites is proposed for Optejet dispenser base manufacture and packaging. This facility has no inspection history. PAI was deemed needed after CDRH facility consult in 12/2022. The inspection of the Technology Way site was conducted during the week of March 27th to April 5th, Form 483 issued. The other site (b) (4) applicant withdrew (b) (4) upon receiving Information Request dated 04-11-2023.
- As a response to the 04-11-2023 IR, the applicant also formally withdrew three testing labs, i.e., (b) (4) and updated FDA FORM 356h.
- Three new executed PPQ batch records with Bath number B210268, B210343 and B210276 were received in this resubmission (Sequence #0029 dated 02- 16-2023). The 9-month

long-term stability data along with 6-month data under accelerated conditions were submitted for the three PPQ batches (Sequence #0027 dated 01-20-2023).

- A batch record discrepancy was noticed. The applicant provided an adequate response in SD#0034. There are no addition concerns related to process changes or manufacturing site.

CDRH Review:

The following engineering comment was sent to the sponsor:

1. In your submission, you have provided testing details for the drug dispensing device (Section 3.2.P.7 Container Closure System). However, you have not provided justification for the force requirements in the testing for the mist button actuation force (Section 7.4.2.2), cartridge assembly and separation (Section 7.4.3), or the priming force (Section 7.4.2.1).While you have provided sufficient testing for these deice evaluations, you have not provided information about how the limits were chosen for these assessments. It is essential to know the reasoning for the limits as any limit set above a given value may prevent the effective use of the device by the end user. Please provide the justification of the force acceptance limits for the mist button actuation force, cartridge assembly and separation, or the priming force.

*Engineering Reviewer Comment:*

*The sponsor cited ANSI standards for human factors engineering design of medical devices (ANSI HE75). The sponsor has adequately cited the force testing conditions that are discussed in the standard. Although the ANSI standard is only partially recognized by the FDA, this partial recognition does not impact the acceptability of the limits. Additionally, the file also had additional human factors reviewers from CDER, who also did not have issues with the limits in their review. Therefore, the justification is adequate from an engineering perspective and the concerns with the testing limits have been resolved. RESOLVED*

2. In your submission, you include spray volume testing (Section 3.2.P.7 Container Closure System). However, the interval between the sprays was not specified. Please clarify if you conduct testing for consistency of the spray volume in a case that the residual drug is allowed to dry after delivered dosages. This is a concern because the residual drug after delivery may dry in the fluid path or result in the fowling of the ejector holes or nozzle aperture, resulting in the administration of less than intended dosage of the drug. Please provide this testing or justification as to why the testing was not performed in this manner.

*Engineering Reviewer Comment*

*The sponsor provided information that the device was tested over 35 days, a period that is sufficient to demonstrate the lack of fowling at the nozzle. Therefore, this concern has been addressed and the response is adequate. RESOLVED*

**Table 6: Facilities Table**

| Facility name and address | FEI | Responsibilities and profile code(s) | Status |
|---|---|---|---|
| (b) (4) | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |

| | |
|---|---|
| (b) (4) | Approve - Based on Previous History |
| | Approve - Based on PAI |
| | Approve - Based on Previous History |
| | Approve - Based on Previous History |
| | Withdrawn |
| | Withdrawn |
| | Withdrawn |
| | Withdrawn |
| | Withdrawn |

**OPQ RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY**

The OPQ integrated review of the resubmitted application was completed on 05/03/2023. In the original submission, NDA 215352 was inadequate from a quality microbiology, facilities and CDRH perspective as described on 10/22/2021. Refer to IQA #1.

In the resubmission, quality microbiology has found all the identified deficiencies have been adequately addressed. The compliance status of the device assembly manufacturing facility, Eyenovia (FEI# 3015097092) was determined acceptable based on the most recent inspection performed ending Apr 5, 2023. OPMA issued an overall recommendation of "approval" on May 1, 2023. CDRH review team has found all the previous deficiencies were resolved in a memo dated on 3/20/2023. NDA 215352 is recommended approval from Product Quality perspective.

# 5. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology completed a review of the original application on 8/3/2021. No new nonclinical information was submitted in this resubmission application.

# 6. Clinical Pharmacology

No Clinical Pharmacology information was submitted in this amendment. In the original application, the Applicant relied on the Agency's previous finding of safety for NDA 207926, NDA 022565 (phenylephrine), and NDA 012111 (tropicamide) as well as published literature (both phenylephrine and tropicamide). At the End of Phase 2 meeting held in July 2018, FDA agreed with the Applicant that the collection of PK data for this product is not needed. Therefore, no PK data was included in the application. Accordingly, Clinical Pharmacology role for this application was focused on the proposed labeling.

# 7. Sources of Clinical Data and Review Strategy

## 7.1. Clinical Studies

The safety and efficacy of MYDCOMBI for the proposed indication was demonstrated in the clinical studies listed below during the first review cycle. No new clinical studies were submitted in this submission.

Listing of Clinical Studies

| Phase 3 Study | Design | Key Entry Criteria | Planned number of subjects | Duration |
|---|---|---|---|---|
| EYN-MYD-TP-31 (MIST-1) | DOUBLE-MASKED, ACTIVE-CONTROLLED | Male or female of any age. No history of closed-angle glaucoma or anatomically narrow anterior chamber angles<br><br>Iris or pupil abnormality | Up to 90 volunteer participants will be enrolled and drug administration will be initiated on at least 65 subjects to complete follow-up on 54 subjects | Study drug was administered at 3 treatment visits occurring over a 5 to 15-day period. At each treatment visit, one of the study drugs was administered to both eyes. |
| EYN-MYD-TP-32 (MIST-2) | DOUBLE-MASKED, PLACEBO-CONTROLLED | Same as MIST-1 | Up to 90 volunteer participants will be enrolled and drug administration will be initiated on at | Same as MIST-1 |

| | | | | |
|---|---|---|---|---|
| | | | least 65 subjects to complete follow-up on 54 subjects | |

The safety and efficacy of MYDCOMBI for the proposed indication was demonstrated in the original submission. No new clinical studies were submitted in this submission.

## 8. Integrated Review of Effectiveness

The data from two clinical studies, EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2), contained in the original submission December 28, 2020, established the efficacy of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired. See the combined, original Medical Officer, CDTL, and Division Director Review in DARRTS dated 10/20/21.

## 9. Review of Safety

The data from two clinical studies, EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2), contained in the original submission December 28, 2020, established the safety of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired. See the combined, original Medical Officer, CDTL, and Division Director Review in DARRTS dated 10/20/21.

## 10. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## 11. Labeling Recommendations

See the final labeling located in Section 13.2. of this review.

## 12. Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategies (REMS) will be required for this application.

# 13. Regulatory Action

The submitted studies in NDA 215352 for MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray) 1%/2.5% established safety and efficacy for the dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. The regulatory action for this NDA will be APPROVAL.

# 14. Appendices

## 14.1. Financial Disclosure

No new clinical studies were submitted in this resubmission application. Financial Disclosure information was reviewed in the original NDA submission. See the combined, original Medical Officer, CDTL, and Division Director Review in DARRTS dated 10/20/21.

## 14.2. Labeling

The final agreed up on labeling is contained at the end of this review.

35 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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WILEY A CHAMBERS
05/05/2023 02:30:21 PM

DAVID B SUMMER
05/05/2023 02:32:30 PM

RHEA A LLOYD
05/05/2023 02:34:59 PM

Medical Officer, CDTL, and Division Director Review
David Summer, MD, William M. Boyd, MD, Wiley Chambers, MD
NDA 215352
MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray

MEDICAL OFFICER, CROSS DISCIPLINE TEAM LEADER, and DIVISION DIRECTOR REVIEW OF NDA 215352

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 215352 |
| Priority or Standard | Standard |
| Submit Date(s) | 12/28/2020 |
| Received Date(s) | 12/28/2020 |
| PDUFA Goal Date | 10/28/2021 |
| Division/Office | Division of Ophthalmology/Office of Specialty Medicine |
| Reviewer Name(s) | David B. Summer, MD, William M. Boyd, MD, Wiley A. Chambers., MD |
| Review Completion Date | See DARRTS stamp date |
| Established/Proper Name | tropicamide and phenylephrine hydrochloride ophthalmic solution, 1%/2.5% |
| (Proposed) Trade Name | MYDCOMBI |
| Applicant | Eyenovia, Inc. |
| Dosage Form(s) | Ophthalmic solution administered via ophthalmic spray |
| Proposed Dosing Regimen(s) | Administer one metered spray to the cornea of each eye to be dilated. Repeat after 5 minutes. |
| Applicant Proposed Indication(s)/Population(s) | Indicated to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired |
| Recommendation on Regulatory Action | Complete Response |

| Material Reviewed/Consulted<br>OND Action Package, including: | Names of discipline reviewers |
|---|---|
| Regulatory Project Manager | Michael Puglisi |
| Medical Officer Review | David Summer |
| Statistical Review | Solomon Chefo |
| Pharmacology Toxicology Review | Maria Rivera |
| OPQ Review | Chunchun Zhang, Elise Luong, Daniel Jansen, Tim Zhou<br>Catherine Gilbert |
| Clinical Pharmacology Review | N/A |
| OPDP | N/A |
| OSI | Lin Yang |
| CDTL Review | William M. Boyd |
| OSE/DMEPA | Nasim Roosta |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

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## Glossary

| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |

| | |
|---|---|
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Phenylephrine is an α-adrenergic receptor agonist that has been used clinically since the 1930s to induce pupil dilation. Phenylephrine is commercially available for eyedrop administration in either 2.5% or 10% concentrations. Tropicamide is a rapid-acting anticholinergic agent that causes pupil dilation by blocking muscarinic acetylcholine receptor-mediated responses of, and thereby paralyzing, the iris sphincter muscle and the ciliary muscle. Tropicamide ophthalmic solution is commonly used in either 0.5% or 1.0% concentrations; tropicamide 0.5% produces mydriasis with only slight cycloplegia, while 1.0% eyedrops results in a temporarily decrease accommodation. The ocular safety of tropicamide and phenylephrine is well established, with a long history of co-administration as the standard of care for mydriasis in the U.S. Eyenovia's Optejet Dispenser is intended to deliver ophthalmic solutions to the ocular surface with a controlled microdroplet spray. Eyenovia's fixed combination MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray is intended to achieve mydriasis in routine diagnostic procedures and in conditions where short term pupil dilation is desired. This is a 505(b)(2) application which identifies NDA 012111 tropicamide ophthalmic solution, 0.5% and 1% and NDA 207926 phenylephrine ophthalmic solution, 2.5% and 10% as the listed drug products that are the basis for the submission.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 21352 is recommended for approval with the labeling revisions found in this review once outstanding Chemistry/Manufacturing issues are resolved. The application supports the safety and effectiveness of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray for dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired.

The compliance status of the drug product manufacturing facility, (b) (4) was determined to be unacceptable based on the most recent inspection performed. There are additional OPQ deficiencies. See Section 4.2 of this review. The regulatory action for this application will be Complete Response.

## 1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray by demonstrating that it is effective in the dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. Transient blurred vision, reduced visual acuity, moderate photophobia, superficial punctate keratitis, and mild eye discomfort associated with drug administration may occur. Increased intraocular pressure has been reported following the use of mydriatics.

