CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217064Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW of NDA 217064

Application Type	NDA
Application Number(s)	217064
Priority or Standard	Standard
Submit Date(s)	November 28, 2022
Received Date(s)	November 28, 2022
PDUFA Goal Date	September 28, 2023
Division/Office	DO/OND/OSM
Reviewer Name(s)	Shilpa Rose, MD
Review Completion Date	See DAARTS stamp date
Established/Proper Name	Phentolamine mesylate ophthalmic solution
Code Names	Nyxol, POS
Proposed Trade Name	Ryzumvi
Applicant	Ocuphire Pharma, Inc
Dosage Form(s)	Topical ophthalmic solution
Applicant Proposed Dosing Regimen(s)	The recommended dose is one to two drops in adults and children aged 12 years and older and one drop in children aged 3 to 11 years following the completion of ophthalmic examination procedure to reverse mydriasis
Applicant Proposed Indication(s)/Population(s)	Treatment of pharmacologically-induced mydriasis produced by adrenergic agonists or parasympathetic agents, or a combination thereof
Recommendation on Regulatory Action	Recommend Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults and children aged 12 years and older, one to two drops following the completion of the ophthalmic examination procedure to reverse mydriasis. In children aged (b)(4) to 11 years: one drop in each dilated eye following the completion of the ophthalmic examination or procedure to reverse mydriasis.

Table of Contents

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
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

Phentolamine Ophthalmic Solution, 0.75% (POS) is a sterile, solution of phentolamine mesylate, USP (1%) without an antimicrobial preservative formulated for topical ophthalmic administration for the treatment of physiologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents. Phentolamine mesylate is a non-selective α-1 and α-2 adrenergic antagonist known to inhibit contraction of the iris dilator muscle, resulting in a smaller pupil size. Phentolamine Ophthalmic Solution is provided as a 0.75% solution: each mL of solution contains 10 mg phentolamine mesylate equivalent to 7.5 mg of phentolamine. The product, Nyxol, was previously described as "phentolamine mesylate ophthalmic solution (PMOS) 1% (b) (4)" and is now described as "phentolamine ophthalmic solution (POS) 0.75% (or (b) (4)", which expresses the content as the free base.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 217064 for Ryzumvi (phentolamine ophthalmic solution) 0.75% is recommended for approval for the reversal of pharmacologically-induced mydriasis produced by adrenergic agonists or parasympathetic agents. Two trials (MIRA-2 and MIRA-3) were submitted with this NDA to support the approval. Ryzumvi is more effective in reversing Phenylephrine than Tropicamide or Paramyd.

MIRA-2 and MIRA-3 met their primary efficacy endpoints. Both studies demonstrated the safety and efficacy of Ryzumvi (phentolamine ophthalmic solution) 0.75% by showing that the percentage of subjects treated two drops of Ryzumvi (phentolamine ophthalmic solution) 0.75% one hour after dosing with a mydriatic agent had reversal of mydriasis to ≤ 0.2 mm of their baseline pupillary diameter (PD) at 90 min compared to patients treated with placebo.

Study MIRA-4 was conducted in pediatric patients aged 4-14 years who were dosed with one drop of Ryzumvi (phentolamine ophthalmic solution) 0.75% one hour after dosing with a mydriatic agent had reversal of mydriasis to ≤ 0.2 mm of their baseline pupillary diameter (PD) at 90 min compared to patients treated with placebo.

The most common adverse events reported in Ryzumvi (phentolamine ophthalmic solution) 0.75% treated patients were instillation site burning/stinging/discomfort (13%) conjunctival hyperemia (12%), and instillation site erythema (4.4%). No adverse events were reported in the MIRA-4 study conducted in pediatric patients.

The results of these clinical trials support the use of Ryzumvi (phentolamine ophthalmic solution) 0.75% for the treatment of treatment of pharmacologically-induced mydriasis.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The adequate and well-controlled studies (MIRA-2, MIRA-3, MIRA-4) contained in this submission establish the efficacy of Ryzumvi (phentolamine ophthalmic solution) 0.75% dosed one to two drops for the treatment of pharmacologically induced mydriasis. Three studies, MIRA-2, MIRA-3 and MIRA-4 were completed in healthy pediatric and adult subjects. Both MIRA-2 and MIRA-3 met their primary endpoint of the percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline (-1 hour) photopic pupil diameter at 90 minutes. Both studies also met their secondary endpoints. MIRA-4 was a pediatric safety study with no primary efficacy endpoint. The safety of phentolamine ophthalmic solution was assessed in over 593 subjects, across 11 trials dosed with concentrations of 0.75% or higher. The most common adverse event experienced with Ryzumvi was instillation site stinging/pain/discomfort (13%) and conjunctival hyperemia (12%). The benefit of Ryzumvi dosed one to two drops in adults and children aged 12 years or older and one drop dosed in children aged 3 to 11 years following the completion of the ophthalmic examination or procedure is expected to outweigh the risks associated with its use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pupil dilation is commonly used by clinicians to achieve an optimal anterior segment or posterior segment exam or part of other ophthalmic procedures of surgeries. • Pharmacologically induced mydriasis typically dilates the pupil to 6 to 8 mm and can last from a few hours (typically 6 hours) up to 24 hours. • Common side-effects of pupil dilation include sensitivity to light and associated discomfort, in addition to cycloplegia with the loss of accommodation and the	• 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). • Reversal of mydriasis of the pupil can be achieved with α-1 adrenergic antagonists competitively blocking the effect of the mydriatic α-1 agonist (thereby diminishing the action of the iris dilator) or indirectly by limiting the action of the iris dilator, which would otherwise work in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ability to focus on near objects, read, or drive for up to 24 hours.	concert with the mydriatic effect of the muscarinic antagonist. • Ryzumvi is a non-selective α-1 and α-2 adrenergic antagonist known to inhibit contraction of the iris dilator muscle.
Current Treatment Options	• While Rev-Eyes is approved, there are currently no marketed products in the US to reverse pharmacologically-induced mydriasis.	This product, if approved would provide a method of reversing pharmacologically induced mydriasis that takes place during routine eye exams.
• Benefit	• Ryzumvi (phentolamine ophthalmic solution 0.75%) in a non-selective α-1 and α-2 adrenergic antagonist known to inhibit contraction of the iris dilator muscle, resulting in a smaller pupil size. • Ryzumvi demonstrated a statistically significant increase in the percentage of patients returning to ≤ 0.2 mm from baseline pupil diameter compared to placebo at 90 minutes post-treatment.	Two trials, OPI-NYXRM-301 (MIRA-2) and OPI-NYXRM-302 (MIRA-3), demonstrated that Ryzumvi was effective in the treatment of pharmacologically -induced mydriasis produced by adrenergic agonists or parasympathetic agents.
Risk and Risk Management	• The most common adverse events experienced with Ryzumvi were conjunctival hyperemia (12%) and instillation site discomfort (6%)	The risk-benefit profile of treatment with Ryzumvi (phentolamine ophthalmic solution) 0.75% for the reversal of pharmacologically-induced mydriasis favors its use for the intended indication.

1.4. Patient Experience Data

Trials MIRA-2, MIRA-3, and MIRA-4
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		Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	See Section 6
		☐	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

Optometrists and ophthalmologists conduct over 100 million eye exams or other ocular procedures annually. In order to achieve an optimal anterior segment (i.e., lens) or posterior segment (i.e., vitreous, retina, and optic nerve) exam or as part of other ophthalmic procedures/surgeries, dilation of the pupil (pharmacologically induced mydriasis) is necessary.

Regardless of the initial pupillary diameter (PD), pharmacologically induced mydriasis typically dilates the pupil to 6 to 8 mm, a size suitable for ophthalmic examination of the peripheral retina and other structures of the interior of the eye. Such pharmacologically induced mydriasis can last from a few hours (typically 6 hours) up to 24 hours, depending on the medication used, pigmentation of the iris, the age of the subject, and other factors. Common side effects of pupil dilation include sensitivity to light (photophobia) and associated discomfort, in addition to cycloplegia (i.e., loss of accommodation; the ability of the eye to focus on near objects). In turn, these side effects may impair the ability to read drive, or work, for up to 24 hours. Thus, accelerating the reversal of mydriasis after an ophthalmic examination/procedure would be beneficial for many patients.

Pupil size is under the control of two opposing sets of muscles – the iris sphincter muscle controlled by the cholinergic nervous system and the iris dilator muscle controlled by the adrenergic nervous system. The iris dilator muscle contains predominantly α-1 adrenergic receptors. Therefore, mydriasis can be achieved either by directly stimulating the iris dilator muscle with the use of an α-1 agonist (e.g., phenylephrine) or by blocking the iris sphincter muscle with the use of a muscarinic antagonist. Thus, reversal of mydriasis of the pupil can be achieved with α-1 adrenergic antagonists competitively blocking the effect of the mydriatic α-1 agonist (thereby diminishing the action of the iris dilator) or indirectly by limiting the action of the iris dilator, which would otherwise work in concert with the mydriatic effect of the muscarinic antagonist.

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

Analysis of Current Treatment Options

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Rev-Eyes	Treatment of iatrogenically induced mydriasis	1990	Two drops followed by two additional drops five minutes later	Reversal of phenylephrine and tropicamide dilation	Conjunctival injection	Currently not marketed in the US.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Phentolamine Ophthalmic Solution 0.75% has not been marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The clinical development of Ryzumvi (phentolamine mesylate ophthalmic solution), 0.75% was conducted primarily under IND 70499, with some of the early Phase 1 and Phase 2 studies being conducted under INDs (67288, 70736).

Several meetings were held between the Agency and Ocuphire during the development. A type C meeting was held on November 6, 2012. An EOP2 meeting was held on May 11, 2020. A EOP2 meeting was held on April 23, 2021. A Type C meeting took place on February 14, 2022. A Pre-NDA meeting occurred on June 24, 2022.

To support the NDA, Ocuphire relied on the Agency's previous findings of nonclinical systemic safety, clinical pharmacology, and systemic clinical safety for the approved listed drugs (LDs), Regitine® (NDA 8278) and OraVerse® (NDA 22159), in addition to Applicant-conducted studies and information available in the published literature. To enable reliance on the proposed LDs, the Applicant has established a scientific bridge through demonstration of lower systemic phentolamine exposure from Phentolamine Ophthalmic Solution 0.75% compared to data in the published literature for oral submucosal Oraverse at the highest approved dose of 0.8 mg. A scientific bridge between OraVerse and Regitine has already been established in the approval for OraVerse and in the published literature.

3.3. Foreign Regulatory Actions and Marketing History

Ryzumvi (phentolamine mesylate ophthalmic solution), 0.75% has not been approved for marketing in any other country.

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

4.1. Office of Scientific Investigations (OSI)

Clinical data from Protocols OPI-NYXRM-301 (MIRA-2) and OPI-NYXRM-302 (MIRA-3) were submitted to the Agency in support of NDA 217064 for the use of Ryzumvi (phentolamine) for the reversal of pharmacologically induced mydriasis. The clinical investigators, Drs. Day and Foster, and the sponsor, Ocuphire Pharma, Inc., were inspected in support of this NDA. Based on the results of these inspections, the data generated by these clinical sites and submitted by the sponsor and the sponsor's oversight of these studies appear to be acceptable.

4.2. Product Quality

The Phentolamine Ophthalmic Solution Drug Product (DP) is an aqueous solution, 0.31 (b) (4) mL fill within a 0.5 mL single-dose low-density polyethylene (LDPE) blow-fill-seal (BFS) vial without an antimicrobial preservative intended for topical administration directly to the eye. The product is manufactured by (b) (4) The storage temperature is (b) (4) (2°C-8°C). The product density is close to water. The specific gravity for 0.75% phentolamine ophthalmic solution of 1.0197.

Drug Product Composition

Ingredient and Quality Reference	Purpose	Composition (% w/v)	Amount per mL (mg/mL)
Phentolamine Mesylate, cUSP	Drug substance	1.0	10.00
Mannitol, cUSP	(b) (4)		
Sodium Acetate Trihydrate, cUSP			
(b) (4) Sodium Hydroxide, cNF	pH adjustment	Adjust to pH 4.5– (b) (4)	Adjust to pH 4.5 (b) (4)
Hydrochloric Acid, cNF	pH adjustment	Adjust to pH 4.5 (b) (4)	Adjust to pH 4.5
Water for Injection, cUSP	Dilution medium	q.s. to 1.00 g	q.s. to 1.00 mL
Nitrogen, cUSP	(b) (4)	As required	As required

cNF = current National Formulary; cUSP = current United States Pharmacopoeia; q.s. = as much as suffices

4.3. Clinical Microbiology

N/A. The product is not an antimicrobial.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical data presented in this NDA provides adequate safety support for the approval of Phentolamine Ophthalmic Solution 0.75% at the intended marketing dosing recommendation of 1 or 2 drops in the reversal of mydriasis. Pharmacology/Toxicology team recommends approval.

4.5. Clinical Pharmacology

Pharmacokinetic (PK) blood samples for Phentolamine Ophthalmic Solution, 0.75% (POS) were drawn from the PK population of study OPI-NYXRM-302 (MIRA-3), which comprised 24 healthy adult subjects. Each subject received a total of 3 drops (2 in the study eye and 1 in the fellow eye) corresponding to 0.9 mg phentolamine mesylate. Ten mg/mL POS (corresponding to 1% phentolamine mesylate or 0.75% of free phentolamine) is administered as a drop of 0.03 mL, corresponding to 0.3 mg of phentolamine mesylate or 0.225 mg free phentolamine per drop. Pharmacokinetic sampling was taken at 15 min, 60 min, and 3 hours relative to study treatment. Among the POS subjects who had blood samples collected for analysis of phentolamine plasma concentration, mean (SD) phentolamine concentration was 0.6 (0.45) ng/mL at 15 min, 0.5 (0.32) ng/mL at 60 min, and 0.2 (0.19) ng/mL at 3 hours. The majority of subjects reached C_{max} at 15 min (T_{max}) post-dosing. Phentolamine levels decreased over a period of 3 hours, reaching a mean concentration of 0.2 ng/mL at 3 hours. Systemic exposure after POS administration shows a C_{max} of 0.53 ng/mL and exposure over 3 hours period (AUC_{0-3}) of 0.98 hr*ng/mL after POS administration. Dose-normalized C_{max}/D and AUC_{0-3}/D for ophthalmic solution were estimated as 0.59 ng/mL and 1.09 hr*ng/mL/mg, respectively. Refer to Clinical Pharmacology review for additional details.