The potential benefits of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray for dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired outweigh the identified risks as demonstrated in the clinical studies submitted with this application.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Short-term pupil dilation is commonly used by clinicians to facilitate evaluation and treatment of disorders that are detectible through examination of intraocular structures.<br>• Marketed eye drops deliver higher drug volume per eye drop than can be retained within the conjunctival cul-de-sacs | Pharmacologic pupil dilation can be achieved by either stimulating the iris dilator muscle with a sympathomimetic agent (e.g., phenylephrine) and/or by inhibiting the sphincter muscle with an antimuscarinic (anticholinergic) eye drop (e.g., tropicamide). |
| Current Treatment Options | • Tropicamide ophthalmic solution available in 0.5% and 1%, and Phenylephrine ophthalmic solution, available in 2.5% and 10% are the most commonly used, marketed topical agents used for short term mydriasis (pupil dilation) | This product, if approved, would provide an alternative method of delivery of tropicamide and phenylephrine ophthalmic solutions intended for dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | • The MydCombi microspray dispenser allows delivery of a metered spray of a lesser drug volume of ophthalmic solution than is delivered by standard eye dropper bottles<br>• The reduction of dose through microspray delivery of MydCombi may theoretically lower the incidence of adverse reactions | EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) demonstrated that MYDCOMBI was effective in dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired. |
| Risk and Risk Management | • The treatment emergent adverse events for the MydCombi product were consistent with the labeled adverse events for the individual tropicamide and phenylephrine components. | The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of this product could be monitored. The observed events rates with the use of this product were consistent with rates expected for a tropicamide and phenylephrine combination. |

### 1.4. Patient Experience Data

Regarding Clinical Trials EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2)

Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| ☒ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | ☒ | Clinical outcome assessment (COA) data, such as | | See Section 6.1 of this review, Study Endpoints |
| ✓ | | ☐ | Patient reported outcome (PRO) | |
| | | ☒ | Observer reported outcome (ObsRO) | |
| | | ☐ | Clinician reported outcome (ClinRO) | |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | [e.g., Sec 2.1 Analysis of Condition] |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify) | | |
| ☐ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | ☐ | Input informed from participation in meetings with patient stakeholders | |
| | | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| | | ☐ | Observational survey studies designed to capture patient experience data | |
| | | ☐ | Other: (Please specify) | |
| ☐ | Patient experience data was not submitted as part of this application. | | | |

## 2. Therapeutic Context

## 2.1. Analysis of Condition

Pharmacologic pupil dilation can be achieved by either stimulating the iris dilator muscle with a sympathomimetic agent (e.g., phenylephrine) or by inhibiting the sphincter muscle with an antimuscarinic (anticholinergic) eye drop (e.g., tropicamide). Eyenovia's fixed combination MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray is intended to be used to achieve mydriasis in routine diagnostic procedures and in conditions where short term pupil dilation is desired.

## 2.2. Analysis of Current Treatment Options

Table 1: Topical Pharmaceutical Ophthalmic Solutions Used for Pupil Dilation

| PRODUCT | DURATION | ACTION | APPROVED | NOTES |
|---|---|---|---|---|
| Phenylephrine | ~3 to 8 hours | Mydriasis | Yes | 2.5% and 10% solutions |
| Tropicamide | ~6-7 hours | Mydriasis & Cycloplegia | Yes | 0.5% and 1% solutions |
| Cyclopentolate | ~12 hours | Mydriasis & Cycloplegia | Yes | long duration of effect for short term dilation |
| Scopolamine | ~72 hours | Mydriasis & Cycloplegia | No | very long duration of effect for short term dilation |
| Homatropine | ~48 hours | Mydriasis & Cycloplegia | No | very long duration of effect for short term dilation. |
| Atropine | ~12 days | Mydriasis & Cycloplegia, and Treatment of Amblyopia | Yes | Available in ointment and solution. Excessive duration of effect for short term dilation. |

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% is an alpha 1-adrenergic receptor agonist and nonselective cyclooxygenase inhibitor indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative pain. It is added to an irrigation solution used during cataract surgery or intraocular lens replacement.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray is not approved in the U.S.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

FDA provided written comments on September 12, 2017, for PIND 135936.

FDA provided additional written comments on July 16, 2018, for PIND 135936.

Original IND 135936 was submitted October 9, 2018.

## 3.3. Foreign Regulatory Actions and Marketing History

MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray is not approved in any foreign market.

# 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

OSI completed a Clinical Inspection Summary on 9/17/2021.

Clinical data from Studies EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) were submitted to the Agency in support of this New Drug Application (NDA) 215352 for MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray for the proposed indication to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired.

Two clinical investigators (CIs): Dr. David Wirta (Site 02 for Study EYNMYD- TP-31) and Dr. Thomas Walters (Site 04 for Study EYN-MYD-TP-32) were selected for clinical inspections. The inspections verified the sponsor Eyenovia, Inc. (Eyenovia) submitted clinical data with source records at the CI sites. Based on the results of these CI inspections, Studies EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2) appear to have been conducted adequately, and the

data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

## 4.2. Product Quality

OPQ completed their integrated review of the original application on 09/24/2021.

**Drug Substance(s)**

**Table 2: Specifications for Tropicamide, USP**

| Test | Acceptance Criteria | | Analytical Method |
|---|---|---|---|
| | USP | (b) (4) | |
| Description /Appearance | Not performed | White or practically white, crystalline powder odorless or having not more than a slight odor | Visual Observation |
| Identification A: IR | The identification is positive if the sample exhibits maxima only at the same wavelengths as a similar preparation of Tropicamide WS | The identification is positive if the sample exhibits maxima only at the same wavelengths as a similar preparation of tropicamide WS | IR, USP <197> |
| Identification B: HPLC | The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay. | The retention time of the major peak of the sample solution corresponds to that of the standard solution as obtained in the assay | HPLC |
| Assay by HPLC | 98.0% to 102.0% on the dried basis | 98.0% to 102.0% on the dried basis | HPLC |
| Organic Impurities | Related compound A: NMT 0.15%<br>Related compound B: NMT 0.3%<br>Related compound C: NMT 0.15%<br>Related compound D: NMT 0.15%<br>Any individual unspecified impurity: NMT 0.10%<br>Total Impurities: NMT 0.5% | Related compound A: NMT 0.15%<br>Related compound B: NMT 0.3%<br>Related compound C: NMT 0.15%<br>Related compound D: NMT 0.15%<br>Any individual unspecified impurity: NMT 0.10%<br>Total Impurities: NMT 0.5% | HPLC |
| Residue on Ignition | NMT 0.1% | Not More Than 0.1% | USP <281> |

| | | | |
|---|---|---|---|
| Residual Solvents | Not performed | Not More Than (b) (4) ppm | USP<467> |
| | Not performed | Not More Than (b) (4) ppm | |
| Loss on drying | NMT 0.5% | Not More Than 0.5% | USP <731> |
| Heavy Metals | Not performed | Not More Than (b) (4) ppm | USP<231> |

HPLC = high-performance liquid chromatography; IR = infrared; NMT = not more than; USP = United States Pharmacopeia

**Source: Module 3.2.S.4.1**

**Table 3: Specifications for Phenylephrine Hydrochloride, USP**

| Test | Acceptance Criteria | | Method (b) (4) |
|---|---|---|---|
| | (b) (4) | USP | |
| Description | White or practically white, odorless crystals, having a bitter taste | Not Performed | (b) (4) |
| Solubility | Freely soluble in water and in alcohol | Not Performed | |
| Identification | A. Concordant with the IR spectrum of Phenylephrine Hydrochloride reference standard<br>B. Tests for chloride<br>C. The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in Assay | A. Concordant with the IR spectrum of Phenylephrine Hydrochloride reference standard<br>B. Tests for chloride<br>C. The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in Assay | |
| Specific rotation | Between -43.0° and -47.0° | Between -43.0° and -47.0° | |
| Loss on drying | Not more than 1.00% | Not more than 1.0% | |
| Residue on ignition | Not more than 0.20% | Not more than 0.20% | |
| Sulfate | Not more than 0.20% | Not more than 0.20% | |

| | | | |
|---|---|---|---|
| Organic impurities by HPLC | Norphenylephrine: not more than 0.10%<br><br>Phenylephrine related compound C: not more than 0.10%<br><br>Phenylephrine related compound D: not more than 0.10%<br><br>Phenylephrine related compound E: not more than 0.10%<br><br>Any individual unspecified impurity: not more than 0.10%<br><br>Total impurities: not more than 0.20% | Norphenylephrine: not more than 0.10%<br><br>Phenylephrine related compound C: not more than 0.10%<br><br>Phenylephrine related compound D: not more than 0.10%<br><br>Phenylephrine related compound E: not more than 0.10%<br><br>Any individual unspecified impurity: not more than 0.10%<br><br>Total impurities: not more than 0.20% | (b) (4) |
| Assay by HPLC | Between 98.0% and 102.0%, calculated on the dried basis | Between 98.0% and 102.0%, calculated on the dried basis | (b) (4) |
| Residual solvents | (b) (4) | Not Performed | (b) (4) |
| Enantiomeric excess | Not less than (b) (4) | Not Performed | (b) (4) |
| Microbial contamination | Total Aerobic Microbial Count: NMT (b) (4) cfu/g<br>Total combined Yeast & Mold count: NMT (b) (4) cfu/g | Not Performed | USP |
| Endotoxin content | NMT (b) (4) Eu/mg | Not Performed | USP |

HPLC = high-performance liquid chromatography; NMT = not more than; USP = United States Pharmacopeia

Source: Module 3.2.S.4.1

## Drug Product Composition

MYDCOMBI is a sterile, clear, colorless solution fixed-dose combination of an anticholinergic (tropicamide) and an α adrenergic receptor agonist (phenylephrine hydrochloride) for topical ophthalmic use.

Table 4: Composition of MYDCOMBI (tropicamide 1% and phenylephrine hydrochloride 2.5%, USP) Ophthalmic Solution

| Ingredient | Function of Components | Quality Standard | Concentration (w/w %) | Amount (mg/mL) |
|---|---|---|---|---|
| Phenylephrine HCl | Active | USP | 2.5 | 25 |
| Tropicamide | Active | USP | 1.0 | 10 |
| (b) (4)® Benzalkonium Chloride (b) (4) | Preservative | USP/NF | 0.01 | 0.1 |
| Hydrochloride Acid and/or Sodium Hydroxide | pH adjustment | USP/NF | As needed for pH adjustment to 5.0±0.2 | As needed for pH adjustment to 5.0±0.2 |
| Water for Injection | (b) (4) | USP | q. s | q. s |

q. s = quantum satis
Source: Module 3.2.P.1

Drug Product Specifications

Table 5: Quality Control Specifications Tropicamide 1% and Phenylephrine Hydrochloride 2.5% Ophthalmic Solution

| Test | Method | Acceptance Criteria |
|---|---|---|
| Appearance | Visual | Clear, colorless solution free of visible particulates in a clear glass vial with stopper and open top seal. |
| Phenylephrine HCl Identification Retention Time | HPLC | (b) (4) |
| Phenylephrine HCl Identification | HPLC<br>UV Spectrum PDA | |
| Tropicamide Identification | Retention Time HPLC | |

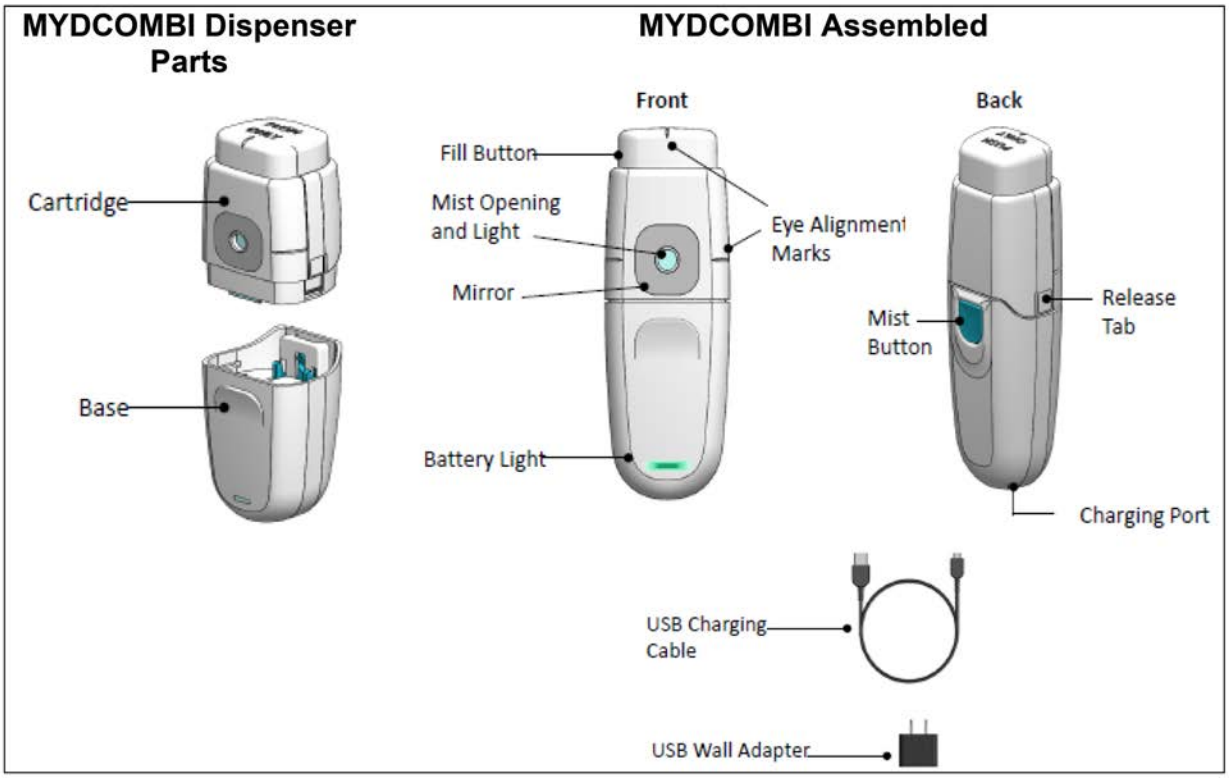
| | | (b) (4) |
|---|---|---|
| Tropicamide Identification | HPLC<br>UV Spectrum PDA | |
| Phenylephrine HCl Assay | HPLC | |
| Phenylephrine HCl Related Substances | HPLC | |
| Tropicamide Assay | HPLC | |
| Tropicamide Related Substances | HPLC | |
| Benzalkonium Chloride Assay | HPLC | |
| pH | USP<791> | |
| Minimum Fill | USP<755> | |
| Osmolality | USP<785> | |
| Viscosity | USP<912> | |
| Particulate Matter | USP<788>, USP<789> | |
| Sterility | USP<71> | |

HPLC = high-performance liquid chromatography; NLT = not less than; NMT = not more than; PDA = Photodiode Array; USP = United States Pharmacopeia; UV = ultraviolet
Source: Module 3.2.P.5

Container Closure Systems

Tropicamide and phenylephrine hydrochloride ophthalmic solution, 1%/2.5% (b) (4) The Optejet is composed of two interdependent components, the base unit and the cartridge. The base unit and cartridge are designed to deliver a dose of an ophthalmic formulation (b) (4) using a (b) (4) microdroplets to coat the ocular surface.

Figure 1: Eyenovia Dispenser (Optejet)




Source: Module 3.2.P.7

The two components need to be coupled prior to activation and dispensation of the drug. The cartridge (upper section of the container) contains the drug product (b) (4) The base unit (bottom section of the container) contains the battery, electronics, light-emitting diode status light, and the Dose Button.

**Figure 2: Base Assembly and Cartridge Assembly**


**Source: Module 3.2.P.7**

Primary Container Closure Component Description

**Table 6: Primary Packaging Components**

| Component | Description | Supplier | DMF Number | Quality Standard |
|---|---|---|---|---|
| Vial (b) (4 | (b) (4) | | | |
| Stopper (b) (4 | | | | |
| Seal (b) (4 | | | | |
| Dispenser (b) (4) | | | | |

**Source: Module 3.2.P.7**

Secondary Container Closure Description

The Optejet cartridge is packaged in a cartridge tray (b) (4) The tray is then inserted into a white carton box 4.05 x 3.82".

Tertiary Container Closure Description

The Optejet Base is packaged into a white carton box 4.05 x 3.82".

**Microbiology**

(b) (4)

There is a list of Microbiology Deficiencies. See OPQ Recommendations and Conclusion on Approvability in this review.

**CDRH**

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including this product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including this product.

Dr. James Bertram (CDRH) confirmed that only a technical/engineering consult review is necessary from CDRH for this product and the device manufacturing facility is acceptable based on the inspection history on (b) (4) Dr. Keith Christopher (CDRH) conducted an engineering review on Optejet dispenser on Sep 3, 2021.

There is a list of CDRH Deficiencies. See OPQ Recommendations and Conclusion on Approvability in this review.

**Facilities**

**Table 7: Facilities Table**

| Facility name and address | FEI | Responsibilities and profile code(s) | Status |
|---|---|---|---|
| (b) (4) | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Withhold - Based on PAI |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |
| | | | Approve - Based on Previous History |

During a recent inspection of the [redacted] (b) (4) drug product manufacturing facility for this application, the FDA field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**OPQ RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY**

Per the OPQ integrated review of the original application completed on 09/24/2021 and the OPQ addendum completed on 10/8/2021:

Satisfactory information and responses have been submitted to support the drug substance, drug product, and manufacturing process aspects. The compliance status of the drug product manufacturing facility, [redacted] (b) (4) was determined unacceptable based on the most recent inspection performed ending [redacted] (b) (4), the response to the 483 observations were not complete at the conclusion of this assessment. Therefore, OPMA issued an overall recommendation of "Withhold" on [redacted] (b) (4) Additionally, there are outstanding deficiencies from the quality microbiology perspective. CDRH was consulted to review the Optejet dispenser and has found three major deficiencies in the consult memo dated on 9/3/2021. In agreement with the above recommendation, NDA 215352 is recommended Complete Response from Product Quality perspective.

<u>OPQ Complete Response Items to be Included in the Action Letter:</u>

**Facilities deficiency:**
During a recent inspection of the [redacted] (b) (4) drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**Microbiology deficiencies:**
1. The [redacted] (b) (4) microbial ingress container closure integrity testing (CCIT) performed [redacted] (b) (4) is acknowledged, [redacted] (b) (4) Please consider the following options to demonstrate the integrity of the assembled device:

[redacted] (b) (4)

(b) (4)

2. It is acknowledged that the Alcami facility has performed (b) (4) Provide the results of this hold time study.

3. The validation information for (b) (4) is acknowledged. Please address the following:

(b) (4)

(b) (4)

**CDRH deficiencies:**

1. In your submission (p. 11), you have stated that the (b) (4) Please clarify the electrical component of your device.

2. In your submission (p. 13), you have stated that the device is (b) (4)

(b) (4) Please clarify the reusability of the device in order to determine if additional testing is needed.

3. In your submission (p.21), you have provided a table of planned validation testing. However, no testing has been included and the list of planned testing does not state specifically what is to be tested. Please perform the following validation testing:

a. You have mentioned conducting transit testing. However, there is no transit testing data included in the submission. Please perform shipping and transit testing mentioned in your submission (ASTM D4169). This is needed in order to ensure a viable product after shipping has consistent performance. Variability of the device after shipping and transit impacts the safety and effectiveness.

b. Actuation force testing should be conducted to demonstrate that the amount of force needed is not excessive as it could impede the ability of the user to deliver the drug formulation and lead to improper dosage which is critical for safety and effectiveness.

c. Leak testing should be performed (b) (4) .

d. Performance testing to confirm that the device does deliver (b) (4) of fluid with each actuation and that there is a low variance of volume delivered.

e. Further performance testing to demonstrate consistent performance of the device over the product lifetime. It is important that the device not suffer fatigue over the recommend use life and deteriorate in performance. The deterioration of the device may result in improper or no dosage of the drug formulation.

f. You mention conducting accelerated aging (ASTM F1980). However, there is no testing data included. Furthermore, there is no real-time aging data or real-time aging protocol as well. This is essential to demonstrate consistent performance and stability of the device over the shelf life. The testing to confirm the viability of the device should be a comparison of the previously mentioned performance tests at time point zero and compare it to the testing for devices at the end of the shelf life after undergoing real-time and accelerated aging, sterilization, and transit testing.

Additional OPQ comments:
1. Your proposed product is a drug-device combination product. For each submission for this application, indicate that the product is a combination product in field #24 of the

FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.

2. Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

3. If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

4. Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

See Section 12 Regulatory Action of this review.

## 4.3. Clinical Microbiology

Not applicable.

## 4.4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology completed a review of the original application on 8/3/2021.

No original nonclinical studies were submitted to support the safety of the combination. The nonclinical support is primarily based on published literature for each individual active component. From a nonclinical perspective, administering a lower dose (in a smaller volume) raises no new safety concerns for topical ocular phenylephrine or tropicamide compared to approved topical ocular drugs. Given the existing clinical experience with both tropicamide 1% and phenylephrine hydrochloride 2.5% used individually or in combination at the intended dosing regimen, and the use of common ocular excipients in the clinical formulation, there are no specific nonclinical concerns regarding the approval of this NDA.

## 4.5. Clinical Pharmacology

Applicant relies on the Agency's previous finding of safety for NDA 207926, NDA 022565 (phenylephrine), and NDA 012111 (tropicamide) as well as published literature (both phenylephrine and tropicamide). At the End of Phase 2 meeting held in July 2018, FDA agreed with the Applicant that the collection of PK data for this product is not needed. Therefore, there is no PK data included in this application. Accordingly, Clinical Pharmacology role for this application was focused on the proposed labeling.

## 4.6. Devices and Companion Diagnostic Issues

See CDRH subsection under Section 4.2 Product Quality of this review.

## 4.7. Consumer Study Reviews

Not applicable.

# 5. Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

Table 8: Listing of Clinical Studies

| Phase 3 Study | Design | Key Entry Criteria | Planned number of subjects | Duration |
|---|---|---|---|---|
| EYN-MYD-TP-31 (MIST-1) | DOUBLE-MASKED, ACTIVE-CONTROLLED | Male or female of any age.<br><br>No history of closed-angle glaucoma or anatomically narrow anterior chamber angles<br><br>Iris or pupil abnormality | Up to 90 volunteer participants will be enrolled and drug administration will be initiated on at least 65 subjects to complete follow-up on 54 subjects | Study drug was administered at 3 treatment visits occurring over a 5 to 15-day period. At each treatment visit, one of the study drugs was administered to both eyes. |
| EYN-MYD-TP-32 (MIST-2) | DOUBLE-MASKED, PLACEBO-CONTROLLED | Same as MIST-1 | Up to 90 volunteer participants will be enrolled and drug administration will be initiated on at least 65 subjects to complete follow-up on 54 subjects | Same as MIST-1 |

### 5.2. Review Strategy

The primary support for efficacy for the MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray product for dilation of the pupil when short-term dilation of the pupil is indicated is based on data from two double-masked, controlled [Trials EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2)] evaluating study drugs administered through Eyenovia's MicroDose Dispenser (MiDD).

The submitted clinical study reports and protocols identified were reviewed and formed the primary basis of efficacy evaluation for this application. Submitted literature was also reviewed.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. EYN-MYD-TP-31

The MIST-1 Study: A Double-Masked, Active-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

#### 6.1.1. Study Design

Overview and Objective

The objective of EYN-MYD-TP-31 was to assess the safety and efficacy of phenylephrine and tropicamide in combination administered with Eyenovia's MiDD for dilation of the pupil as compared to each of the product's individual components.