4.6 Devices and Companion Diagnostic Issues

The Form 356h indicated that it is a combination product (item 24 checked). The dispenser of the product is considered a device. The product is regulated as a drug device combination product. CDRH confirmed that no CDRH consult is necessary for BFS single-dose or multidose eyedropper.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Listing of Clinical Trials Relevant to this NDA

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Randomized Subjects[a]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	OP-NYX-001	To determine the efficacy and safety of PMOS	Double-masked, randomized, single-dose, 3-arm, placebo-controlled, parallel trial	0.2% PMOS*; Single dose; Topical ocular	PMOS*+Visine=15 PMOS*+Placebo=15[b] Visine+Placebo=15 Total=45	Healthy subjects	Single dose (1 day)
Efficacy and Safety	OP-NYX-002	To evaluate the tolerability and efficacy of PMOS	Double-masked, randomized, placebo-controlled, single-dose, incomplete block, 3-period crossover, dose-escalation trial	0.2%, 0.4%, and 0.8% PMOS*; Single dose; Topical ocular	PMOS*=16 Placebo=12 Total=16	Healthy subjects	Single dose (1 day)
Efficacy and Safety	OP-NYX-SNV	To assess the efficacy and safety of PMOS	Double-masked, randomized, placebo-controlled, single-dose trial	1.0% PMOS*; Single dose; Topical ocular	PMOS*=16 Placebo=8 Total=24	Severe DLD subjects	Single dose (1 day)
Efficacy and Safety	OP-NYX-01a2	To assess the efficacy and safety of PMOS	Double-masked, randomized, placebo-controlled, single-dose, 3-arm trial	0.5% and 1.0% PMOS; Single dose; Topical ocular	PMOS=40 Placebo=20 Total=60	Severe DLD subjects	Multiple dose (14 days)
Efficacy and Safety	OPI-NYXG-201 (ORION-1)	To assess the efficacy and safety of PMOS	Double-masked, randomized, placebo-controlled, multiple-dose, multicenter trial	1.0% PMOS; Multiple doses; Topical ocular	PMOS=19 Placebo=20 Total=39	Elderly subjects with glaucoma or OHT	Multiple dose (14 days)
Efficacy and Safety	OPI-NYXRM-201 (MIRA-1)	To assess the efficacy and safety of PMOS in reducing pharmacologically induced mydriasis	Double-masked, randomized, placebo-controlled, crossover, single-dose, multicenter trial	1.0% PMOS; Single dose; Topical ocular	PMOS=31 Placebo=32 Total=32	Healthy subjects/ RM	Single-dose (1 day in each crossover period)
Efficacy and Safety	OPI-NYXRM-301 (MIRA-2)	To assess the efficacy and safety of POS in reducing	Double-masked, randomized, placebo-controlled, parallel-group, single-dose, multicenter trial	0.75% POS; Single dose; Topical ocular	POS=94 Placebo=91 Total=185	Healthy subjects/ RM	Single dose (1 day)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Randomized Subjects[a]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		pharmacologically induced mydriasis					
PK/ Efficacy and Safety	OPI-NYXRM-302 (MIRA-3)	To assess the efficacy and safety of POS in reducing pharmacologically induced mydriasis	Double-masked, randomized, placebo-controlled, parallel group, single-dose, multicenter trial	0.75% POS; Single dose; Topical ocular	POS=244 Placebo=124 Total=368	Healthy subjects/ RM	Single dose (1 day)
Efficacy and Safety	OPI-NYXRMP-303 (MIRA-4)	To assess the efficacy and safety of POS in reducing pharmacologically induced mydriasis	Double-masked, randomized, placebo-controlled, parallel-group, single-dose, multicenter trial in pediatric subjects	0.75% POS; Single dose; Topical ocular	POS=11 Placebo=12 Total=23	Pediatric subjects/ RM	Single dose (1 day)
Efficacy and Safety	OPI-NYXP-201 (VEGA-1)	To assess the safety and efficacy of POS with low-dose (0.4%) pilocarpine eye drops	Double-masked, randomized, placebo-controlled, parallel-group, multicenter study in subjects with presbyopia	0.75% POS +0.4% LDP; Multiple doses; Topical ocular	POS + LDP=44 POS=30 Placebo + LDP=31 Placebo=45 Total=150	Presbyopia subjects	Multiple dose (4-5 days)
Efficacy and Safety	OPI-NYXDLD-301 (LYNX-1)	To assess the safety and efficacy of POS	Double-masked, randomized, placebo-controlled, parallel-group, multiple-doses, multicenter study in subjects with DLD	0.75% POS; Multiple doses; Topical ocular	POS=72 Placebo=73 Total=145	DLD subjects	Multiple dose (14 days)

DLD, dim light vision disturbances; LDP, low-dose pilocarpine; OHT, ocular hypertension; PMOS, phentolamine mesylate ophthalmic solution in proprietary formulation; PMOS, *phentolamine mesylate ophthalmic solution in commercial artificial tears solution; POS, phentolamine mesylate in proprietary formulation; RM, reversal of mydriasis. 1.0% PMOS is equivalent to 0.75% POS. The product, Nyxol, was previously described as "phentolamine mesylate ophthalmic solution (PMOS) 1% (or (b) (4)%)" and is now described as "phentolamine ophthalmic solution (POS) 0.75% (or (b) (4)%)", which expresses the content as the free base as per the requested nomenclature change by the FDA.

[a] Total subject numbers will not equal the sum of the subgroups in cross over studies (OP-NYX-002 and OPI-NYXRM-201).

[b] NYX-001 subjects (b) (6) (all in Arm 2) did not have Study Drug Administration CRF pages, so there is no record of their dosing data; they have been excluded from the Safety Population. Subject (b) (6) (in Arm 2) did not have a Demographic CRF page; they have been excluded from the Safety Population in the Summary of Clinical Safety. All 5 subjects are included in the Summary of Clinical Efficacy and the Tabular Listing of all Clinical Studies.

5.2. Review Strategy

Clinical data for studies MIRA-2, MIRA-3, and MIRA-4 were reviewed to support safety and efficacy. MIRA-2 and MIRA-3 were double-masked, randomized, placebo-controlled, multi-center trials of POS compared with vehicle (placebo) in normal healthy subjects. MIRA-4 was a 1-day, double-masked, randomized, placebo-controlled, single-dose, multi-center study with 23 pediatric subjects, healthy or with ocular conditions. MIRA-3 evaluated the systemic exposure of POS based on pharmacokinetic (PK) sampling.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. OPI-NYXRM-301; MIRA-2

6.1.1. Study Design

Overview and Objective

This study is a randomized, parallel arm, double-masked, placebo-controlled study to assess the efficacy of POS (Phentolamine Ophthalmic Solution, 0.75%) to return subjects to baseline accommodation after use of cycloplegic agents tropicamide and Paremyd®).

The study's objective were:

- To evaluate the efficacy of POS to expedite the reversal of pharmacologically induced mydriasis across multiple mydriatic agents with an emphasis on phenylephrine
- To evaluate the efficacy of POS to return subjects to baseline accommodation after worsening (with cycloplegic agents tropicamide and Paremyd®)
- To evaluate the safety of POS
- To evaluate any additional benefits of the reversal of pharmacologically induced mydriasis

Trial Design

This was a Phase 3, multi-center randomized, parallel arm, double-masked, placebo-controlled study with 185 randomized subjects. The study included 14 pediatric subjects aged 12 to 17 years) was conducted to evaluate the safety and efficacy of POS in subjects with pharmacologically induced mydriasis. Following the successful completion of screening, each subject was stratified by eye color and then simultaneously randomized to mydriatic agent (unmasked) and treatment (masked).

Treatment randomization was 1:1, POS or placebo (vehicle), and stratification by iris color was 1:1, light or dark irides. The mydriatic agent randomization was 3:1:1 (2.5% phenylephrine:1%

tropicamide: Paremyd). That is, approximately 60% of the randomized subjects received 1 drop of 2.5% phenylephrine in both eyes (OU) 1 hour before treatment (96 evaluable subjects), approximately 20% received 1 drop of 1% tropicamide OU 1 hour before treatment (32 evaluable subjects), and approximately 20% received 1 drop of Paremyd OU 1 hour before treatment (32 evaluable subjects).

Treatment (POS or placebo) was administered OU, with the study eye defined as the right eye (OD) and the non-study eye was defined as the left eye (OS). Adult subjects (≥ 18 years old) had 2 drops of treatment administered 5 min apart in the study eye (OD) and 1 drop of treatment administered in the non-study eye (OS) 1 hour after mydriatic drug instillation. Pediatric subjects had 1 drop of treatment administered OU 1 hour after mydriatic drug instillation. The study and non-study eyes were both evaluated at all assessments.

Inclusion criteria
For inclusion into the trial, subjects were required to fulfill all of the following criteria:
1. Males or females ≥ 12 years of age.
2. Healthy and well-controlled subjects.
3. Ability to comply with all protocol-mandated procedures independently and to attend all scheduled office visits.
4. Adults (≥ 18 years of age) willing to give written informed consent to participate in this study. Children aged 12 to 17 years to provide signed assent form, as well as a separate parental/Legal Guardian consent.

Exclusion criteria
Any of the following was regarded as a criterion for exclusion from entry into the trial:

Ophthalmic (in either eye)
1. Clinically significant ocular disease as deemed by the investigator (e.g., cataract, glaucoma, corneal edema, uveitis, severe keratoconjunctivitis sicca) that might have interfered with the study.
2. Unwilling or unable to discontinue use of contact lenses at Screening until study completion.
3. Unwilling or unable to suspend use of topical medication at Screening until study completion.
4. Ocular trauma, ocular surgery, or non-refractive laser treatment within the 6 months prior to Screening.
5. Use of any topical prescription or over-the-counter (OTC) ophthalmic medications of any kind within 7 days of Screening, with the exception of lid scrubs with OTC products (e.g., OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.).
6. Recent (within 7 days) or current evidence of ocular infection or inflammation in either eye (such as current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at Screening in either eye).
7. History of diabetic retinopathy or diabetic macular edema.

8. Closed or very narrow angles that, in the investigator's opinion, were potentially occludable if the subject's pupil was dilated.
9. History of any traumatic (surgical or nonsurgical) or non-traumatic condition affecting the pupil or iris (e.g., irregularly shaped pupil, neurogenic pupil disorder, iris atrophy, iridotomy, iridectomy, etc.).
10. Known allergy or contraindication to any component of the mydriatic agents or the vehicle formulation.
11. History of cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal.

Systemic
1. Known hypersensitivity or contraindication to α- and/or β-adrenoceptor antagonists (e.g., chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure [BP] or heart rate [HR]; second or third-degree heart block or congestive heart failure; severe diabetes).
2. Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might have interfered with the study.
3. Initiation of treatment with or any changes to the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs within 7 days prior to Screening or during the study.
4. Participation in any investigational study within 30 days prior to Screening.
5. Females of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods included the use of at least one of the following: intrauterine device, hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. A female was considered to be of childbearing potential unless she was premenstrual, 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential, including those with post-tubal ligation, must have had a negative urine pregnancy test result at Visit 1 Screening and must have intended to not become pregnant during the study.
6. Resting HR outside the normal range (50-110 beats per minute) at the Screening Visit. Heart rate could be repeated only once if outside the normal range following at least a 5-minute rest period in the sitting position.
7. Hypertension with resting diastolic BP > 105 mmHg or systolic BP > 160 mmHg at the Screening Visit. Blood pressure could be repeated only once if outside the specified range following at least a 5-minute rest period in the sitting position.

Schedule of Procedures

	Screening Visit	Visit 1[a] Mydriasis/Treatment									Visit 2 Follow-Up
Day	1	1									2
Time relative to study treatment		-1 h Baseline	0 min ± 5 min (Max)	30 min ± 5 min	60 min ± 5 min	90 min ± 5 min	2 h ± 5 min	3 h ± 10 min	4 h ± 10 min	6 h ± 15 min	24 h + 6 h
Informed consent/Assent	X										
Screening # assigned	X										
Medical/Ophthalmic history	X										
Demographics	X										
Prior/Concomitant medications[b]	X									X	X
Urine pregnancy test[c]	X										
HR/BP	X									X	X
Pupil diameter[d]		X	X	X	X	X	X	X	X	X	X
BCDVA		X	X			X				X	X
DCNVA		X	X			X				X	X
Accommodation[e]		X	X		X	X	X	X	X	X	
Conjunctival hyperemia		X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
Ocular tolerability[f]			X								
Mydriatic agent[g]		X									
IOP[h]	X									X	
Biomicroscopy	X										
Ophthalmoscopy[i]	X										
Questionnaire[j]		X	X		X	X		X		X	X
Randomization # assigned	X										
Treatment: Nyxol/Placebo			X								

BCDVA, best-corrected distance visual acuity; BP, blood pressure; DCNVA, distance-corrected near visual acuity; HR, heart rate; IOP, intraocular pressure; Max, timepoint of expected maximum pupillary dilation; RAF, Royal Air Force.
[a]If subject qualifies at the Screening Visit, the Screening Visit becomes Visit 1.
[b]Investigators to note changes to concomitant medications at any time throughout the visit.
[c]For females of childbearing potential only.
[d]NeurOptics VIP-300 pupillometer (mm).
[e]RAF Near Point Rule.
[f]4-point scale.
[g]Mydriatic agent should be instilled after all baseline assessments are completed.
[h]Tono-Pen.
[i]Direct or indirect ophthalmoscopy without dilation. Use of 90D lens (indirect) is allowed.
[j]Subject questionnaire is a brief symptom survey.

Study Endpoints

The primary efficacy endpoint was the <u>percentage of subjects' study eyes returning to baseline photopic PD (defined as PD ≤ 0.2 mm above baseline PD) at 90 min post-treatment</u>.

The right eye (OD) was the study eye and OS was the fellow eye. Unless specified, the study and fellow eyes were both evaluated at all assessments.

Secondary efficacy endpoints were analyzed by study eye and fellow eye unless otherwise indicated, and included:

- Percentage of subjects returning to ≤ 0.2 mm from baseline (-1 hr) photopic PD at each remaining time point (0 min, 30 min, 60 min, 90 min [fellow eye], 2 hours, 3 hours, 4 hours, 6 hours, and 24 hours)
- Change (in mm) in photopic PD from max pupil dilation (0 min) at each time point (30 min, 60 min, 90 min, 2 hours, 3 hours, 4 hours, 6 hours, and 24 hours)
- Percentage of subjects with unchanged accommodation from baseline (-1 hr) at 0 min, 90 min, 2 hours, 3 hours, and 6 hours
- Change (in diopters) from baseline accommodation (-1 hr) at each time point (0 min, 60 min, 90 min, 2 hours, 3 hours, 4 hours and 6 hours

- Time (hours) to return to ≤ 0.2 mm from baseline (-1 hr) photopic PD (time-savings analysis)

Some of the efficacy endpoints were analyzed overall, by mydriatic agent, and by light/dark irides. The primary safety measures were conjunctival hyperemia, impairment in visual acuity (BCDVA and DCNVA), subjective ocular tolerability, and AEs. Conjunctival hyperemia was assessed visually with the CCLRU bulbar redness scale. Other safety measures were IOP, subject questionnaire, and systemic safety, as measured by HR and BP. Urine pregnancy tests for females of childbearing potential were conducted at screening prior to dosing of study medication.