Trial Design

This was a double-masked, active-controlled, 3-period cross-over superiority study evaluating 3 study drugs administered by Eyenovia's MiDD. The drugs evaluated were:

- Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution (PH-TR)
- Phenylephrine 2.5% ophthalmic solution (PH), and
- Tropicamide 1% ophthalmic solution (TR).

Subjects meeting all inclusion/exclusion criteria were scheduled for 3 treatment visits occurring at least 2 days, but no more than 7 days apart. Subjects were equally randomized to receive all 3 study drugs according to one of the 6 possible sequences of study drug administration. At each treatment visit, pre-treatment baseline measurements were taken, then the assigned

study drug was administered in both eyes twice, approximately 5 minutes apart. Afterwards, efficacy and safety assessments were performed at specific time intervals.

This study was double-masked so that there were no differences in study drug presentation (each drug was administered as a multi-dose microdroplet spray using the Eyenovia dispenser). To maintain masking of the treatment assignments for staff administering study drug and/or performing clinical evaluations, a pharmacy associated with the study site prepared, stored and managed the study drugs. During the study, drug administration was performed by 7 different clinicians who had been trained on administration technique. Clinicians who administered study drug were not allowed to perform post-drug administration ophthalmic assessments.

Investigators

Table 9: EYN-MYD-TP-31 (The MIST-1 Study) List of Investigators, Sub-Investigators

| Site Number | Principal Investigator | Facility Address | Sub-Investigators/ Clinical Research Coordinators |
|---|---|---|---|
| 02 | D.L. Wirta, MD | WCCT Global, Inc.<br>5630 W. Cerritos Ave<br>Cypress, CA 90630<br>Phone: 714-252-0700 | David Salvay, MD<br>Ira Vidor, MD<br>David Nguyen, MD<br>Robina Smith, MD<br>Dana Yee, MD<br>Deidre Heimer, PA-C<br>Lan Quach, PA-C<br>Andy Pham, PharmD<br>Evelyn Hernandez, CRC |

Inclusion Criteria

The study population consisted of healthy volunteers of any age who met all of the following inclusion criteria:

a. Male or female of any age.
b. Female subjects had to be either pre-menarche, 1-year postmenopausal, surgically sterilized, or, if of childbearing potential, had a negative urine pregnancy test during the Screening Visit and agreed to use an acceptable form of contraception throughout the study. Acceptable methods included 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.
c. Ability to provide signed written consent prior to participation in any study-related procedures. Subjects under the age required for informed consent had to have the ability to provide additional written assent and/or parental consent, as required by the reviewing IRB.

d. Ability to return for all study treatment visits.
e. Photopic screening pupil diameter ≤ 3.5 mm in each eye.

Exclusion Criteria

Candidates were excluded if any of the following exclusion criteria were present:
a. Pregnancy or lactation.
b. Allergy to phenylephrine hydrochloride.
c. Allergy to tropicamide.
d. Allergy to benzalkonium chloride.
e. History of benign prostatic hyperplasia.
f. Use of a benzodiazepine, monoamine oxidase inhibitor, tricyclic antidepressant, anticonvulsant, or cholinergic drug at screening or anticipated during the study period.
g. 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.
h. History of closed-angle glaucoma.
i. Anatomically narrow anterior chamber ang1es (Van Herrick grade ≤ 2 in either eye).
j. Ocular surgery or laser treatment of any kind prior to the Screening Visit.
k. History of chronic or acute uveitis.
l. History of traumatic iritis or hyphema.
m. History of traumatic mydriasis or angle recession.
n. History of heterochromia.
o. Irregularly-shaped pupil secondary to ocular trauma or congenital defect.
p. History of neurogenic pupil disorder (e.g., Horner's syndrome, third cranial nerve palsy, Adie's pupil, Argyl Robertson syndrome, etc.).
q. History of anterior chamber intraocular lens (IOL) or iris-fixated IOL.
r. History of iris surgery of any kind (e.g., iridotomy, iridectomy, coreoplasty).
s. History of iris atrophy.
t. History of iris – cornea apposition/touch.
u. Unwilling or unable to discontinue use of contact lenses at treatment visits.
v. Current active eye disease for which topical or systemic ophthalmic medication was necessary, except for dry eye disease managed using artificial tears (AT). ATs had to be discontinued on the day of each treatment visit.
w. Presence of a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, precluded study treatment and/or follow-up.

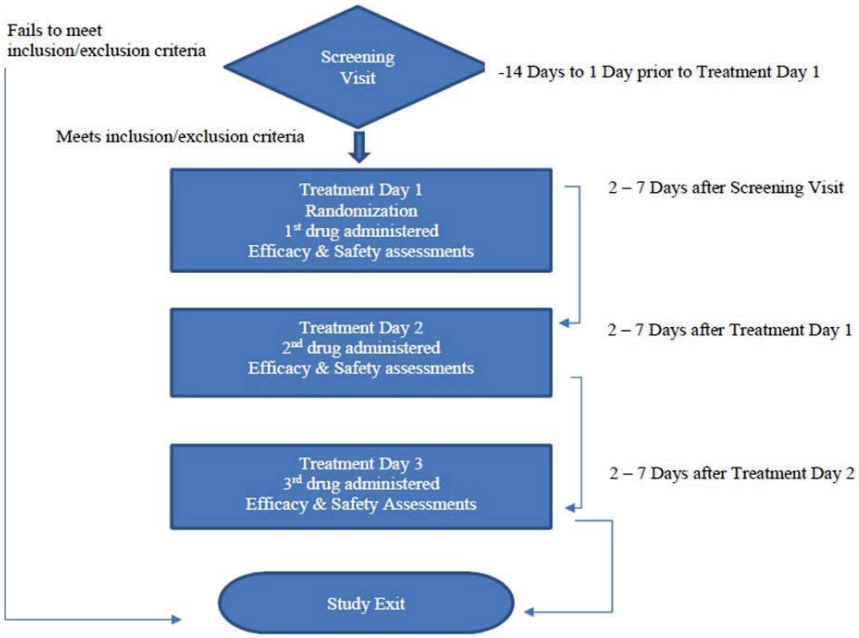
Study Endpoints

The primary performance endpoint was mean change in pupil diameter at 35 minutes from baseline in the PP population as measured by digital pupillometry in highly photopic conditions.

Statistical Analysis Plan

Baseline in the setting of the primary variable refers to the period-specific baseline on the applicable day of treatment. The primary analysis was to be conducted on the Per Protocol (PP) population. The PP population consisted of all Intent-to-Treat (ITT) subjects who completed all planned assessments without a major protocol deviation. Subjects who did not receive each study drug were excluded from the PP population. Subjects in the PP population were analyzed according to the sequence of treatments received. The ITT population consisted of all randomized subjects who received a dose of study drug.

Figure 3: EYN-MYD-TP-31 Study Visit Flow Chart




Source: Module 5.3.5.1 CSR EYN-MYD-TP-31

Study Schedule

Table 10: EYN-MYD-TP-31 Study Schedule

| Assessment/Procedure | Screening Visit (Day -14 to Day -1) | Treatment Visit 1 (Day 1)[1], Visit 2[1] and Visit 3[1] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline[0] | Time 0[2] | 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[3] | X | | | | | X[3] | | | | |
| Manifest refraction (OU) | X | | | | | | | | | |
| BCDVA (OU)[4] | X | X | | | | | | | | X |
| Study drug administration sequence determination (OU) | | X | | | | | | | | |
| Study drug administration (OU) | | | X | | | | | | | |
| Slit lamp biomicroscopy (OU)[5] | X | X | | | | | | | | X |
| Van Herrick Angle Assessment (OU)[6] | X | | | | | | | | | |
| IOP (OU)[7] | X | X | | | | | X | | | |
| Pupil diameter assessment (OU)[8] | 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 |

[0] Baseline referred to evaluations made at each Treatment Day prior to study medication administration.
[1] Treatment Visit 1, 2 and 3 had to be separated by at least 2 days; but could be up to 7 days apart to allow for scheduling flexibility.
[2] Time 0 started at the point the first of two study medication doses was administered in second eye of the study subject.
[3] A urine pregnancy test was conducted in females of childbearing potential at the Screening Visit and at the last visit (Treatment Visit 3). If the subject terminated study participation prior to Treatment Visit 3, this test had to be administered at the time of study termination.
[4] BCDVA was measured using ETDRS methods. For younger pediatric subjects, UCDVA could be measured using age-appropriate methods per investigator's usual practice.
[5] For younger pediatric subjects who could not cooperate with a traditional slit lamp biomicroscopy, a portable slit lamp model could be used, if necessary.
[6] Performed as part of slit lamp examination.
[7] IOP was measured using Goldmann Applanation tonometry. For younger pediatric subjects, IOP could be measured using age-appropriate methods per investigator's usual practice.
[8] Performed using Neuroptics pupillometer – VIP 300. For younger pediatric subjects for whom the pupillometer could not be successfully used, a ruler or pupil gauge was used.

Source: Module 5.3.5.1 CSR EYN-MYD-TP-31

### 6.1.2. Study Results

Compliance with Good Clinical Practices
This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Financial Disclosure
See Section 13.1 of this review.

Patient Disposition
A total of 70 subjects were enrolled in this study and 64 of these subjects were randomized to treatment. Two subjects withdrew consent and terminated the study after their first treatment visit and the remaining 62 subjects completed all study visits; therefore, the PP population consists of 62 subjects. No subjects were lost to follow-up, and no subjects were terminated from the study. Of the 6 subjects not randomized, 4 failed to meet all study eligibility criteria (inability to return for all study treatment visits [n=2] and prior ocular surgery or laser treatment [n=2]). One subject was exited after screening because the investigator believed a sufficient number of subjects had been randomized, and one subject displayed combative/poor behavior resulting in the investigator's decision to exit the subject during the Screening Visit.

Table 11: EYN-MYD-TP-31 Subject Disposition (Enrolled Subjects)

| | All Subjects |
|---|---|
| All Enrolled Subjects | 70 |
| Number of Not Randomized Subjects | 6 |
| Number of Randomized Subjects | 64 |
| Analysis Populations | |
| Intent-to-Treat (ITT) | 64 (100.0%) |
| Per Protocol (PP) | 62 ( 96.9%) |
| Modified Per Protocol (mPP) | |
| Phenylephrine 2.5%-tropicamide 1% | 62 ( 96.9%) |
| Tropicamide 1% | 64 (100.0%) |
| Phenylephrine 2.5% | 62 ( 96.9%) |
| Safety | |
| Phenylephrine 2.5%-tropicamide 1% | 62 ( 96.9%) |
| Tropicamide 1% | 64 (100.0%) |
| Phenylephrine 2.5% | 62 ( 96.9%) |

Source: Table 14.1.1.1
Enrolled subjects included all subjects who signed the informed consent form, not randomized included all screen failures as well as subjects that were not randomized for other administrative reasons.
The ITT population consisted of all randomized subjects who received a dose of study medication.
The PP population consisted of all ITT subjects who completed all planned assessments without major protocol violations. Subjects who did not receive all 3 treatments were excluded from the PP population.
The modified per protocol (mPP) population was defined similarly to the PP population, except that classification was made for each subject at the individual treatment level, rather than at the subject level. Unlike the PP population, subjects who only completed 1 or 2 of the 3 treatment visits were included.
For treatment assignment, the ITT, PP and mPP populations used the treatment to which a subject was randomized, and the Safety Population used the actual treatment received.