Statistical Analysis Plan
The primary efficacy endpoint was the percentage of subjects returning to ≤ 0.2 mm from baseline PD at 90 min post-treatment in the study eye. Subjects who did not have an increase of > 0.2 mm in PD in the study eye at the maximum time point were not counted as returning to ≤ 0.2 mm from baseline PD.

The primary efficacy endpoint was analyzed using a logistic regression model with treatment, mydriatic agent, and light/dark irides as factors and the baseline PD as a covariate. The percentage of subjects in each treatment group meeting the criteria, the OR with 95% CI, and p-value are provided. In addition, the primary efficacy endpoint was analyzed by mydriatic agent and by light/dark irides using the same model indicated above but without mydriatic agent or irides as a factor, as appropriate. For these subgroup analyses, observed case data only were used; that is, missing values were not imputed. Each mydriatic agent was analyzed individually, and an additional mydriatic agent subgroup, combining 1% tropicamide and the Paremyd subjects into a "tropicamide or Paremyd" group, was analyzed.

A comparison of the study eye and non-study eye for each subject was completed for the primary efficacy endpoint, as well as by mydriatic agent. This analysis was by treatment and was analyzed using a logistic regression model with eye type (study eye or non-study eye), mydriatic agent, and light/dark irides as fixed effects, subject as a random effect, and the average baseline PD across eye type as a covariate. The percentage of eyes meeting the criteria, the OR with 95% CI, and p-value were provided. Secondary efficacy endpoints were analyzed by study eye and non-study eye, unless otherwise indicated. Binocular accommodation was analyzed separately.

All safety analyses were conducted using the Safety Population. All safety analyses were completed using the actual treatment a subject received. Observed case data were used; no imputation was performed for missing safety data except for the limited situations described in the SAP.

Protocol Amendments

Significant Changes in the Conduct of the Study

The original protocol, dated August 20, 2020, was amended 1 time: Amendment 1 (February 5, 2021). Changes made in Amendment 1:

- Clarified that evaluable subjects, who are defined within the protocol, will be used for efficacy analysis
- Clarified that room lights were to be on during accommodation measurements
- Clarified the PP Population as having an increase of > 0.2 mm in PD in the study eye at Time 0 min compared to Baseline
- Per FDA feedback, defined and used the mITT Population as well as imputation methods for missing data for primary efficacy analysis.
- Harmonized the protocol with the final version of the SAP (V1.0)

6.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted per the principles of Good Clinical Practices (GCP).

Patient Disposition

One hundred eighty-five subjects (POS group, n=94; placebo group, n=91) were enrolled and randomized into the study. All 185 subjects received at least one dose of study medication and therefore were included in the Safety Population and had a Visit 1 PD measurement; therefore, all 185 subjects were included in both the Safety Population and mITT Population. Twenty subjects were excluded from the PP Population, because the study eye did not have an increase of > 0.2 mm at time 0 compared to baseline and 14 pediatric subjects because they received only one drop of study medication (instead of 2); therefore, 165 subjects were included in the PP Population.

Subject Disposition (All Randomized Population)

	POS n (%)	Placebo n (%)
ARP, n	94	91
Completed study	94 (100%)	91 (100%)
Discontinued study medication early	0	0

Source: Table 14.1.1 generated 26 Aug 2021. ARP, All Randomized Population.ARP is defined as all randomized subjects.

Data Sets Analyzed

	POS n (%)	Placebo n (%)
All Randomized Population, n	94	91
Safety Population	94 (100.0)	91 (100.0)
mITT Population	94 (100.0)	91 (100.0)
Per Protocol Population	84 (89.4)	81 (89.0)

Source: Table 14.1.1 generated 26 Aug 2021.
ARP, All Randomized Population; mITT, modified Intention-to-Treat; PD, pupil diameter; PP, Per Protocol.
NOTE: The ARP is defined as all randomized subjects. The Safety Population includes randomized subjects who have received at least 1 dose of study medication. The mITT Population includes randomized subjects who received study treatment and have a Visit 1 PD measurement. The PP Population includes subjects in the mITT who received 2 drops of study medication in their study eye, have all Visit 1 PD measurements, had an increase of > 0.2 mm in PD in the study eye at time 0 min compared to baseline (-1 hr), and had no major protocol deviations.

Protocol Violations/Deviations

Twelve subjects had a total of 16 minor protocol deviations; there were no major protocol deviations during this study.

Table of Demographic Characteristics

The demographics and baseline characteristics of the ARP (which is also the Safety Population and the mITT population) are presented in Table 6.

Demographic Characteristics (ARP)

Demographic Characteristic Statistic	POS (n=94)	Placebo (n=91)
Age, years		
Mean (SD)	33.9 (14.04)	32.8 (13.55)
Median	31.0	30.0
Min, max	12, 70	13, 73
Gender, n (%)		
Male	36 (38.3)	36 (39.6)
Female	58 (61.7)	55 (60.4)
Race, n (%) [a]		
White	70 (74.5)	74 (81.3)
American Indian or Alaska Native	1 (1.1)	1 (1.1)
Native Hawaiian or Other Pacific Islander Black or African American	1 (1.1)	0
Asian	17 (18.1)	16 (17.6)
	6 (6.4)	3 (3.3)
Ethnicity, n (%) Hispanic or Latino	4 (4.3)	8 (8.8)
Not Hispanic or Latino	90 (95.7)	83 (91.2)

Study eye, n (%) OD	94 (100)	91 (100)
Iris color, n (%)		
Light blue	16 (17.0)	17 (18.7)
Dark blue	4 (4.3)	3 (3.3)
Blue with peripupillary brown	11 (11.7)	9 (9.9)
Uniform green	3 (3.2)	7 (7.7)
Green with brown iris ring	11 (11.7)	9 (9.9)
Central brown and peripheral green	7 (7.4)	7 (7.7)
Brown with some peripheral green	20 (21.3)	10 (11.0)
Brown	22 (23.4)	29 (31.9)
Irides type, n (%)		
Light	45 (47.9)	45 (49.5)
Dark	49 (52.1)	46 (50.5)

Source: Table 14.1.2.1 generated 26 Aug 2021.

a. Subjects can be included in more than one category, so the sum of the percentages may be greater than 100%.

Baseline Ocular Characteristics

Baseline Ocular Characteristic Statistic	POS (n=94)	Placebo (n=91)
Distance vision/Near vision correction needed, n (%)		
Yes	59 (62.8)	53 (58.2)
No	35 (37.2)	38 (41.8)
Type of vision correction, n (%)		
Glasses	59 (62.8)	53 (58.2)
Contact lenses	0	0
Other	0	0
Spectacle correction type, n (%) [a]		
Near spectacle correction	16 (17.0)	9 (9.9)
Distance spectacle correction	55 (58.5)	50 (54.9)
Other	0	0
Mydriatic agent, n (%)		
Phenylephrine	56 (59.6)	55 (60.4)
Tropicamide	19 (20.2)	18 (19.8)
Paremyd	19 (20.2)	18 (19.8)
PD (-1 hr) in the study eye, mm		
Mean (SD)	5.085 (0.9295)	5.177 (0.9678)
Median	5.020	5.190
Minimum, maximum	2.91, 7.88	3.07, 7.68
PD (-1 hr) in the non-study eye, mm		
Mean (SD)	5.049 (0.9707)	5.220 (0.9633)
Median	4.980	5.230
Minimum, maximum	2.90, 7.30	2.89, 7.33

Baseline Ocular Characteristic Statistic	POS (n=94)	Placebo (n=91)
Maximum PD (0 min) in the study eye, mm		
Mean (SD)	7.207 (1.0240)	7.197 (1.1717)
Median	7.245	7.370
Minimum, maximum	4.04, 9.28	4.50, 9.14
Maximum PD (0 min) in the non-study eye, mm		
Mean (SD)	7.169 (1.1117)	7.241 (1.1099)
Median	7.230	7.330
Minimum, maximum	3.67, 9.53	4.56, 9.12
Accommodation (-1 hr) in the study eye, D		
Mean (SD)	10.47 (20.373)	8.25 (5.230)
Median	7.28	7.41
Minimum, maximum	2.1, 200.0	2.2, 33.3
Accommodation (-1 hr) in the non-study eye, D		
Mean (SD)	10.25 (20.396)	8.26 (5.105)
Median	6.78	7.14
Minimum, maximum	2.2, 200.0	2.3, 33.3
Accommodation (0 min) in the study eye, D		
Mean (SD)	5.43 (3.773)	5.50 (3.280)
Median	4.08	4.35
Minimum, maximum	2.0, 20.0	2.0, 20.0
Accommodation (0 min) in the non-study eye, D		
Mean (SD)	5.42 (3.550)	5.47 (3.261)
Median	4.26	4.44
Minimum, maximum	2.0, 20.0	2.1, 20.0
BCDVA (-1 hr) in the study eye, letters [b]		
Mean (SD)	57.0 (4.10)	58.6 (4.49)
Median	56.5	59.0
Minimum, maximum	44, 69	49, 70
BCDVA (-1 hr) in the non-study eye, letters [b]		
Mean (SD)	57.0 (3.94)	58.7 (3.98)
Median	56.0	59.0
Minimum, maximum	45, 68	49, 70
BCDVA (0 min) in the study eye, letters [b]		
Mean (SD)	55.0 (4.44)	56.4 (5.37)
Median	55.0	57.0
Minimum, maximum	40, 67	44, 69
BCDVA (0 min) in the non-study eye, letters [b]		
Mean (SD)	55.1 (5.11)	56.7 (5.35)
Median	55.0	56.0
Minimum, maximum	35, 67	43, 70
DCNVA (-1 hr) in the study eye, letters		

Baseline Ocular Characteristic Statistic	POS (n=94)	Placebo (n=91)
Mean (SD)	65.6 (10.63)	67.0 (9.74)
Median	70.0	70.0
Minimum, maximum	24, 80	27, 80
DCNVA (-1 hr) in the non-study eye, letters		
Mean (SD)	65.7 (10.34)	67.4 (9.70)
Median	70.0	70.0
Minimum, maximum	30, 79	31, 80
DCNVA (0 min) in the study eye, letters		
Mean (SD)	58.1 (13.98)	60.8 (13.68)
Median	63.0	65.0
Minimum, maximum	15, 75	25, 80
DCNVA (0 min) in the non-study eye, letters	59.4 (12.72)	61.3 (13.62)
Mean (SD)	63.0	65.0
Median	19, 77	24, 78
Minimum, maximum		
IOP (screening) in the study eye, mmHg		
Mean (SD)	15.3 (2.78)	15.1 (2.95)
Median	15.0	15.0
Minimum, maximum	7, 21	9, 22
IOP (screening) in the non-study eye, mmHg		
Mean (SD)	15.4 (2.89)	15.1 (2.79)
Median	15.0	15.0
Minimum, maximum	5, 21	8, 21

Source: Table 14.1.2.1 generated 26 Aug 2021.
BCDVA, best-corrected distance visual acuity; D, diopters; DCNVA, distance-corrected near visual acuity; IOP, intraocular pressure; OD, right eye; PD, pupil diameter; SD, standard deviation.
a. Subjects can be included in more than one category, so the sum of the percentages may be greater than 100%.
b. For BCDVA, the number of letters read is from the 4-meter distance only, so that 55 letters read is equivalent to a Snellen acuity of 20/20.

Reviewer's Comment: *Sixty percent of study subjects received one drop of phenylephrine 2.5% , 20% received one drop of tropicamide 1% and 20% received one drop of Paremyd as their mydriatic agent.*

Efficacy Results – Primary Endpoint

Percent of Subject Study Eyes Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)

Study Eye Time point Category	POS (n=94) n (%)	Placebo (n=91) n (%)	POS vs placebo [a]	
			Odds ratio (95% CI)	p-value
30 min	1 (1.1)	3 (3.3)	0.53 (0.09, 2.98)	0.4688
60 min	26 (27.7)	2 (2.2)	18.27 (4.75, 70.19)	<0.0001
90 min	46 (48.9)	6 (6.6)	25.93 (9.37, 71.79)	<0.0001
2 hr	55 (58.5)	10 (11.0)	22.99 (8.92, 59.27)	<0.0001
3 hr	75 (79.8)	16 (17.6)	23.85 (10.25, 55.49)	<0.0001
4 hr	77 (81.9)	27 (29.7)	14.04 (6.41, 30.72)	<0.0001
6 hr	85 (90.4)	41 (45.1)	12.03 (5.29, 27.34)	<0.0001
24 hr	86 (91.5)	60 (65.9)	5.37 (2.35, 12.28)	<0.0001

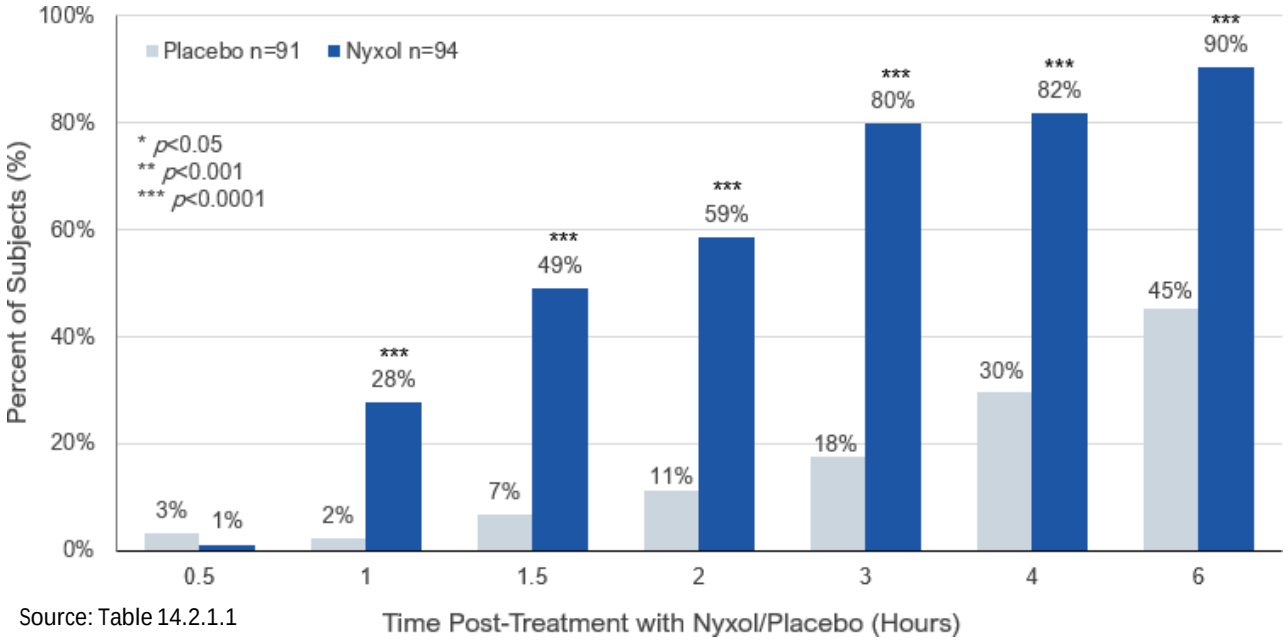
Reviewer's Comment: *The study met its primary efficacy endpoint. In the mITT Population, the percentage of subjects treated with POS had study eyes that showed reversal of mydriasis, using a PD threshold of ≤ 0.2 mm from baseline at 90 min (primary endpoint) compared with the placebo treatment (48.9% vs 6.6%, respectively; OR 25.93 [9.37, 71.79]; p<0.0001.*

Percent of Subject Fellow Eyes Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)

Fellow Eye Time point Category	POS (n=94) n (%)	Placebo (n=91) n (%)	POS vs placebo [a]	
			Odds ratio (95% CI)	p-value
30 min	2 (2.1)	2 (2.2)	0.96 (0.20, 4.59)	0.9554
60 min	23 (24.5)	5 (5.5)	6.74 (2.42, 18.82)	0.0003
90 min	46 (48.9)	5 (5.5)	38.03 (12.40, 116.67)	<0.0001
2 hr	48 (51.1)	9 (9.9)	22.18 (8.21, 59.87)	<0.0001
3 hr	64 (68.1)	13 (14.3)	27.53 (10.57, 71.71)	<0.0001
4 hr	71 (75.5)	22 (24.2)	14.16 (6.38, 31.42)	<0.0001
6 hr	81 (86.2)	41 (45.1)	10.66 (4.71, 24.12)	<0.0001
24 hr	83 (88.3)	62 (68.1)	3.59 (1.65, 7.79)	0.0012

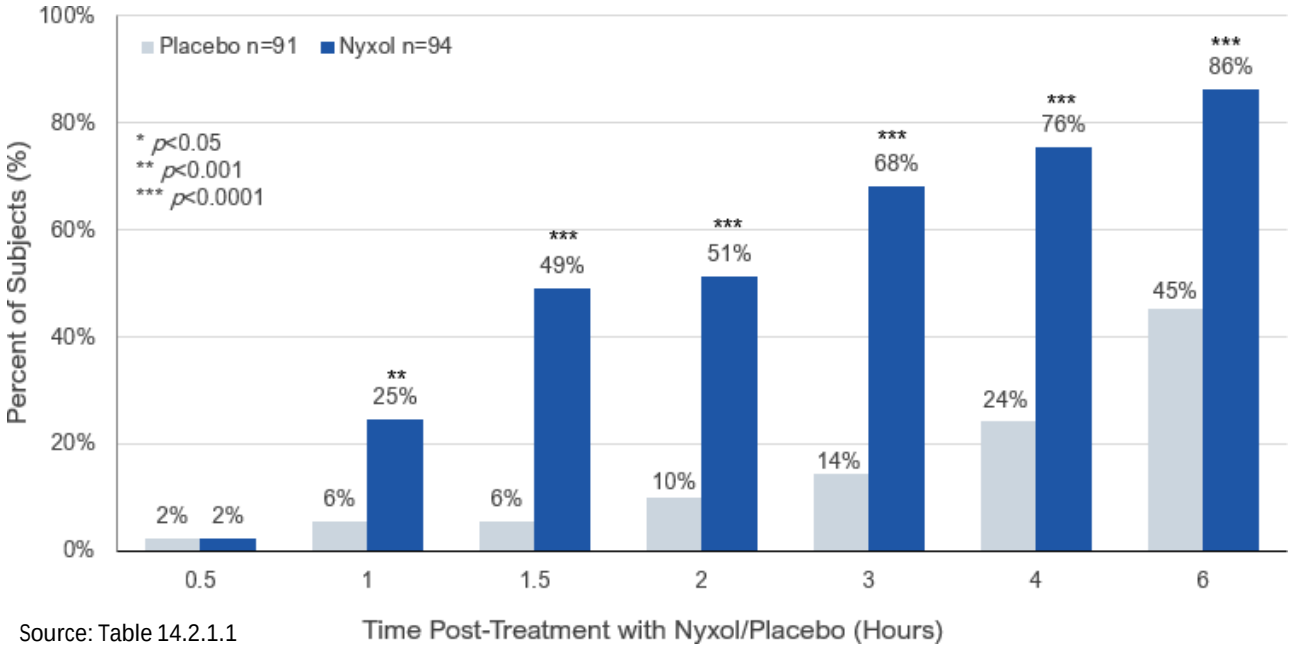
Source: Table 14.2.1.1 generated 26 Aug 2021. CI, confidence interval; PD, pupil diameter.
[a] From a logistic regression model with treatment, mydriatic agent, and light/dark irides as factors and the baseline PD as a covariate.

Percent of Subjects with Study Eye Returning to ≤ 0.2mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



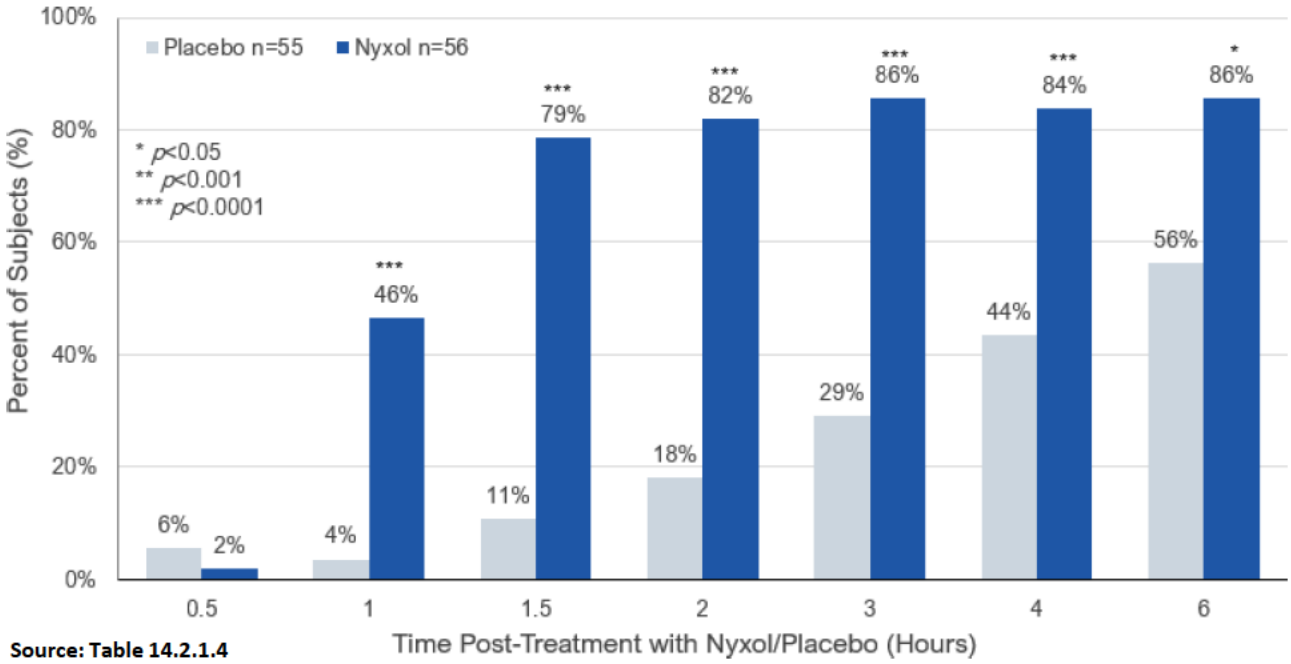
Source: Table 14.2.1.1

Percent of Subjects With Non-Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



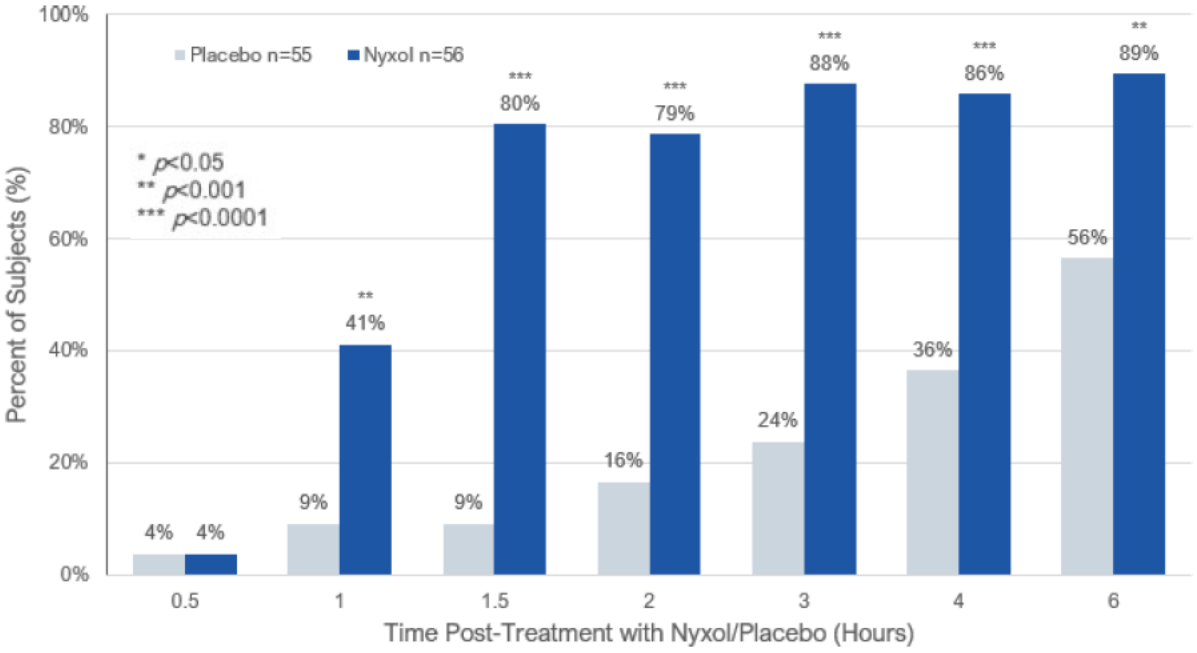
Source: Table 14.2.1.1

Percent of Subjects Receiving Phenylephrine With Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



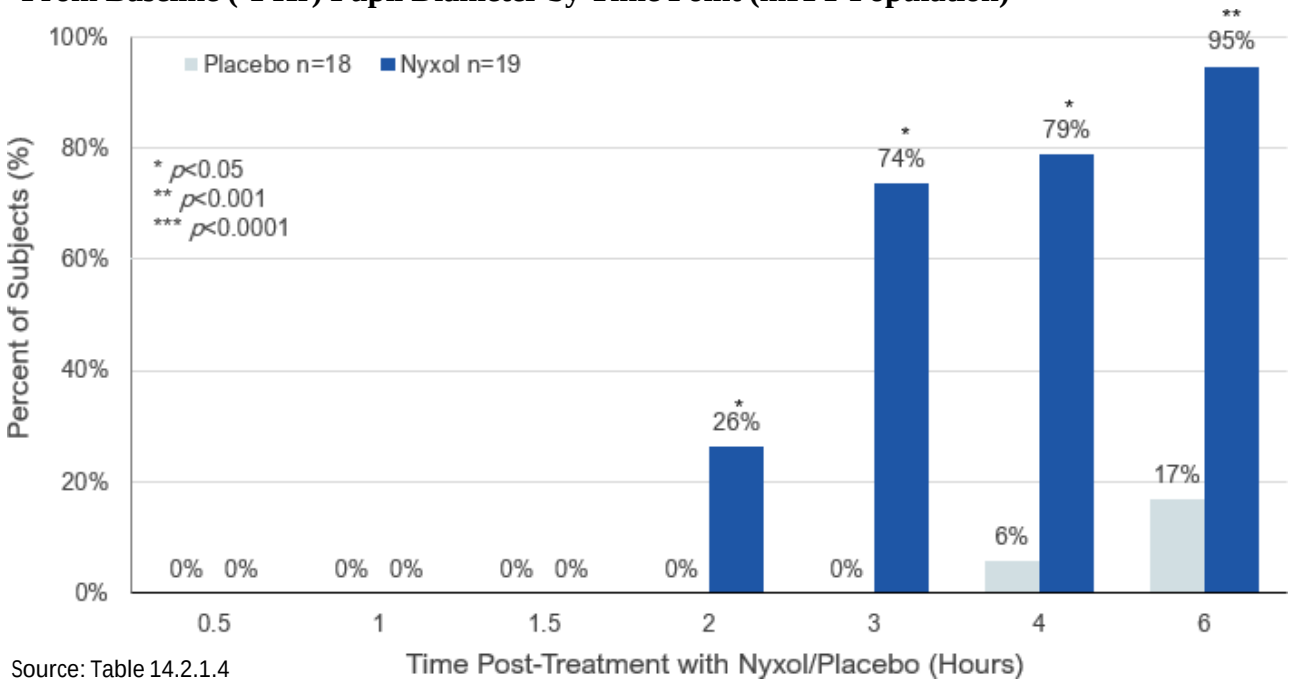
Source: Table 14.2.1.4

Percent of Subjects Receiving Phenylephrine With Non-study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



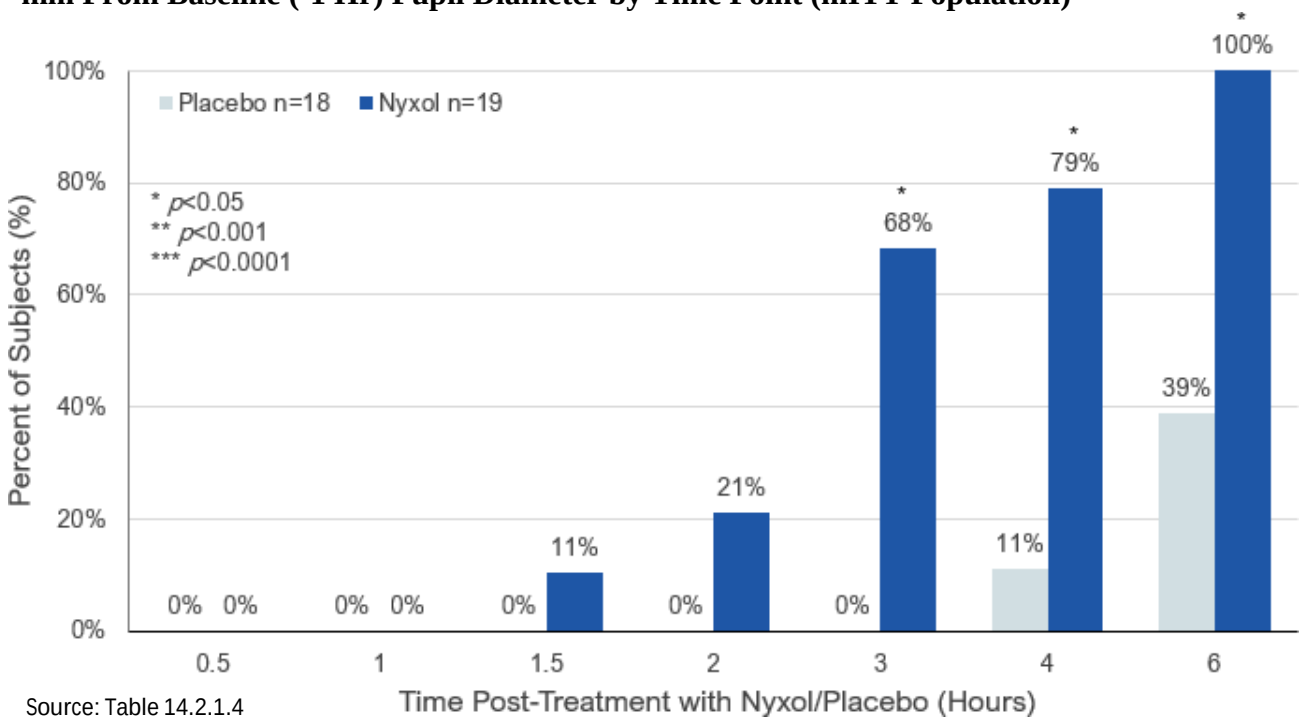
Source: Table 14.2.1.4

Percent of Subjects Receiving Tropicamide With Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