Source: Module 5.3.5.1 CSR EYN-MYD-TP-31

Protocol Violations/Deviations

Deviations to the protocol were reported for 30 subjects; however, none of the deviations were categorized as major in that they did not significantly affect the completeness, accuracy, and/or reliability of study data or significantly affect any subject's rights, safety, or well-being.
All protocol deviations involved performance of 1 or more study assessments outside the protocol specified time window, with more than half being the assessment of pupil diameter from 1 to 6 minutes earlier than the time window specified in the study protocol, thus potentially underreporting the magnitude of pupil dilation at these intervals. The majority of the pupil diameter measurement deviations occurred during a single afternoon when a slight adjustment in the study drug administration schedule was not communicated to personnel performing post-drug administration assessments.

Table 12: EYN-MYD-TP-31 Protocol Deviations (Enrolled Subjects)

| | Number of Subjects with Any Deviation |
|---|---|
| Major Deviations | 0 |
| Minor Deviations | 30 (46.9%) |

Source: Table 14.1.1.1

Source: Module 5.3.5.1 CSR EYN-MYD-TP-31

Table of Demographic Characteristics

Table 13: EYN-MYD-TP-31 Demographics ITT Population

| | All Subjects (n=64) |
|---|---|
| Age (Years) | |
| Mean (SD) | 39.4 (12.00) |
| Median | 36.5 |
| Min-Max | 12, 64 |
| Age Categories (Years) | |
| < 17 years | 1 ( 1.6%) |
| ≥ 17 years | 63 ( 98.4%) |
| Age Quartiles (Years) | |
| < 31.0 | 16 (25.0%) |
| ≤ 31.0 < 36.5 | 16 (25.0%) |
| ≤36.5 < 49.0 | 16 (25.0%) |
| ≥ 49.0 | 16 (25.0%) |
| Sex: n (%) | |
| Male | 37 (57.8%) |
| Race: n (%) | |
| Asian | 8 (12.5%) |
| Black or African American | 19 (29.7%) |
| White | 35 (54.7%) |
| Multi-Race | 2 ( 3.1%) |
| Ethnicity: n (%) | |
| Hispanic or Latino | 22 (34.4%) |
| Not Hispanic or Latino | 42 (65.6%) |
| Iris Color: n (%) | |
| Brown | 54 (84.4%) |
| Hazel | 5 ( 7.8%) |
| Blue | 4 ( 6.3%) |
| Green | 1 ( 1.6%) |
| Black | 0 ( 0.0%) |
| Gray | 0 ( 0.0%) |
| Iris Color Strata: n (%) | |
| Light | 10 (15.6%) |
| Dark | 54 (84.4%) |

Source: Table 14.1.3.1
Multi-Race was marked if subjects had 2 or more races selected on eCRFs.
Age was calculated as: (informed consent date – date of birth) / 365.25 truncated as an integer.
Iris color 'Dark' includes brown and black, 'Light' includes blue, gray, green, and hazel.

Source: Module 5.3.5.1 CSR EYN-MYD-TP-31

One enrolled subject (b) (6)) was less than 18 years of age. Slightly more subjects were male (57.8%), and the iris color category was predominantly dark (84.4%).

Efficacy Results – Primary Endpoint

Table 14: EYN-MYD-TP-31 Change in Pupil Diameter from Period-Dependent Baseline at 35 Minutes Fixed Effects ANOVA (PP Population)

| Combined Visits (1, 2, 3) | Phenylephrine 2.5%-tropicamide 1% | | Tropicamide 1% | | Phenylephrine 2.5% | |
|---|---|---|---|---|---|---|
| **Pupil Diameter (mm)** | **OD (N=62)** | **OS N=62)** | **OD (N=62)** | **OS N=62)** | **OD (N=62)** | **OS N=62)** |
| **Baseline** | | | | | | |
| Mean (SD) | 2.672 (0.5683) | 2.583 (0.4674) | 2.657 (0.6016) | 2.569 (0.5211) | 2.651 (0.5749) | 2.584 (0.5344) |
| Median | 2.690 | 2.560 | 2.580 | 2.565 | 2.570 | 2.570 |
| Min, Max | 1.46, 4.70 | 1.61, 3.55 | 1.45, 4.60 | 1.44, 3.80 | 1.40, 4.28 | 1.59, 3.84 |
| **35 Min Post Dose** | | | | | | |
| Mean (SD) | 7.301 (0.8943) | 7.329 (0.9771) | 6.762 (0.8619) | 6.690 (0.8682) | 3.388 (0.8950) | 3.552 (0.9340) |
| Median | 7.410 | 7.490 | 6.795 | 6.850 | 3.225 | 3.270 |
| Min, Max | 3.29, 8.97 | 3.66, 9.04 | 5.03, 8.76 | 4.44, 8.62 | 1.72, 6.16 | 2.00, 6.06 |
| **Change from Baseline** | | | | | | |
| Mean (SD) | 4.629 (0.8343) | 4.746 (0.8173) | 4.105 (0.7207) | 4.121 (0.6839) | 0.737 (0.7939) | 0.969 (0.8943) |
| Median | 4.660 | 4.860 | 4.230 | 4.225 | 0.585 | 0.685 |
| Min, Max | 0.84, 6.20 | 1.31, 6.25 | 2.39, 5.38 | 2.23, 5.92 | -0.45, 3.75 | -0.14, 3.49 |
| Two-Sided 95% CI | (4.417, 4.841) | (4.539, 4.954) | (3.921, 4.288) | (3.947, 4.294) | (0.535, 0.939) | (0.741, 1.196) |
| LS Means Treatment Group Difference (SE) PH-TR – TR | | | | 0.440 (0.1839) | | |
| Two-Sided 95% CI | | | | (0.076, 0.804) | | |
| p-value | | | | 0.0183 | | |
| LS Means Treatment Group Difference (SE) PH-TR – PH | | | | 3.638 (0.1817) | | |
| Two-Sided 95% CI | | | | (3.279, 3.998) | | |
| p-value | | | | <0.0001 | | |

Source: Table 14.2.1.1
ANOVA=analysis of variance; CI=confidence interval; LS = least squares; NE = Not Estimable; SE=standard error.
Fixed-effects analysis of variance model contained effects due for subject, eye, period (1, 2, or 3), direct effect of treatment, cross-treatment carryover effect (AB, AC, BA, BC, CA, CB, null), period-dependent baseline pupil diameter, and iris color (dark vs light)

Source: Module 5.3.5.1 CSR EYN-MYD-TP-31

Reviewer Comments: *The mean change in post-dose pupil diameter at 35 minutes with PH-TR was 4.6 mm (OD) and 4.7 mm (OS), which was clinically significant. The treatment group difference between PH-TR and TR was 0.440 mm (SE 0.1839, 95% CI [0.08, 0.80]), which was statistically significant (p = 0.0183). The treatment group difference between PH-TR and PH was 3.638 mm (SE 0.1817, 95% CI [3.28, 4.00]), which was also statistically significant (p < 0.01).*

Subgroup Analyses

Analyses were performed to determine whether demographic parameters were significant predictors of change from baseline in pupil diameter at 35 minutes post-dose. Neither age, sex, nor race were clinically significant predictors of outcome.

Data Quality and Integrity

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Durability of Response and Persistence of Effect

Table 15: EYN-MYD-TP-31 Change in Pupil Diameter from Baseline by Timepoint and Treatment (PP Population)

| Combined Visits (1, 2, 3) | | Phenylephrine 2.5%-tropicamide 1% | | Tropicamide 1% | | Phenylephrine 2.5% | |
|---|---|---|---|---|---|---|---|
| Change in Pupil Diameter (mm) | | OD (N=62) | OS N=62) | OD (N=62) | OS N=62) | OD (N=62) | OS N=62) |
| 20 Min | Mean (SD) | 3.418 (1.2263) | 3.524 (1.0680) | 2.961 (0.9384) | 2.953 (1.0094) | 0.199 (0.3705) | 0.257 (0.4003) |
| | Median | 3.760 | 3.705 | 3.010 | 3.070 | 0.115 | 0.160 |
| | Min, Max | 0.10, 5.24 | 0.35, 5.65 | 0.56, 4.66 | 0.57, 5.02 | -0.48, 1.76 | -0.32, 1.81 |
| 35 Min | Mean (SD) | 4.629 (0.8343) | 4.746 (0.8173) | 4.105 (0.7207) | 4.121 (0.6839) | 0.737 (0.7939) | 0.969 (0.8943) |
| | Median | 4.660 | 4.860 | 4.230 | 4.225 | 0.585 | 0.685 |
| | Min, Max | 0.84, 6.20 | 1.31, 6.25 | 2.39, 5.38 | 2.23, 5.92 | -0.45, 3.75 | -0.14, 3.49 |
| 50 Min | Mean (SD) | 5.059 (0.8191) | 5.133 (0.7536) | 4.279 (0.7561) | 4.380 (0.6617) | 1.358 (1.0603) | 1.719 (1.1673) |
| | Median | 5.170 | 5.195 | 4.295 | 4.450 | 1.215 | 1.435 |
| | Min, Max | 1.53, 6.99 | 2.44, 6.46 | 1.97, 5.47 | 2.39, 6.28 | -0.44, 5.04 | 0.10, 5.33 |
| 65 Min | Mean (SD) | 5.118 (0.7717) | 5.258 (0.7813) | 4.338 (0.6766) | 4.352 (0.7089) | 1.727 (1.2141) | 2.146 (1.2501) |
| | Median | 5.230 | 5.350 | 4.410 | 4.425 | 1.585 | 1.935 |
| | Min, Max | 2.43, 6.40 | 2.94, 7.63 | 2.44, 5.50 | 2.35, 5.99 | -0.44, 5.22 | 0.31, 5.12 |
| 80 Min | Mean (SD) | 5.191 (0.7748) | 5.273 (0.7881) | 4.344 (0.6764) | 4.371 (0.6889) | 1.766 (1.2123) | 2.263 (1.2314) |
| | Median | 5.290 | 5.345 | 4.370 | 4.450 | 1.745 | 2.100 |
| | Min, Max | 2.47, 6.57 | 2.84, 6.91 | 2.55, 5.69 | 2.40, 6.94 | -0.35, 5.47 | 0.12, 5.23 |
| 120 Min | Mean (SD) | 5.115 (0.8926) | 5.167 (0.7568) | 4.152 (0.6927) | 4.167 (0.6542) | 1.620 (1.1298) | 1.991 (1.2274) |
| | Median | 5.270 | 5.295 | 4.170 | 4.245 | 1.445 | 1.830 |
| | Min, Max | 1.93, 6.71 | 2.95, 6.62 | 2.52, 5.60 | 2.32, 5.38 | -0.28, 5.12 | 0.07, 5.08 |
| 180 Min | Mean (SD) | 4.717 (0.9496) | 4.789 (0.8926) | 3.631 (0.7885) | 3.644 (0.7067) | 1.014 (0.9563) | 1.378 (1.1003) |
| | Median | 4.920 | 4.780 | 3.770 | 3.755 | 0.805 | 1.260 |
| | Min, Max | 0.90, 6.59 | 1.57, 7.20 | 1.55, 4.96 | 1.28, 4.91 | -0.42, 4.50 | -0.34, 4.51 |

Source: Table 14.2.2.1 and Table 14.2.3

Source: Module 5.3.5.1 CSR EYN-MYD-TP-31

Reviewer Comments: *Differences in mean pupil diameter among the treatments were observed as early as 20 minutes and were still present at 180 minutes post-dose, the end of the protocol-specified observation period. A maximum mean change was measured at 80 minutes post-dose.*

## 6.2. EYN-MYD-TP-32

The MIST-2 Study: 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

### 6.2.1. Study Design

Overview and Objective

Same as EYN-MYD-TP-31

Trial Design

This was a prospective, multicenter, double-masked, placebo-controlled, 3-period crossover superiority study evaluating 2 study drugs administered by Eyenovia's MiDD. The drugs evaluated were Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution (PH-TR) and placebo.