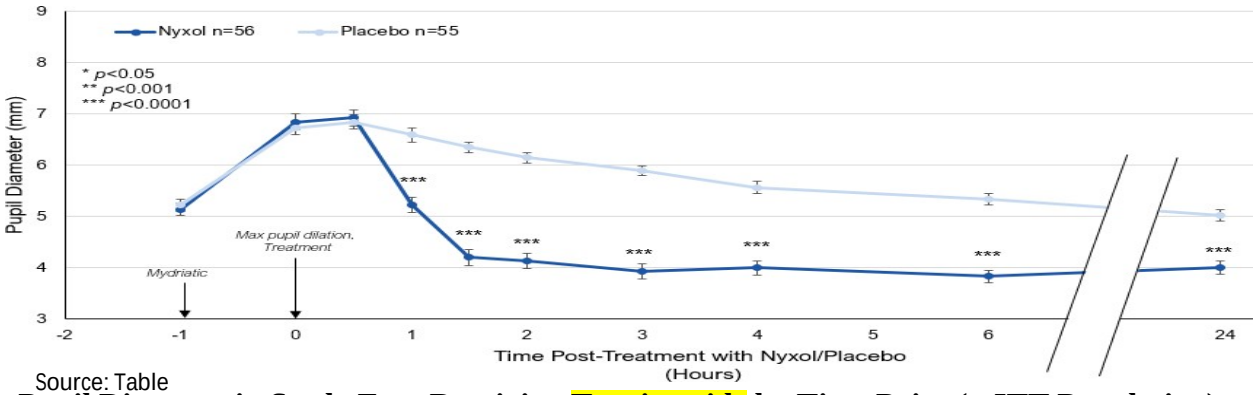
Source: Table 14.2.1.4

Figure 6: Percent of Subjects Receiving Paremyd With Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



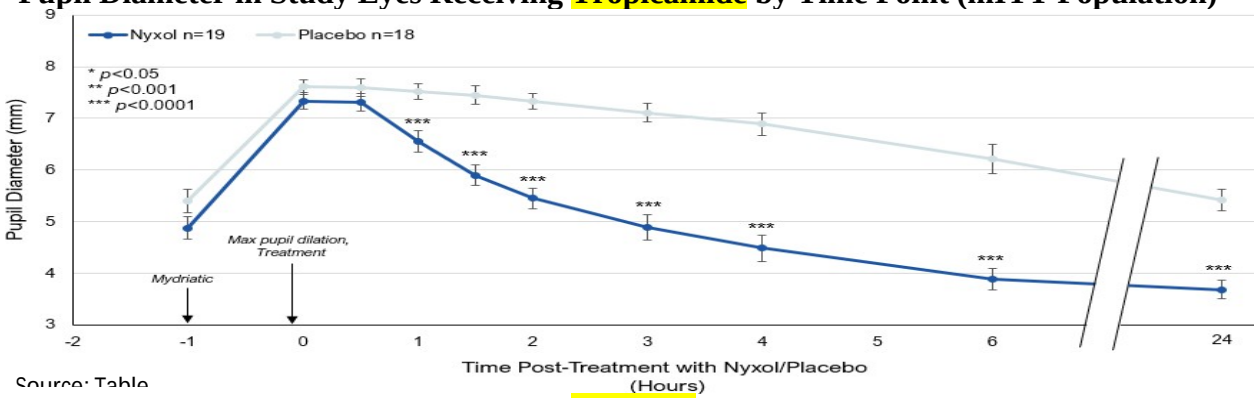
Source: Table 14.2.1.4

Pupil Diameter in Study Eyes Receiving Phenylephrine by Time Point (mITT Population)



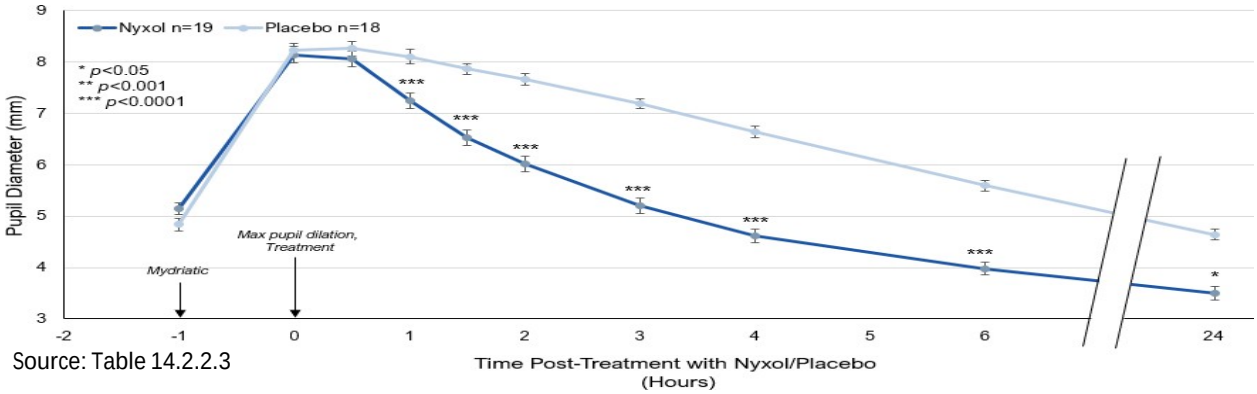
Source: Table

Pupil Diameter in Study Eyes Receiving Tropicamide by Time Point (mITT Population)



Source: Table

Pupil Diameter in Study Eyes Receiving Paremyd by Time Point (mITT Population)



Source: Table 14.2.2.3

Reviewer's Comments: *The effectiveness of Ryzumvi in reversing mydriasis is dependent on the agent used to induce the mydriasis. Ryzumvi was significantly more effective by 1-2 hours in subjects dilated with phenylephrine than with either Tropicamide or Paramyd. It is also notable that in the Ryzumvi group, the pupil constricts to a position more miotic (1 mm less) than baseline.*

Data Quality and Integrity
This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Dose/Dose Response
Dose response was not evaluated in this development program.

Durability of Response
The primary efficacy outcome was also measured at 2 hours, 3 hours, 4 hours, 6 hours, and 24 hours post-baseline. The percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline pupil diameter for those treated with POS vs. vehicle continued to increase.

6.2. OPI-NYXRM-302 MIRA-3

6.2.1. Study Design

Overview and Objective	-Same as MIRA-2
Trial Design	-Same as MIRA-2 except that will be 330 randomized and sampling for POS PK measurements were conducted in a subset of approximately 30 adult subjects at 2 study sites.
Inclusion Criteria	-Same as MIRA-2
Exclusion Criteria	-Essentially the same as MIRA-2
Schedule of Procedures	-Essentially the same as MIRA-2
Study Endpoints	-Essentially the same as MIRA-2, Pupil diameter and pupillary light reflex was measured with a NeurOptics VIP-300 pupillometer (mm). Accommodation was measured by the Royal Air Force (RAF) Near Point Rule (measured in cm and then converted to diopters). Glare testing was performed using the Marco BAT 2000, Glare discomfort was measured on a 4-point scale from 0 (none) to 3 (severe).

Protocol Amendments
The original clinical study protocol (Version 01) was issued on 23 September 2021. There were no protocol amendments.

6.2.2. Study Results

Compliance with Good Clinical Practices
This study was conducted per the principles of Good Clinical Practices (GCP).
Financial Disclosure
See Appendix 13.2 of this review.

Patient Disposition
A total of 368 subjects were enrolled and randomized into the study (POS group, n=244; placebo group, n=124). All 368 subjects received at least 1 dose of study medication and therefore were included in the Safety Population. All 368 subjects also had a Visit 1 PD measurement and therefore were included in the mITT Population. Twenty-three subjects were excluded from the PP Population; therefore, 345 subjects were included in the PP Population. Twenty-four subjects in the POS group were included in the PK Population (targeted at least 20 subjects for analysis).

Data Sets Analyzed

	POS n (%)	Placebo n (%)
All Randomized Population (ARP), n	244	124
Completed study	244	124
Safety Population	244	124
mITT Population	244	124
PP Population	230 (94.3)	115 (92.7)
PK Population	24 (9.8)	0

Source: Table 14.1.1 generated 31 Mar 2022.
ARP, All Randomized Population; mITT, modified Intent-to-Treat; PD, pupil diameter; PK, Pharmacokinetic; PP, Per Protocol. The Safety Population includes randomized subjects who received at least 1 dose of study medication. The mITT Population includes randomized subjects who received study treatment and had a Visit 1 PD measurement. The PP Population includes subjects in the mITT Population who had all Visit 1 PD measurements, had an increase > 0.2 mm in PD in the study eye at 0 min compared to baseline (-1 hr), and had no major protocol deviations considered to have significant impact on treatment outcome. The PK Population includes subjects in the POS group who had at least 1 PK sample taken at any post-treatment time point. There were 2 subjects with significant protocol deviations for failing to meet eligibility criteria, and 1 subject had a significant protocol deviation due to study treatment administration and PD assessment drastically out of window. In addition, there were 21 subjects who failed to reach dilation at 0 min from Baseline (pupil dilation ≤ 0.2 mm), including 1 of the protocol deviation subjects, for a total of 23 exclusions in the PP Population from the mITT Population.

Protocol Violations/Deviations

Sixty-one subjects had a total of 82 minor protocol deviations and 2 major protocol deviations (who were randomized subjects who failed to meet inclusion/exclusion criteria) during this study.

Demographic Characteristics (Safety Population)

Demographic Characteristic Statistic	POS (n=244)	Placebo (n=124)
Age, years		
Mean (SD)	34.2 (15.61)	35.6 (17.58)
Median	31.0	30.0
Min, max	12, 80	12, 80
Sex, n (%)		
Male	92 (38%)	59 (48%)
Female	152 (62%)	65 (52%)
Race, n (%) [a]		
White	182 (74.6)	93 (75.0)
American Indian or Alaska Native	1 (0.4)	0
Native Hawaiian or Other Pacific Islander Black or	4 (1.6)	0
African American	38 (15.6)	21 (16.9)
Asian	22 (9.0)	9 (7.3)
Other	0	1 (0.8)
Ethnicity, n (%)		
Hispanic or Latino	21 (8.6)	9 (7.3)
Not Hispanic or Latino	223 (91.4)	115 (92.7)
Study eye, n (%)		
OD	244 (100)	124 (100)
Iris color, n (%)		
Light blue Dark	39 (16.0)	18 (14.5)
blue	10 (4.1)	5 (4.0)
Blue with peripupillary brown	24 (9.8)	9 (7.3)
Uniform green	24 (9.8)	12 (9.7)
Green with brown iris ring	16 (6.6)	14 (11.3)
Central brown and peripheral green	19 (7.8)	11 (8.9)
Brown with some peripheral green	27 (11.1)	13 (10.5)
Brown	85 (34.8)	42 (33.9)
Irides type, n (%)		
Light	113 (46.3)	58 (46.8)
Dark	131 (53.7)	66 (53.2)

Baseline Ocular Characteristic Statistic	POS (n=244)	Placebo (n=124)
Distance vision/Near vision correction needed, n (%)		
Yes	156 (63.9)	78 (62.9)
No	88 (36.1)	46 (37.1)
Type of vision correction, n (%)	156 (63.9)	78 (62.9)
Glasses		
Spectacle correction type, n (%) [a]		
Near spectacle correction Distance	48 (19.7)	31 (25.0)
spectacle correction	143 (58.6)	68 (54.8)
Other	0	3 (2.4)
Mydriatic agent, n (%)		
Phenylephrine	146 (59.8)	74 (59.7)
Tropicamide	50 (20.5)	26 (21.0)
Paremyd	48 (19.7)	24 (19.4)
PD (-1 hr) in the study eye, mm		4.932 (1.1682)
Mean (SD)	5.141 (1.2558)	4.885
Median	5.265	2.12, 7.56
Minimum, maximum	2.06, 7.97	
PD (-1 hr) in the fellow eye, mm		4.828 (1.2283)
Mean (SD)	5.131 (1.2665)	4.750
Median	5.145	2.20, 7.34
Minimum, maximum	2.03, 8.02	
Maximum PD (0 min) in the study eye, mm		7.082 (1.2749)
Mean (SD)	7.214 (1.3165)	7.275
Median	7.475	4.12, 9.43
Minimum, maximum	2.22, 9.49	
Maximum PD (0 min) in the fellow eye, mm		
Mean (SD)	7.176 (1.3524)	7.057 (1.3360)
Median	7.385	7.265
Minimum, maximum	2.32, 9.85	3.25, 9.38
Accommodation (-1 hr) in the study eye, D		
Mean (SD)	7.44 (4.135)	7.62 (4.321)
Median	6.90	7.85
Minimum, maximum	2.0, 20.0	2.0, 22.2
Accommodation (-1 hr) in the fellow eye, D		
Mean (SD)	7.27 (4.046)	7.42 (4.001)
Median	6.90	6.90
Minimum, maximum	2.0, 22.2	2.0, 20.0
Accommodation (0 min) in the study eye, D		
Mean (SD)	5.49 (3.390)	5.47 (3.854)
Median	4.40	4.12
Minimum, maximum	2.0, 20.0	0.0, 25.0
Accommodation (0 min) in the fellow eye, D		
Mean (SD)	5.56 (3.686)	5.30 (3.322)
Median	4.26	4.00
Minimum, maximum	2.0, 25.0	0.0, 16.7

Baseline Ocular Characteristic Statistic	POS (n=244)	Placebo (n=124)
BCDVA (-1 hr) in the study eye, letters [b]		
Mean (SD)	56.9 (6.05)	56.7 (5.56)
Median	57.0	57.5
Minimum, maximum	13, 70	32, 70
BCDVA (-1 hr) in the fellow eye, letters [b]		
Mean (SD)	57.1 (4.65)	56.9 (4.76)
Median	57.0	57.0
Minimum, maximum	35, 70	39, 70
BCDVA (0 min) in the study eye, letters [b]		
Mean (SD)	55.3 (7.04)	54.7 (6.75)
Median	55.0	55.0
Minimum, maximum	11, 69	20, 70
BCDVA (0 min) in the fellow eye, letters [b]		
Mean (SD)	55.7 (5.67)	55.2 (5.56)
Median	55.0	55.0
Minimum, maximum	25, 70	38, 70
DCNVA (-1 hr) in the study eye, letters		
Mean (SD)	64.9 (11.19)	65.0 (11.89)
Median	70.0	70.0
Minimum, maximum	23, 83	30, 83
DCNVA (-1 hr) in the fellow eye, letters		
Mean (SD)	65.5 (10.99)	64.8 (11.87)
Median	70.0	69.5
Minimum, maximum	29, 85	30, 80
DCNVA (0 min) in the study eye, letters		
Mean (SD)	58.5 (14.34)	58.5 (14.23)
Median	64.0	64.0
Minimum, maximum	21, 85	23, 83
DCNVA (0 min) in the fellow eye, letters		
Mean (SD)	60.1 (13.39)	59.1 (13.56)
Median	64.5	64.0
Minimum, maximum	10, 85	25, 77
IOP (Screening) in the study eye, mmHg		
Mean (SD)	16.2 (2.90)	16.1 (2.79)
Median	16.0	16.0
Minimum, maximum	8, 30	8, 23
IOP (Screening) in the fellow eye, mmHg		
Mean (SD)	16.0 (2.68)	15.8 (2.90)
Median	16.0	16.0
Minimum, maximum	9, 24	7, 24

Reviewer's Comment: *Sixty percent of study subjects received one drop of phenylephrine 2.5% , 21% received one drop of tropicamide 1%, and 20% received one drop of Paremyd as their mydriatic agent.*

Efficacy Results – Primary Endpoint

Primary Endpoint: Percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline pupil diameter at 90 min.

Percent of Study Eyes Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)

Study Eye Time point	POS (n=244) n (%)	Placebo (n=124) n (%)	POS vs placebo [a]	
			Odds ratio (95% CI)	p-value
30 min	10 (4.1)	5 (4.0)	0.95 (0.33, 2.72)	0.9264
60 min	103 (42.2)	3 (2.4)	24.92 (8.34, 74.42)	<0.0001
90 min	142 (58.2)	7 (5.6)	21.38 (9.78, 46.73)	<0.0001
2 hr	162 (66.4)	9 (7.3)	23.54 (11.50, 48.17)	<0.0001
3 hr	193 (79.1)	17 (13.7)	23.03 (12.66, 41.92)	<0.0001
4 hr	210 (86.1)	21 (16.9)	29.06 (16.05, 52.60)	<0.0001
6 hr	221 (90.6)	44 (35.5)	16.69 (9.49, 29.32)	<0.0001
24 hr	218 (89.3)	89 (71.8)	3.36 (1.91, 5.91)	<0.0001

Source: Table 14.2.1.10 generated 31 Mar 2022. CI, confidence interval; PD, pupil diameter.
[1] From a logistic regression model with treatment as a factor and the baseline PD as a covariate.

Reviewer's comment: *In the mITT Population, a statistically significant greater percent of subjects treated with POS had study eyes that showed reversal of mydriasis, using a PD threshold of ≤ 0.2 mm from baseline at 90 min (primary endpoint) compared with the placebo treatment (58% vs 6%, respectively; OR 55.64 [23.04, 134.39]; p<0.0001.*

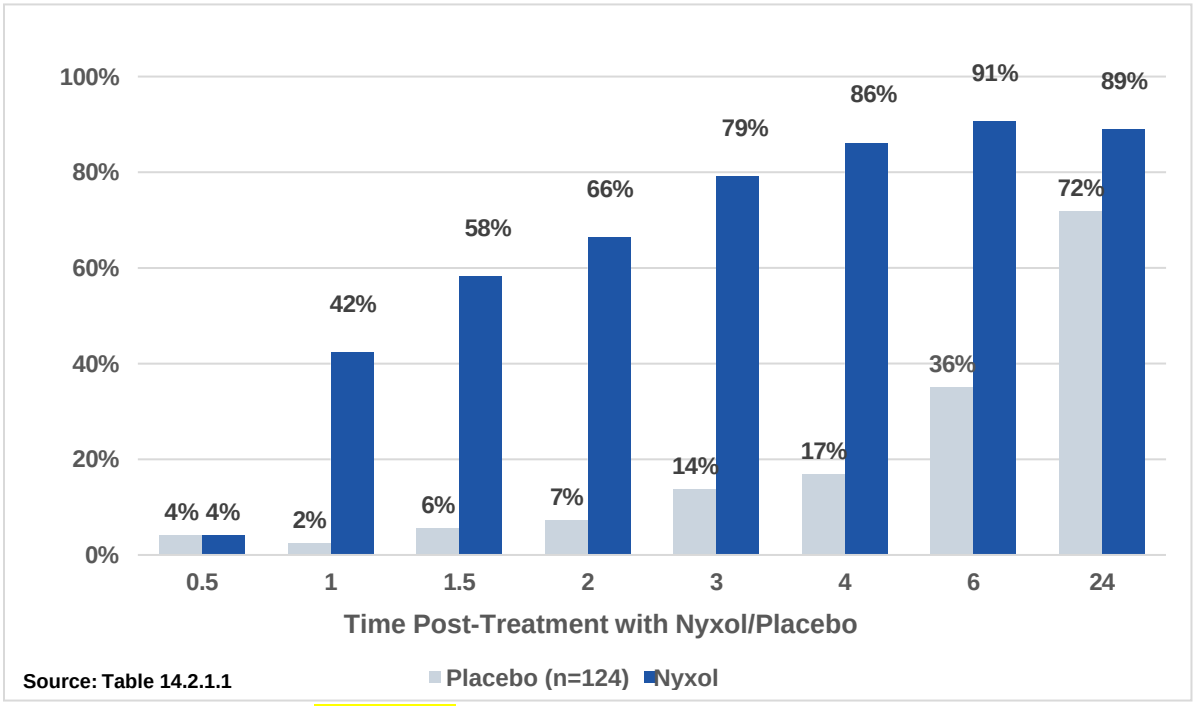
Percent of Fellow Eyes Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)

Fellow Eye Timepoint	POS (n=244) n (%)	Placebo (n=124) n (%)	POS vs placebo [a]	
			Odds ratio (95% CI)	p-value
30 min	9 (3.7)	5 (4.0)	0.78 (0.27, 2.29)	0.6511
60 min	67 (27.5)	6 (4.8)	6.71 (2.89, 15.54)	<0.0001
90 min	127 (52.0)	6 (4.8)	19.69 (8.57, 45.21)	<0.0001
2 hr	158 (64.8)	9 (7.3)	21.54 (10.55, 43.98)	<0.0001
3 hr	182 (74.6)	18 (14.5)	16.47 (9.23, 29.39)	<0.0001
4 hr	206 (84.4)	13 (10.5)	44.83 (22.79, 88.19)	<0.0001
6 hr	220 (90.2)	38 (30.6)	19.49 (11.07, 34.34)	<0.0001
24 h	221 (90.6)	80 (64.5)	5.04 (2.86, 8.85)	<0.0001

Source: Table 14.2.1.10 generated 31 Mar 2022. CI, confidence interval; PD, pupil diameter.
[1] From a logistic regression model with treatment as a factor and the baseline PD as a covariate.

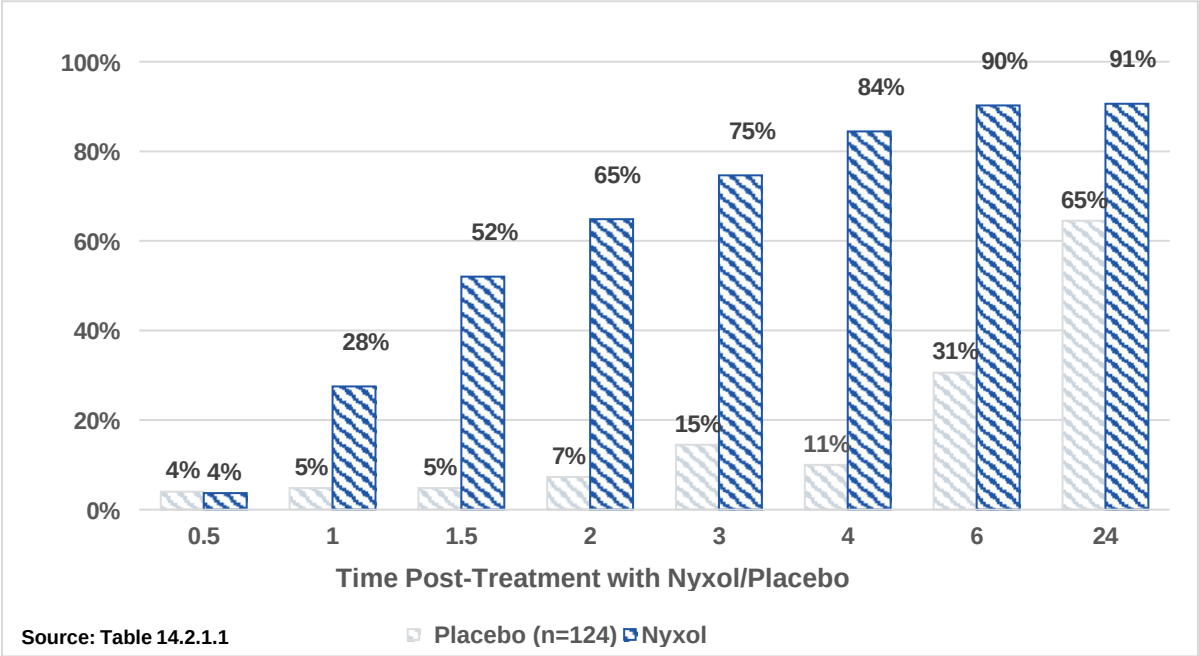
Reviewer's comment: *In the mITT Population, a statistically significant greater percent of subjects treated with POS had fellow eyes that showed reversal of mydriasis, using a PD threshold of ≤ 0.2 mm from baseline beginning at 60 min compared with the placebo treatment.*

Percent of Subjects with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



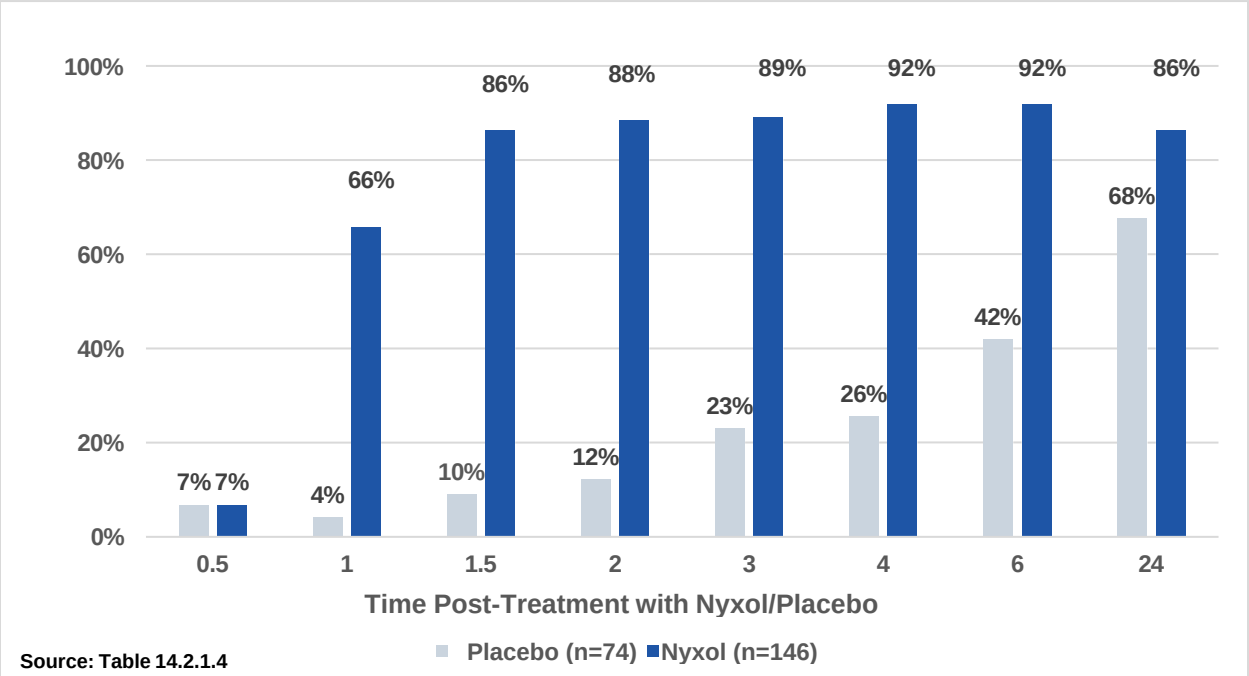
Source: Table 14.2.1.1

Percent of Subjects With Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



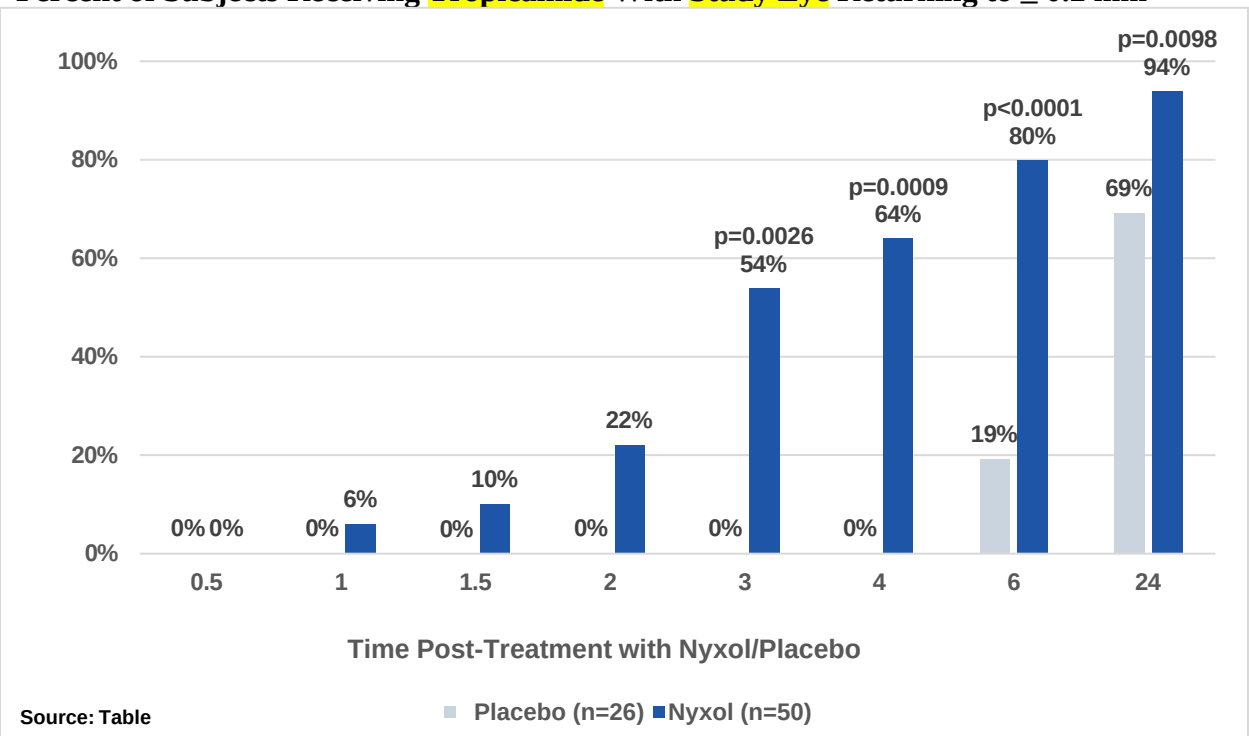
Source: Table 14.2.1.1

Percent of Subjects Receiving Phenylephrine With Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