Subjects meeting all inclusion/exclusion criteria were scheduled for 3 treatment visits occurring at least 2 days, but no more than 7 days apart. A 2 sequence, 3 period crossover design was used. At each treatment visit, pre-treatment baseline measurements were taken, then the assigned study drug was administered in both eyes (OU) twice, approximately 5 minutes apart. Only 1 drug was administered per treatment visit, and subjects were equally randomized based on iris color category (dark irides were either black or brown in color, while light irides were all other colors) to one of two sequences - ABB and BAA, where A was PH-TR and B was the placebo. Afterwards, efficacy and safety assessments were performed at specific time intervals.

This study was double-masked so that there were no differences in presentation (PH-TR and placebo were administered as a multi-dose microdroplet spray using the Eyenovia MiDD). To maintain masking of the treatment assignments for staff administering investigational product and/or performing clinical evaluations, a pharmacy associated with the study site prepared, stored and managed the study drugs. During the study, drug administration was performed by 2 different clinicians at each site who had been trained on administration technique. Clinicians who administered study drug were not allowed to perform post-drug administration ophthalmic assessments.

Investigators

Table 16: EYN-MYD-TP-32 (The MIST-2 Study) List of Investigators, Sub-Investigators

| Site Number | Principal Investigator | Site and Facility Address(es) | Sub-Investigators/ Clinical Research Coordinators | Subjects Randomized |
|---|---|---|---|---|
| 03 | William J. Flynn, MD | R and R Eye Research, LLC<br>5430 Fredericksburg Rd. Suite 100<br>San Antonio, TX 78229 | Edward R. Rashid, MD<br>Charles D. Reilly, MD<br>Gregory Brunin, MD<br>Catherin Hazen<br>Michelle Jackson<br>Griselda Rodriquez<br>Frederick Prasse | 34 |
| 04 | Thomas R. Walters, MD | Keystone Research, Ltd<br>Texan Eye, PA<br>5717 Balcones Drive<br>Austin, TX 78731 | Robert E. Marquis, MD<br>Yen D. Nieman, MD<br>Blythe E. Monheit, MD | 36 |

Inclusion and Exclusion Criteria

Identical to EYN-MYD-TP-31.

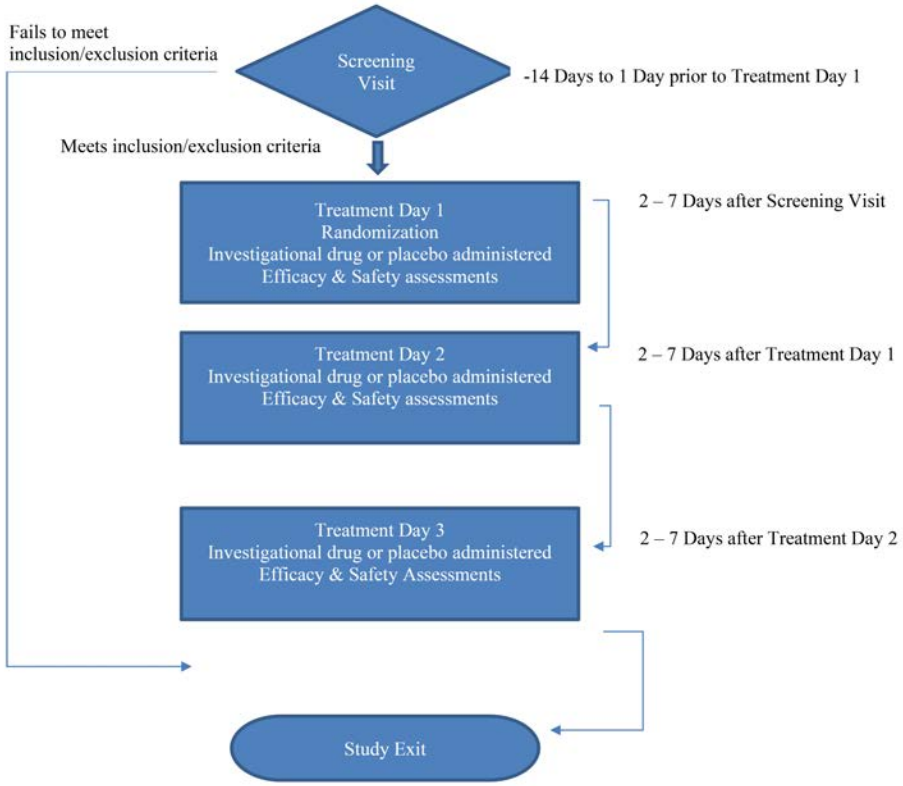
Study Endpoints

The primary performance endpoint was mean change in pupil diameter at 35 minutes from baseline in the PP population.

Statistical Analysis Plan

The primary performance endpoint was mean change in pupil diameter at 35 minutes from baseline as measured by digital pupillometry in highly photopic conditions. Baseline in the setting of the primary variable refers to the period-specific baseline on the applicable day of treatment. The primary analysis was to be conducted on the Per Protocol (PP) population. The PP population consisted of all Intent-to-Treat (ITT) subjects who completed all planned assessments without a major protocol deviation. Subjects who did not receive each study drug were excluded from the PP population. Subjects in the PP population were analyzed according to the sequence of treatments received. The ITT population consisted of all randomized subjects who received a dose of study drug.

Figure 4: EYN-MYD-TP-32 Study Visit Flow Chart




Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

Study Schedule

Table 17: EYN-MYD-TP-32 Study Schedule

| Assessment/Procedure | Screening Visit (Day -14 to Day -1) | Treatment Visit 1 (Day 1)[1], Visit 2[1] and Visit 3[1] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline[0] | Time 0[2] | 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)[9] |
| Informed consent | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Ocular history | X | | | | | | | | | |
| Prior/concomitant medication use | X | | | | | | | | | |
| Urine pregnancy test[3] | X | | | | | X[3] | | | | |
| Manifest refraction (OU) | X | | | | | | | | | |
| BCDVA (OU)[4] | X | X | | | | | | | | X |
| Study drug administration sequence determination (OU) | | X | | | | | | | | |
| Study drug administration (OU) | | | X | | | | | | | |
| Slit lamp biomicroscopy (OU)[5] | X | X | | | | | | | | X |
| Van Herrick Angle Assessment (OU)[6] | X | | | | | | | | | |
| IOP (OU)[7] | X | X | | | | | X | | | |
| Pupil diameter assessment (OU)[8] | 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 |

[0] Baseline referred to evaluations made at each Treatment Day prior to study medication administration.

[1] Treatment Visit 1, 2 and 3 had to be separated by at least 2 days; but could be up to 7 days apart to allow for scheduling flexibility.

[2] Time 0 started at the point the first of two study medication doses was administered in second eye of the study subject

[3] A urine pregnancy test was conducted in females of childbearing potential at the Screening Visit and at the last visit (Treatment Visit 3). The test was administered at any time during the Screening and Treatment Day 3 Visits. If the subject terminated study participation prior to Treatment Visit 3, this test had to be administered promptly at the time of termination.

[4] BCDVA was measured using ETDRS methods. For younger pediatric subjects, UCDVA could be measured using age-appropriate methods per investigator's usual practice.

[5] For younger pediatric subjects who could not cooperate with a traditional SLE, a portable slit lamp model could be used, if necessary.

[6] Performed as part of slit lamp examination.

[7] IOP was measured using Goldmann Applanation tonometry. For younger pediatric subjects, IOP could be measured using age-appropriate methods per investigator's usual practice.

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

Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

### 6.2.2. Study Results

Compliance with Good Clinical Practices

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Financial Disclosure

See Section 13.1 of this review.

Patient Disposition

A total of 76 subjects were enrolled at two study sites, and 70 of these subjects were randomized to treatment. One subject withdrew consent and terminated the study after the first treatment visit and the remaining 69 subjects completed all study visits; therefore, the PP population consists of 69 subjects. No subjects were lost to follow-up or were terminated from the study.

Of the 6 subjects not randomized, 4 failed to meet all study eligibility criteria (anatomically narrow anterior chamber angles [n=2] and prior ocular surgery or laser treatment [n=2]) and 2 subjects screened were exited because a sufficient number of subjects had been randomized.

Table 18: EYN-MYD-TP-32 Subject Disposition (Enrolled Subjects)

| | All Subjects |
|---|---|
| All Enrolled Subjects | 76 |
| Number of Screen Failures | 6 |
| Number of Randomized Subjects | 70 |
| Analysis Populations | |
| Intent-to-Treat (ITT) | 70 (100.0%) |
| Per Protocol (PP) | 69 ( 98.6%) |
| Modified Per Protocol (mPP) | |
| Phenylephrine 2.5%-tropicamide 1% | 69 ( 98.6%) |
| Placebo | 70 (100.0%) |
| Safety | |
| Phenylephrine 2.5%-tropicamide 1% | 69 ( 98.6%) |
| Placebo | 70 (100.0%) |

Source: Table 14.1.1.1
Enrolled subjects included all subjects who signed the informed consent form, not randomized included all screen failures as well as subjects that were not randomized for other administrative reasons.
The ITT population consisted of all randomized subjects who received a dose of study medication.
The PP population consisted of all ITT subjects who completed all planned assessments without major protocol violations. Subjects who did not receive all 3 treatments were excluded from the PP population.
The modified per protocol (mPP) population was defined similarly to the PP population, except that classification was made for each subject at the individual treatment level, rather than at the subject level. Unlike the PP population, subjects who only completed 1 or 2 of the 3 treatment visits were included.
For treatment assignment, the ITT, PP and mPP populations used the treatment to which a subject was randomized, and the Safety Population used the actual treatment received.

Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

## Protocol Violations/Deviations

Deviations to the protocol were reported for 24 subjects; however, none of the deviations were categorized as major in that they did not significantly affect the completeness, accuracy, and/or reliability of study data or significantly affect any subject's rights, safety, or well-being. The most frequently occurring minor deviation involved assessment of IOP out of the specified 65 ± 10-minute window post-dosing (23 subjects). Pupillary diameter assessment was performed outside of the specified window for 7 subjects; however, for all but a single subject, measurement was earlier than specified in the study protocol, thus potentially underreporting the magnitude of pupil dilation at the designated interval. Pupillary diameter assessment in the 7th subject was performed 2 minutes later than the 20 ± 2-minute assessment window.

Table 19: EYN-MYD-TP-32 Protocol Deviations (Enrolled Subjects)

| | Number of Subjects with Any deviation |
|---|---|
| Major Deviations | 0 |
| Minor Deviations | 24 (34.3%) |

Source: Table 14.1.1.1

Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

Table of Demographic Characteristics

Table 20: EYN-MYD-TP-32 Demographics ITT Population

| | All Subjects (n=70) |
|---|---|
| Age (Years) | |
| Mean (SD) | 35.4 (14.55) |
| Median | 33.5 |
| Min-Max | 13, 66 |
| Age Categories (Years) | |
| < 17 years | 5 ( 7.1%) |
| ≥ 17 years | 65 (92.9%) |
| Age Quartiles (Years) | |
| ≤ 23.0 | 19 (27.1%) |
| > 23.0 ≤ 33.5 | 16 (22.9%) |
| > 33.5 ≤ 47.0 | 18 (25.7%) |
| > 47.0 | 17 (24.3%) |
| Sex: n (%) | |
| Male | 37 (52.9%) |
| Race: n (%) | |
| Asian | 1 ( 1.4%) |
| Black or African American | 7 (10.0%) |
| White | 62 (88.6%) |
| Ethnicity: n (%) | |
| Hispanic or Latino | 35 (50.0%) |
| Not Hispanic or Latino | 35 (50.0%) |
| Iris Color: n (%) | |
| Blue | 1 ( 1.4%) |
| Brown | 50 (71.4%) |
| Black | 0 ( 0.0%) |
| Green | 3 ( 4.3%) |
| Hazel | 16 (22.9%) |
| Iris Color Strata: n (%) | |
| Light | 20 (28.6%) |
| Dark | 50 (71.4%) |

Source: Table 14.1.3.1
Age was calculated as: (informed consent date – date of birth) / 365.25 truncated as an integer.
Iris color 'Dark' included brown and black, 'Light' included blue, gray, green, and hazel.

Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

Five subjects were 17 years of age or younger. Slightly more subjects were male (52.9%), and the iris color category was predominantly dark (71.4%).

Efficacy Results – Primary Endpoint

Table 21: EYN-MYD-TP-32 Change in Pupil Diameter from Period-Dependent Baseline at 35 Minutes Fixed Effects ANOVA (PP Population)

| Combined Visits (1, 2, 3) | Phenylephrine 2.5%-tropicamide 1% | | Placebo | |
|---|---|---|---|---|
| **Pupil Diameter (mm)** | **OD (N=69)** | **OS (N=69)** | **OD (N=69)** | **OS (N=69)** |
| **Baseline** | | | | |
| Mean (SD) | 2.597 (0.4784) | 2.524 (0.4802) | 2.632 (0.5202) | 2.559 (0.4666) |
| Median | 2.565 | 2.490 | 2.530 | 2.500 |
| Min, Max | 1.62, 3.51 | 1.54, 3.89 | 1.53, 4.20 | 1.53, 4.01 |
| **35 Min Post Dose** | | | | |
| Mean (SD) | 7.344 (0.7981) | 7.304 (0.8264) | 2.766 (0.6598) | 2.590 (0.5892) |
| Median | 7.290 | 7.380 | 2.645 | 2.485 |
| Min, Max | 5.15, 8.98 | 4.90, 8.93 | 1.68, 5.31 | 1.70, 5.46 |
| **Change from Baseline** | | | | |
| Mean (SD) | 4.747 (0.7301) | 4.779 (0.8032) | 0.134 (0.4972) | 0.032 (0.4983) |
| Median | 4.695 | 4.810 | 0.115 | -0.020 |
| Min, Max | 3.06, 6.12 | 2.51, 6.52 | -0.53, 3.09 | -0.98, 3.22 |
| Two-Sided 95% CI | (4.572, 4.923) | (4.586, 4.972) | (0.015, 0.254) | (-0.088, 0.152) |
| LS Means Treatment Group Difference (SE) PH-TR - placebo | | | 4.631 (0.0544) | |
| Two-Sided 95% CI | | | (4.523, 4.740) | |
| p-value | | | <0.0001 | |

Source: Table 14.2.1.1
ANOVA = Analysis of Variance; CI = Confidence interval; LS = Least Squares; SE = Standard Error.
Fixed-effects analysis of variance model contained effects due for subject, eye, period (1, 2, or 3), direct effect of treatment, first order carryover, period-dependent baseline pupil diameter, and iris color (dark vs light).

Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

Reviewer Comments: *The mean change in post-dose pupil diameter at 35 minutes with PH-TR was 4.7 mm (OD) and 4.8 mm (OS), which was clinically significant. The treatment group difference between PH-TR and placebo was 4.631 mm (SE 0.0544, 95% CI [4.52, 4.74]), which was statistically significant (p<0.01). As expected, no meaningful mydriatic effect was observed in the placebo group.*

Subgroup Analyses
Analyses were performed to determine whether demographic parameters were significant predictors of change from baseline in pupil diameter at 35 minutes post-dose. Neither age, nor sex were clinically significant predictors of outcome.

Table 22: EYN-MYD-TP-32 Change from Baseline in Pupil Diameter at 35 Minutes Post-Dose by Iris Color Category (PP Population)

| Combined Visits (1, 2, 3) | Phenylephrine 2.5%-tropicamide 1% | | Placebo | |
|---|---|---|---|---|
| **Pupil Diameter (mm)** | **Dark Iris Color (N=49)** | **Light Iris Color (N=20)** | **Dark Iris Color (N=49)** | **Light Iris Color (N=20)** |
| **Baseline** | | | | |
| n | 98 | 40 | 98 | 40 |
| Mean (SD) | 2.543 (0.5055) | 2.604 (0.4092) | 2.618 (0.5248) | 2.540 (0.4085) |
| Median | 2.510 | 2.603 | 2.513 | 2.540 |
| Min, Max | 1.54, 3.89 | 1.95, 3.54 | 1.53, 4.20 | 1.84, 3.52 |
| **35 Min Post Dose** | | | | |
| n | 98 | 40 | 98 | 40 |
| Mean (SD) | 7.334 (0.8245) | 7.300 (0.7818) | 2.708 (0.6854) | 2.606 (0.4644) |
| Median | 7.370 | 7.285 | 2.535 | 2.510 |
| Min, Max | 4.95, 8.98 | 4.90, 8.76 | 1.68, 5.46 | 1.75, 3.78 |
| **Change from Baseline** | | | | |
| .n | 98 | 40 | 98 | 40 |
| Mean (SD) | 4.791 (0.7591) | 4.697 (0.7846) | 0.090 (0.5661) | 0.066 (0.2750) |
| Median | 4.795 | 4.590 | 0.030 | 0.110 |
| Min, Max | 2.51, 6.39 | 2.94, 6.52 | -0.98, 3.22 | -0.53, 0.76 |
| Two-Sided 95% CI | (4.638, 4.943) | (4.446, 4.948) | (-0.024, 0.204) | (-0.022, 0.154) |

Source: Table 14.2.7.2

Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

Reviewer Comments: *The effect of iris color category was negligible in each treatment group. The effect of iris color and race in the development of mydriasis, while measurable, is clinically insignificant at 35 minutes post drop installation, i.e., the primary study endpoint.*

Data Quality and Integrity

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Durability of Response and Persistence of Effect

Table 23: EYN-MYD-TP-32 Change in Pupil Diameter from Baseline by Timepoint and Treatment (PP Population)

| Combined Visits (1, 2, 3) | Phenylephrine 2.5%-tropicamide 1% | | Placebo | |
|---|---|---|---|---|
| Change in Pupil Diameter (mm) | OD (N=69) | OS (N=69) | OD (N=69) | OS N=69) |
| 20 Min Mean (SD) | 3.822 (0.9387) | 3.679 (1.0109) | 0.117 (0.4007) | -0.021 (0.3086) |
| Median | 3.795 | 3.635 | 0.030 | -0.035 |
| Min, Max | 1.23, 5.41 | 0.71, 5.96 | -0.61, 1.07 | -0.76, 0.77 |
| 35 Min Mean (SD) | 4.747 (0.7301) | 4.779 (0.8032) | 0.134 (0.4972) | 0.032 (0.4983) |
| Median | 4.695 | 4.810 | 0.115 | -0.020 |
| Min, Max | 3.06, 6.12 | 2.51, 6.52 | -0.53, 3.09 | -0.98, 3.22 |
| 50 Min Mean (SD) | 5.030 (0.7267) | 5.138 (0.7770) | 0.134 (0.5211) | 0.131 (0.5644) |
| Median | 4.975 | 5.130 | 0.045 | 0.010 |
| Min, Max | 3.41, 6.44 | 2.87, 6.85 | -0.68, 3.37 | -0.66, 3.64 |
| 65 Min Mean (SD) | 5.110 (0.7737) | 5.220 (0.7679) | 0.132 (0.5225) | 0.080 (0.5556) |
| Median | 5.080 | 5.255 | 0.125 | 0.020 |
| Min, Max | 2.92, 6.45 | 3.00, 6.78 | -0.65, 3.41 | -0.56, 3.98 |
| 80 Min Mean (SD) | 5.160 (0.7761) | 5.263 (0.7416) | 0.122 (0.5262) | 0.078 (0.5668) |
| Median | 5.200 | 5.270 | 0.070 | 0.030 |
| Min, Max | 3.35, 6.89 | 3.81, 7.02 | -0.89, 3.46 | -0.83, 3.84 |
| 120 Min Mean (SD) | 4.833 (0.8279) | 5.095 (0.8773) | 0.163 (0.5152) | 0.071 (0.4988) |
| Median | 4.850 | 5.100 | 0.125 | 0.010 |
| Min, Max | 2.51, 6.41 | 2.73, 7.29 | -0.86, 3.12 | -0.89, 3.06 |
| 180 Min Mean (SD) | 4.117 (1.0255) | 4.291 (0.9813) | 0.097 (0.4390) | -0.038 (0.3834) |
| Median | 4.180 | 4.340 | 0.075 | -0.050 |
| Min, Max | 1.41, 6.16 | 1.63, 6.00 | -1.02, 2.12 | -1.20, 1.84 |

Source: Module 5.3.5.1 CSR EYN-MYD-TP-32

Peak effect was measured at the 80-minute evaluation. .

# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

The data from two clinical studies, EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2), contained in this submission establishes the efficacy of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray to induce mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired.

# 8. Review of Safety

## 8.1. Safety Review Approach

The primary support for safety for the MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray product for dilation of the pupil when short-term dilation of the pupil is indicated is based on data from two double-masked, controlled [Trials EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2)] evaluating study drugs administered through Eyenovia's MicroDose Dispenser (MiDD) and publications documenting over 50 years of higher amounts of these two drugs.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

Table 24: Pooled Treatment Exposure (Safety Population)

| | TR-PH (N=131 subjects) | TR (N=64 subjects) | PH (N=62 subjects) | Placebo (N=70 subjects) |
|---|---|---|---|---|
| **Number of Treatment Attempts/Eye** | 163 | 64 | 62 | 107 |
| **Received at Least One Successful Spray: n (%)** | | | | |
| OD | 163 (100.0%) | 64 (100.0%) | 62 (100.0%) | 107 (100.0%) |
| OS | 163 (100.0%) | 64 (100.0%) | 62 (100.0%) | 107 (100.0%) |
| **Received Two Successful Sprays: n (%)** | | | | |
| OD | 162 (99.4%) | 64 (100.0%) | 62 (100.0%) | 107 (100.0%) |
| OS | 163 (100.0%) | 64 (100.0%) | 62 (100.0%) | 107 (100.0%) |

% = n/(number of treatment attempts)
The protocol required 2 sprays topically administered within a 5-minute period to both eyes. If spray administration was unsuccessful, another was given. In MIST-2 eyes were randomized to treatment sequences ABB or BAA; thus, each eye had 2 attempted treatments with either Placebo or TR-PH. The total number of treatment attempts includes these repeated treatments.
Source: Module 5.3.5.3 ISS

A total of 131 subjects have been exposed to TR-PH across these 2 studies.

### 8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat.

The demographic and baseline characteristics of the ITT population were similar across the 2 studies. Demographics for the ITT population are provided in the following table.