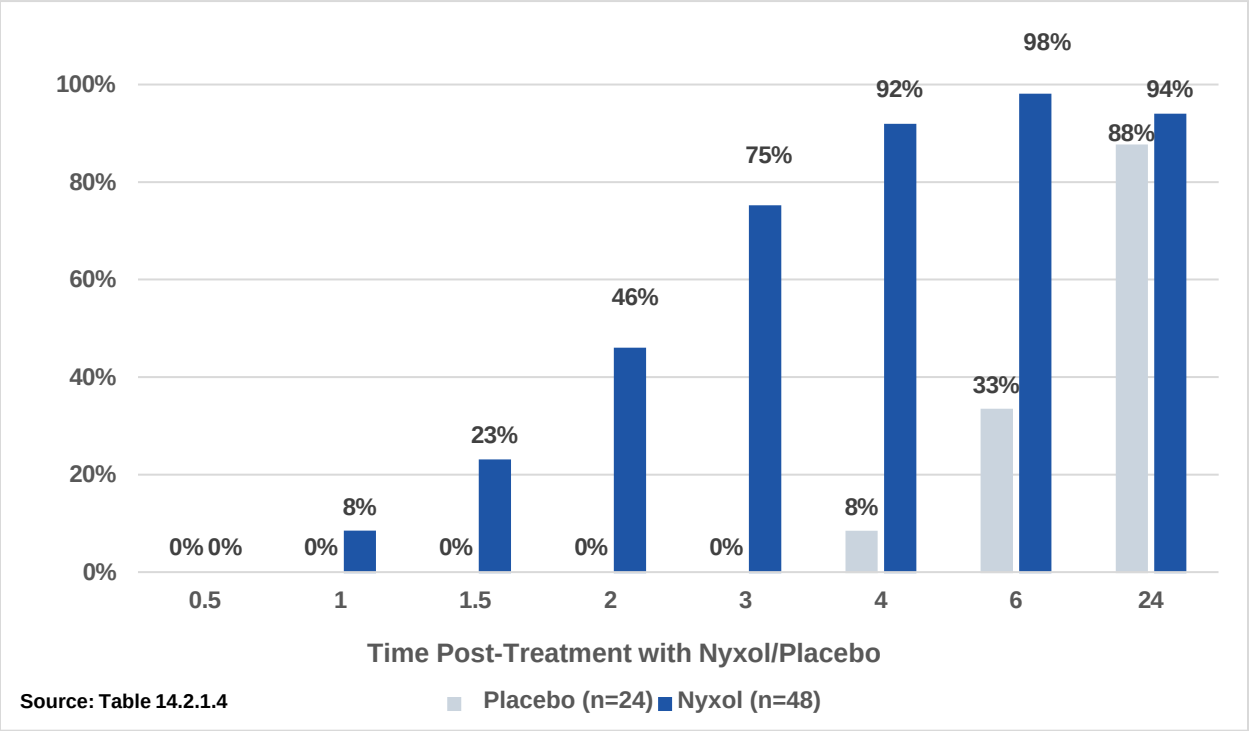
Source: Table 14.2.1.4

Percent of Subjects Receiving Tropicamide With Study Eye Returning to ≤ 0.2 mm



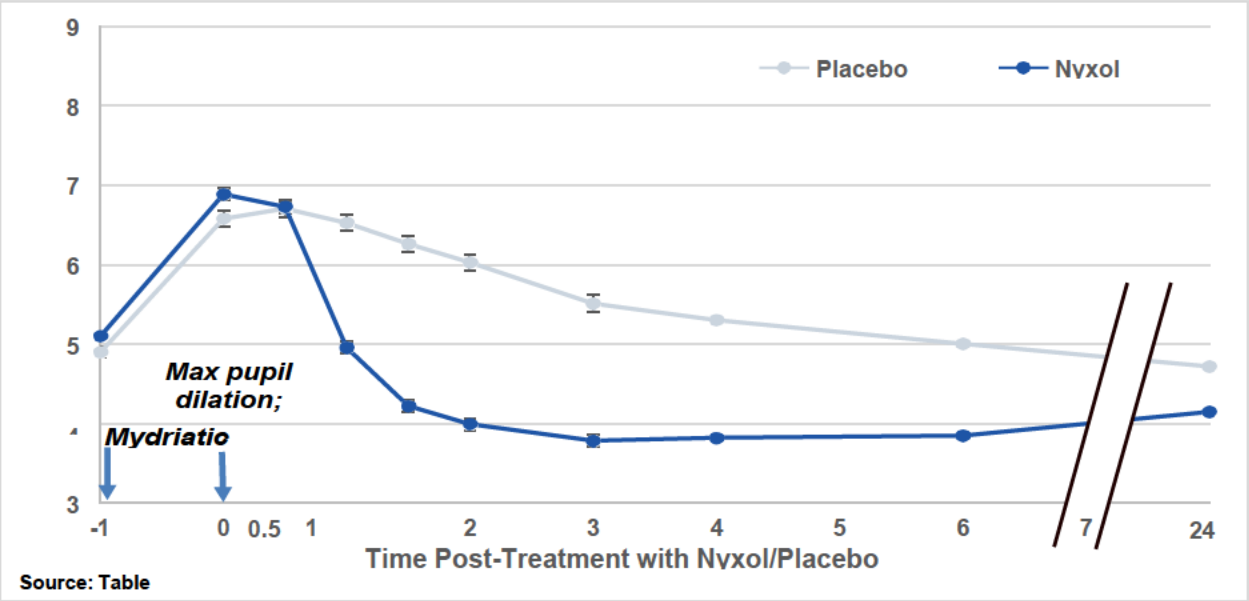
Source: Table

Percent of Subjects Receiving Paremyd With Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



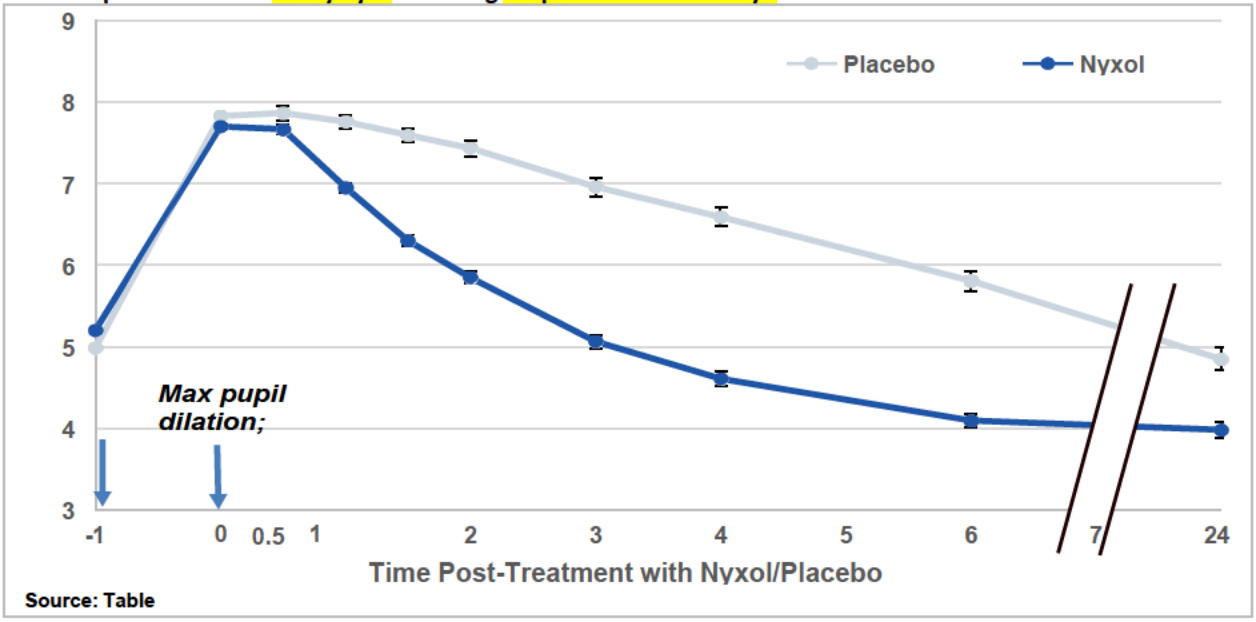
Source: Table 14.2.1.4

Mean Pupil Diameter in Study Eyes receiving Phenylephrine



Source: Table

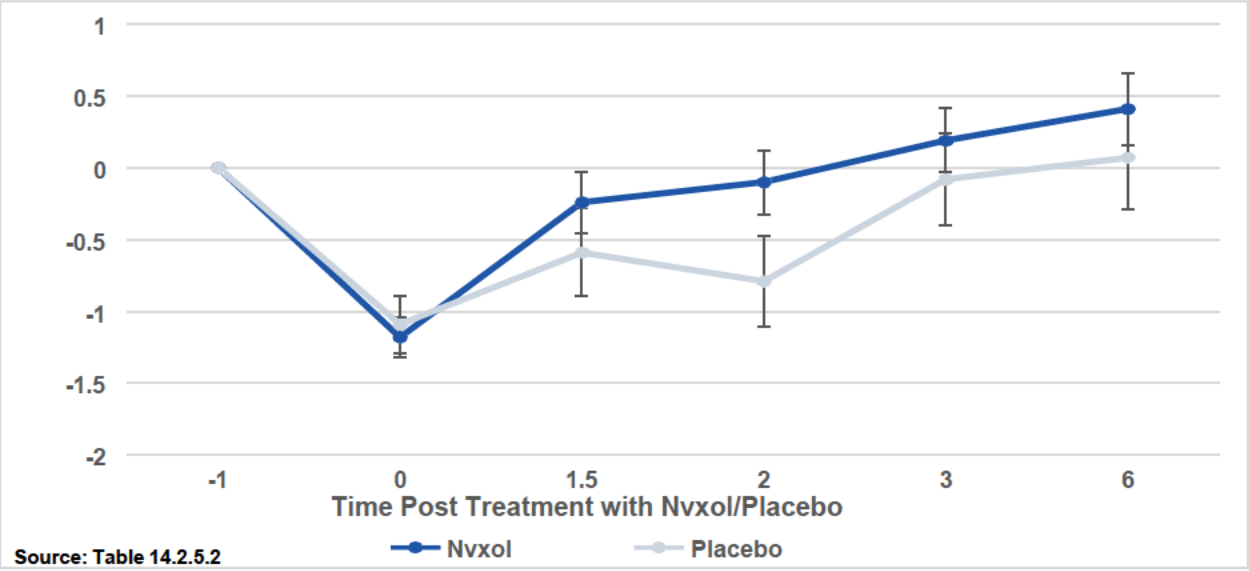
Mean Pupil Diameter in Study Eyes receiving Tropicamide or Paremyd



Source: Table

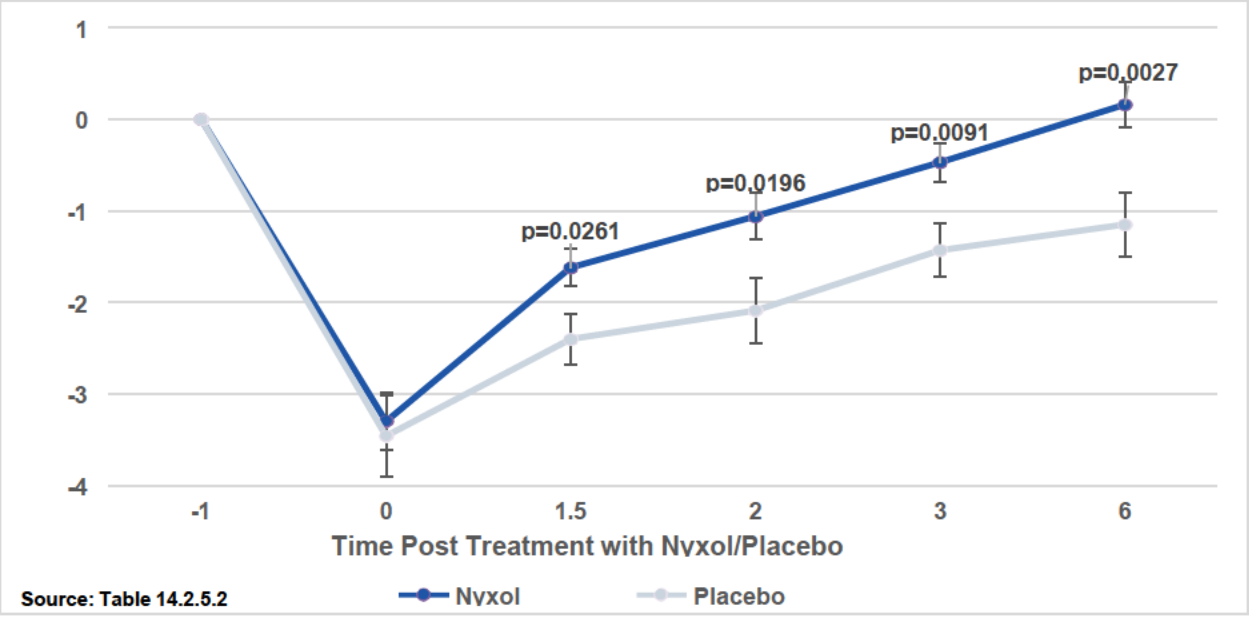
Reviewer's Comments: *The effectiveness of Ryzumvi in reversing mydriasis is dependent on the agent used to induce the mydriasis. Ryzumvi was significantly more effective by 1-2 hours in subjects dilated with phenylephrine than with either Tropicamide or Paramyd. It is also notable that in the Ryzumvi group, the pupil constricts to a position more miotic (1 mm less) than baseline.*