Table 25: Pooled Demographics ITT Population

| | MIST-1 | MIST-2 | POOLED |
|---|---|---|---|
| **N (subjects)** | 64 | 70 | 134 |
| **Age (years)** | | | |
| Mean (SD) | 39.4 (12.0) | 35.4 (14.5) | 37.3 (13.5) |
| Median | 36.5 | 33.5 | 36.0 |
| Min, Max | [12.0, 64.0] | [13.0, 66.0] | [12.0, 66.0] |
| **Gender** n (%) | | | |
| Male | 37 (57.8%) | 37 (52.9%) | 74 (55.2%) |
| Female | 27 (42.2%) | 33 (47.1%) | 60 (44.8%) |
| **Race** n (%) | | | |
| Asian | 8 (12.5%) | 1 ( 1.4%) | 9 ( 6.7%) |
| Black/African American | 19 (29.7%) | 7 (10.0%) | 26 (19.4%) |
| Multiple | 2 ( 3.1%) | 0 ( 0.0%) | 2 ( 1.5%) |
| White | 35 (54.7%) | 62 (88.6%) | 97 (72.4%) |
| **Ethnicity** n (%) | | | |
| Hispanic or Latino | 22 (34.4%) | 35 (50.0%) | 57 (42.5%) |
| Not Hispanic or Latino | 42 (65.6%) | 35 (50.0%) | 77 (57.5%) |
| **Iris Color** n (%) | | | |
| Blue | 4 ( 6.2%) | 1 ( 1.4%) | 5 ( 3.7%) |
| Brown | 54 (84.4%) | 50 (71.4%) | 104 (77.6%) |
| Green | 1 ( 1.6%) | 3 ( 4.3%) | 4 ( 3.0%) |
| Hazel | 5 ( 7.8%) | 16 (22.9%) | 21 (15.7%) |
| **Iris Color Stratum** n (%) | | | |
| Dark | 54 (84.4%) | 50 (71.4%) | 104 (77.6%) |
| Light | 10 (15.6%) | 20 (28.6%) | 30 (22.4%) |

MIST-1 refers to Study Protocol EYN-MYD-TP-31, which compared TR-PH to individual components.
MIST-2 refers to Study Protocol EYN-MYD-TP-32, which compared TR-PH to placebo.
Iris color 'Dark' includes brown and black irides, 'Light' includes blue, gray, green, and hazel irides.

Source: Module 5.3.5.3 ISS

### 8.2.3. Adequacy of the safety database:

A total of 131 subjects have been exposed to TR-PH across these 2 studies. This safety database, in combination with the submitted literature describing the use of tropicamide and phenylephrine hydrochloride ophthalmic solutions alone and in combination, is adequate.

## 8.3. Safety Results

### 8.3.1. Deaths

There were no deaths reported in the two clinical studies, EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2).

### 8.3.2. Dropouts and/or Discontinuations Due to Adverse Effects

No treatment emergent adverse events (TEAEs) led to dropouts or early treatment discontinuation in either of the two clinical studies, EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2).

### 8.3.3. Significant Adverse Events

There were no serious adverse events reported in the two clinical studies, EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2).

Table 26: Overall Summary of TEAEs by Treatment (Safety Population)

| Event | TR-PH | TR | PH | Placebo |
|---|---|---|---|---|
| **N (subjects)** | 131 | 64 | 62 | 70 |
| **N (encounters)**[1] | 163 | 64 | 62 | 107 |
| **Any TEAE** | | | | |
| Number of TEAEs[1] | 4 ( 2.5%) | 4 ( 6.2%) | 4 ( 6.5%) | 0 ( 0.0%) |
| Number of Subjects with TEAEs | 4 ( 3.1%) | 4 ( 6.2%) | 4 ( 6.5%) | 0 ( 0.0%) |
| **Ocular TEAE** | | | | |
| Number of TEAEs[2] | 4 ( 2.5%) | 4 ( 6.2%) | 4 ( 6.5%) | 0 ( 0.0%) |
| Number of Subjects with TEAEs | 4 ( 3.1%) | 4 ( 6.2%) | 4 ( 6.5%) | 0 ( 0.0%) |
| **TEAEs** | | | | |
| Vital dye staining cornea present | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 1.6%) | 0 ( 0.0%) |
| Eye pain | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 1.6%) | 0 ( 0.0%) |
| Vision blurred | 1 ( 0.8%) | 3 ( 4.7%) | 1 ( 1.6%) | 0 ( 0.0%) |
| Visual acuity reduced | 1 ( 0.8%) | 1 ( 1.6%) | 1 ( 1.6%) | 0 ( 0.0%) |
| Photophobia | 1 ( 0.8%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Instillation site pain | 1 ( 0.8%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |

TEAEs are Adverse Events (AEs) that started or worsened on or after the date of first dose. Unless otherwise noted, percentages are based on the number of subjects receiving each treatment across both studies. Note that some subjects experienced TEAEs for more than one treatment. The total number of treatment encounters, on a per-subject basis, including repeat treatments per subject in MIST- 2.
Source: Module 5.3.5.3 ISS

#### 8.3.4. Laboratory Findings

Laboratory evaluations were not performed in the two studies supporting this application.

#### 8.3.5. Vital Signs

Vital sign evaluations were not performed in the two studies supporting this application.

#### 8.3.6. Electrocardiograms (ECGs)

ECGs were not performed in the two studies supporting this application.

#### 8.3.7. QT

Not applicable.

#### 8.3.8. Immunogenicity

Not applicable.

### 8.4. Analysis of Submission-Specific Safety Issues

There were no submission specific safety issues for this application.

### 8.5. Safety Analyses by Demographic Subgroups

Analyses of AEs by various subgroups did not reveal a pattern based on age, sex, race, ethnicity or eye color.

### 8.6. Specific Safety Studies/Clinical Trials

There were no specific safety studies for this supplement.

### 8.7. Additional Safety Explorations

#### 8.7.1. Human Carcinogenicity or Tumor Development

From the Pharmacology/Toxicology review of the original application completed on 8/3/2021:

Given the single day use of the intended product (1 spray at (b) (4) 5-minute intervals up to a maximum of 3 sprays per eye), lack of a reason for concern from the available genetic toxicity and carcinogenicity data, and/or long history of clinical use of phenylephrine or tropicamide, the inclusion of these data in the label is not considered clinically relevant in this case. This approach is consistent with other phenylephrine and tropicamide approved products for individual use.

#### 8.7.2. Human Reproduction and Pregnancy

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

#### 8.7.3. Pediatrics and Assessment of Effects on Growth

This application triggers PREA as a new dosage form. It was presented at the Pediatric Review Committee (PeRC) on September 21, 2021. The PeRC and the Division discussed the Applicant's 505(b)(2) NDA submission containing the pediatric assessment for pediatric patients from birth to less than 17 years of age for the proposed indication. The Division noted that the efficacy of tropicamide 1% and phenylephrine 2.5%, used alone or in combination, are well-established with a long history of use in pediatric patients undergoing diagnostic assessments. The dosing and administration and adverse reactions sections of the labeling for the drug product is recommended to be consistent with tropicamide ophthalmic solution 1% and phenylephrine ophthalmic solution 2.5%. The PeRC agreed that this product has been fully assessed for pediatric patients from birth to less than 17 years of age.

#### 8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

MYDCOMBI is not a narcotic and does not have abuse potential.

### 8.8. Safety in the Postmarket Setting

#### 8.8.1. Safety Concerns Identified Through Postmarket Experience

The following safety concerns for the individual components of MYCOMBI have been identified through post-market experience and will be included in the product labeling:

> Dryness of the mouth, tachycardia, headache, allergic reactions, nausea, vomiting, pallor, central nervous system disturbances and muscle rigidity have been reported with the use of tropicamide. Psychotic reactions, behavioral disturbances, and vasomotor or cardiorespiratory collapse in children have been reported with the use of anticholinergic drugs.
>
> A marked increase in blood pressure has been reported with the use of phenylephrine, particularly, but not limited to, low weight premature neonates, infants and hypertensive patients.

#### 8.8.2. Expectations on Safety in the Post-market Setting

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

#### 8.8.3. Additional Safety Issues From Other Disciplines

There are no specific safety concerns from other disciplines.

The Division of Medication Error Prevention and Analysis (DMEPA) completed a review dated 10/12/2021 which includes language intended for the Complete Response letter regarding drug–device combination products. See Section 12 Regulatory Action of this review.

### 8.9. Integrated Assessment of Safety

The application supports the safety of MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray for dilation of the pupil in routine diagnostic procedures and in conditions where short term pupil dilation is desired.

The dosing and administration and adverse reactions sections of the labeling for the drug product are recommended to be consistent with tropicamide ophthalmic solution 1% and phenylephrine ophthalmic solution 2.5%.

## 9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## 10. Labeling Recommendations

#### 10.1.1. Prescription Drug Labeling

See the labeling recommendations in Section 13.2.

## 11. Risk Evaluation and Mitigation Strategies (REMS)

The regulatory action for this application will be Complete Response based on Chemistry Manufacturing and Inspection Issues.

## 12. Regulatory Action

NDA 215352 MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic solution) 1%/2.5% ophthalmic spray will receive a Complete Response letter because the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211, and the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product.

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

If utilizing a streamlined approach, the applicant must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, the applicant may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4 for the applicant, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

The following Complete Response statements should be included in the CR letter:

1. During a recent inspection of the [redacted] (b) (4) drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. The [redacted] (b) (4) microbial ingress container closure integrity testing (CCIT) performed [redacted] (b) (4) is acknowledged, [redacted] (b) (4) Please consider the following options to demonstrate the integrity of the assembled device:

[redacted] (b) (4)

3. It is acknowledged that the Alcami facility has performed [redacted] (b) (4) Provide the results of this hold time study.

4. The validation information for (b) (4) is acknowledged. Please address the following:

(b) (4)

(b) (4)

6. In your submission, you have stated that the (b) (4)

Please clarify the electrical component of your device.

7. In your submission, you have stated that the device is (b) (4)

Please clarify the reusability of the device in order to determine if additional testing is needed.

8. In your submission, you have provided a table of planned validation testing. However, no testing has been included and the list of planned testing does not state specifically what is to be tested. Please perform the following validation testing:

a. You have mentioned conducting transit testing. However, there is no transit testing data included in the submission. Please perform shipping and transit testing mentioned in your submission (ASTM D4169). This is needed in order to ensure a viable product after shipping has consistent performance. Variability of the device after shipping and transit impacts the safety and effectiveness.

b. Actuation force testing should be conducted to demonstrate that the amount of force needed is not excessive as it could impede the ability of the user to deliver the drug formulation and lead to improper dosage which is critical for safety and effectiveness.

c. Leak testing should be performed [redacted] (b) (4)

d. Performance testing to confirm that the device does deliver [redacted] (b) (4) of fluid with each actuation and that there is a low variance of volume delivered.

e. Further performance testing to demonstrate consistent performance of the device over the product lifetime. It is important that the device not suffer fatigue over the recommend use life and deteriorate in performance. The deterioration of the device may result in improper or no dosage of the drug formulation.

f. You mention conducting accelerated aging (ASTM F1980). However, there is no testing data included. Furthermore, there is no real-time aging data or real-time aging protocol as well. This is essential to demonstrate consistent performance and stability of the device over the shelf life. The testing to confirm the viability of the device should be a comparison of the previously mentioned performance tests at time point zero and compare it to the testing for devices at the end of the shelf life after undergoing real-time and accelerated aging, sterilization, and transit testing.

9. Your proposed product is a drug-device combination product. For each submission for this application, indicate that the product is a combination product in field #24 of the FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.

10. Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

11. You have not submitted human factors validation study data to demonstrate that your user interface supports the safe and effective use of your product by the intended users, for intended uses, and in the intended use environment. As such we request you submit the following to the Agency for review:

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies.

This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information. Guidance on human factors procedures to follow can be found in the following guidance documents: *Applying Human Factors and Usability Engineering to Medical Devices Guidance on Safety Considerations for Product Design to Minimize Medication Errors.*

# 13. Appendices

## 13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2)

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 3 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) N/A |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) N/A |

## 13.2. Labeling

Formal labeling review and negotiation is deferred until additional data is submitted to support the application. See Section 12 Regulatory Action of this review.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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DAVID B SUMMER
10/19/2021 10:30:40 AM

WILLIAM M BOYD
10/19/2021 11:35:48 AM

WILEY A CHAMBERS
10/20/2021 10:40:00 AM