Mean Change in Accommodation in Study Eyes Receiving Phenylephrine (PP Population)



Source: Table 14.2.5.2

Mean Change in Accommodation in Study Eyes Receiving Tropicamide or Paremyd (PP Population)



Source: Table 14.2.5.2

Reviewer's Comments: *There is no significant change in accommodation in the subjects dilated with phenylephrine because these subjects did not lose accommodation.*

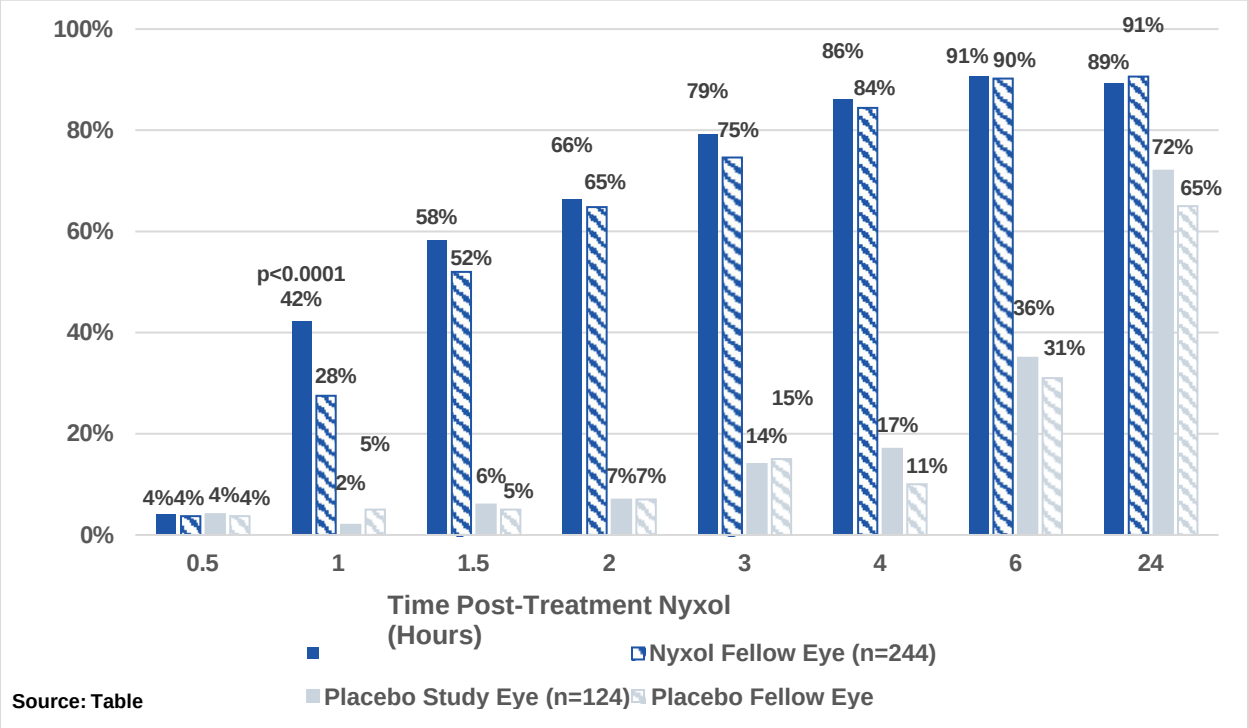
Data Quality and Integrity
This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

Percent study and fellow eyes returning to ≤ 0.2 mm from baseline PD:

For the PP Population, a similar percent of eyes treated with 2 drops (study eyes) or 1 drop (non-study eyes) of POS returned to baseline PD at 60 min and 90 min. Significantly more study eyes treated with 2 drops of POS showed a return to ≤ 0.2 mm from baseline PD compared with non-study eyes treated with 1 drop of POS at 2 hours (61.9% vs 51.2%; p=0.0363) and 3 hours (84.5% vs 69.0%; p=0.0063); the percentage of eyes treated with placebo that showed a return to ≤ 0.2 mm from baseline PD did not differ significantly between study eyes and non-study eyes at any time point.

Comparison of Study Eyes and Fellow Eyes Treated with POS Returning to ≤ 0.2 mm from Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)



Source: Table

6.3. OPI-NYXRMP-303 - MIRA-4

6.3.1. Study Design

Overview and Objective -Same as MIRA-2 except patient population is 3 to 11 years of age
Trial Design -Same as MIRA-2 except smaller number of subjects (23)
Inclusion criteria -Same as MIRA-2 except patient population is 3 to 11 years of age
Exclusion criteria -Similar to MIRA-2

Schedule of Procedures

	Screening Visit [a]	Visit 1 Mydriasis/Treatment				Visit 2 Follow-Up
Day	**1**	**1**				**2**
Time relative to study medication [b]		**-1 h Baseline**	**0 min ±5 min**	**90 min ±10 min**	**3 h ± 10 min**	**24 h +6 h**
Informed consent/Assent	X					
Subject identification number assigned	X					
Medical/Ophthalmic history	X					
Demographics	X					
Prior/Concomitant medications	X	X	X	X	X	X
HR/BP	X				X	X
Pupil diameter		X	X	X	X	X
BCDVA		X	X	X	X	X
Conjunctival hyperemia	X	X	X	X	X	X
Biomicroscopy	X					
Study medication kit number assigned (randomization)	X					
Mydriatic agent administration		X				
Nyxol/placebo administration			X			
AEs	X	X	X	X	X	X

AE, adverse event; BCDVA, best-corrected distance visual acuity; BP, blood pressure; ETDRS, Early Treatment Diabetic Retinopathy Study; HR, heart rate; PD, pupil diameter.
a. Screening Visit: if subject qualifies, this becomes Treatment Visit 1. The mydriatic agent will be given at -1 hour.
b. Assessments at each time point are shown in the order performed.
BCDVA will be measured in photopic conditions by a standard ETDRS illuminated chart (on wall or stand) at 4 m (letters recorded). For subjects who are unable to read the letters on a ETDRS chart, the Patti Pics Series ETDRS chart will be used. The same method will be used consistently for each subject (when possible).
c. It is recommended that a table-top slit lamp be used if at all possible. The use of a portable slit lamp or a hand-held light source should be reserved for subjects who cannot comply with the table-top slit lamp exam. The same method will be used consistently for each subject (when possible).

Study Endpoints

Efficacy was measured by assessment of PD. Safety and tolerability were evaluated by assessment of conjunctival hyperemia, BCDVA, HR and BP, and AEs. Pupil diameter was measured in mm under photopic conditions using the NeurOptics Pupillometer VIP-300, held close to the eye and the measurement taken when the circle on the screen was centered on the pupil. All pupil measurements were taken in the Light Off mode.

Conjunctival hyperemia was graded with a Cornea and Contact Lens Research Unit (CCLRU) card 4-point grading scale:

- None (0) = Normal. Appears white with a small number of conjunctival blood vessels easily observed
- Mild (+1) = Prominent, pinkish-red color of both the bulbar and palpebral conjunctiva
- Moderate (+2) = Bright, scarlet red color of the bulbar and palpebral conjunctiva
- Severe (+3) = Beefy red with petechiae, dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage

Best-corrected distance visual acuity was measured in photopic conditions by a standard Early Treatment Diabetic Retinopathy Study (ETDRS) illuminated chart (on wall or stand) at 4 m (letters recorded). Resting HR and BP were assessed as per the site's normal equipment and procedures. Efficacy endpoints were analyzed by study eye and fellow eye and included:

- Percentage of subjects returning to ≤ 0.2 mm from baseline (-1 hr) photopic PD at each remaining time point (0 min, 90 min, 3 hours, and 24 hours)
- Change (in mm) in photopic PD from max pupil dilation (0 min) at each time point (90 min, 3 hours, and 24 hours)
- Time (hours) to return to ≤ 0.2 mm from baseline (-1 hr) photopic PD (time-savings analysis)

The primary safety measures were conjunctival hyperemia, impairment in visual acuity (BCDVA), vital signs (HR and BP), and AEs.

Safety analyses included:

- Change from baseline (-1 hr) in conjunctival hyperemia grading (CCLRU images) at each time point (0 min, 90 min, 3 hours, and 24 hours) for the study eye and fellow eye
- Change from baseline (-1 hr) in BCDVA at 0 min, 90 min, 3 hours, and 24 hours for the study eye and fellow eye
- Change from baseline (-1 hr) in vital signs (HR and BP) at 3 hours and 24 hours

Protocol Amendments

The original clinical study protocol (Version 01) was issued on 26 October 2021. There were no protocol amendments. This study was conducted per the principles of Good Clinical Practices (GCP).

6.3.2 Study Results

Patient Disposition

Twenty-three subjects (POS group, n=11; placebo group, n=12) were enrolled and randomized into the study; all subjects completed the study and completed study medication dosing. All 23 subjects received at least 1 dose of study medication and therefore were included in the Safety Population. All 23 subjects also had a Visit 1 PD measurement and therefore were included in the mITT Population. One subject was excluded from the PP Population (from the POS group due to lack of dilation); therefore, 22 subjects were included in the PP Population.

Subject Disposition (ARP)

	POS n (%)	Placebo n (%)
All Randomized Population (ARP), n	11	12
Completed study Discontinued study early	11 (100%) 0	12 (100%) 0

Source: Table 14.1.1 generated 26 Apr 2022. ARP, All Randomized Population.
NOTE: The ARP is defined as all randomized subjects.

Data Sets Analyzed

	POS n (%)	Placebo n (%)
ARP, n	11	12
Safety Population	11	12
mITT Population	11	12
PP Population	10 (90.9%)	12

Source: Table 14.1.1 generated 26 Apr 2022.
ARP, All Randomized Population; mITT, modified Intent-to-Treat; PD, pupil diameter; PP, Per Protocol.
NOTE: The ARP is defined as all randomized subjects. The Safety Population is randomized subjects who received at least 1 dose of study medication. The mITT Population is randomized subjects who received study medication and had a Visit 1 post-baseline PD measurement in the study eye. The PP Population is subjects in the mITT Population who had all Visit 1 PD measurements in the study eye, had an increase of > 0.2 mm in PD in the study eye at 0 min compared to baseline (-1 hr), and had no major protocol deviations considered to have significant impact on treatment outcome.

Protocol Violations/Deviations

One subject had 1 minor protocol deviation during this study, in which assessment was 2 min early at the 3-hour time point. There were no major protocol deviations during this study.

Demographics Characteristics (ARP)

Demographic Characteristic Statistic	POS (n=11)	Placebo (n=12)
Age, years		
n	11	12
3 to 5	5 (45.5)	6 (50.0)
6 to 11	6 (54.5)	6 (50.0)
Mean (SD)	6.9 (2.74)	5.8 (2.66)
Median	7.0	5.5
Min, max	3, 11	3, 10
Sex, n (%)		
Male	6 (54.5)	5 (41.7)
Female	5 (45.5)	7 (58.3)
Race, n (%) [a]		
White	11 (100)	10 (83.3)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander Black	0	0
or African American	0	2 (16.7)
Asian	0	0
Ethnicity, n (%)		
Hispanic or Latino	2 (18.2)	1 (8.3)
Not Hispanic or Latino	9 (81.8)	11 (91.7)
Study eye, n (%)		
OD	11 (100)	12 (100)
Iris color, n (%)		
Light blue	0	3 (25.0)
Dark blue	1 (9.1)	0
Blue with peripupillary brown	3 (27.3)	1 (8.3)
Uniform green	1 (9.1)	1 (8.3)
Green with brown iris ring	0	1 (8.3)
Central brown and peripheral green	0	2 (16.7)
Brown with some peripheral green	3 (27.3)	2 (16.7)
Brown	3 (27.3)	2 (16.7)
Irides type, n (%)		
Light	5 (45.5)	6 (50.0)
Dark	6 (54.5)	6 (50.0)

Baseline Ocular Characteristic Statistic	POS (n=11)	Placebo (n=12)
Age, years 3 to 5	5 (45.5)	6 (50.0)
6 to 11	6 (54.5)	6 (50.0)
Mean (SD)	6.9 (2.74)	5.8 (2.66)
Median	7.0	5.5
Min, max	3, 11	3, 10
Sex, n (%) Male	6 (54.5)	5 (41.7)
Female	5 (45.5)	7 (58.3)
Race, n (%) [a] White	11 (100)	10 (83.3)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander Black or	0	0
African American	0	2 (16.7)
Asian	0	0
Ethnicity, n (%) Hispanic or Latino	2 (18.2)	1 (8.3)
Not Hispanic or Latino	9 (81.8)	11 (91.7)
Study eye, n (%)		
OD	11 (100)	12 (100)
Iris color, n (%) Light blue	0	3 (25.0)
Dark blue	1 (9.1)	0
Blue with peripupillary brown	3 (27.3)	1 (8.3)
Uniform green	1 (9.1)	1 (8.3)
Green with brown iris ring	0	1 (8.3)
Central brown and peripheral green	0	2 (16.7)
Brown with some peripheral green	3 (27.3)	2 (16.7)
Brown	3 (27.3)	2 (16.7)
Irides type, n (%) Light	5 (45.5)	6 (50.0)
Dark	6 (54.5)	6 (50.0)
Mydriatic agent, n (%) Phenylephrine	7 (63.6)	7 (58.3)
Tropicamide	2 (18.2)	2 (16.7)
Paremyd	2 (18.2)	3 (25.0)
PD (-1 hr) in the study eye, mm Mean (SD)	6.067 (0.5570)	5.853 (0.5763)
Median	5.860	5.805
Minimum, maximum	5.37, 7.13	5.03, 6.76
PD (-1 hr) in the fellow eye, mm	6.074 (0.5839)	5.947 (0.6157)
Mean (SD) Median	5.900	5.945
Minimum, maximum	5.02, 7.01	4.85, 7.02
Maximum PD (0 min) in the study eye, mm	7.319 (1.0262)	7.333 (0.7815)
Mean (SD) Median	7.250	7.220
Minimum, maximum	5.91, 9.01	6.14, 8.35
Maximum PD (0 min) in the fellow eye, mm	7.376 (0.9858)	7.188 (0.7983)
Mean (SD) Median	7.490	7.210
Minimum, maximum	5.80, 9.04	5.85, 8.70
BCDVA (-1 hr) in the study eye, letters [b]	55.1 (4.04)	53.8 (4.90)
Mean (SD) Median	56.0	54.5

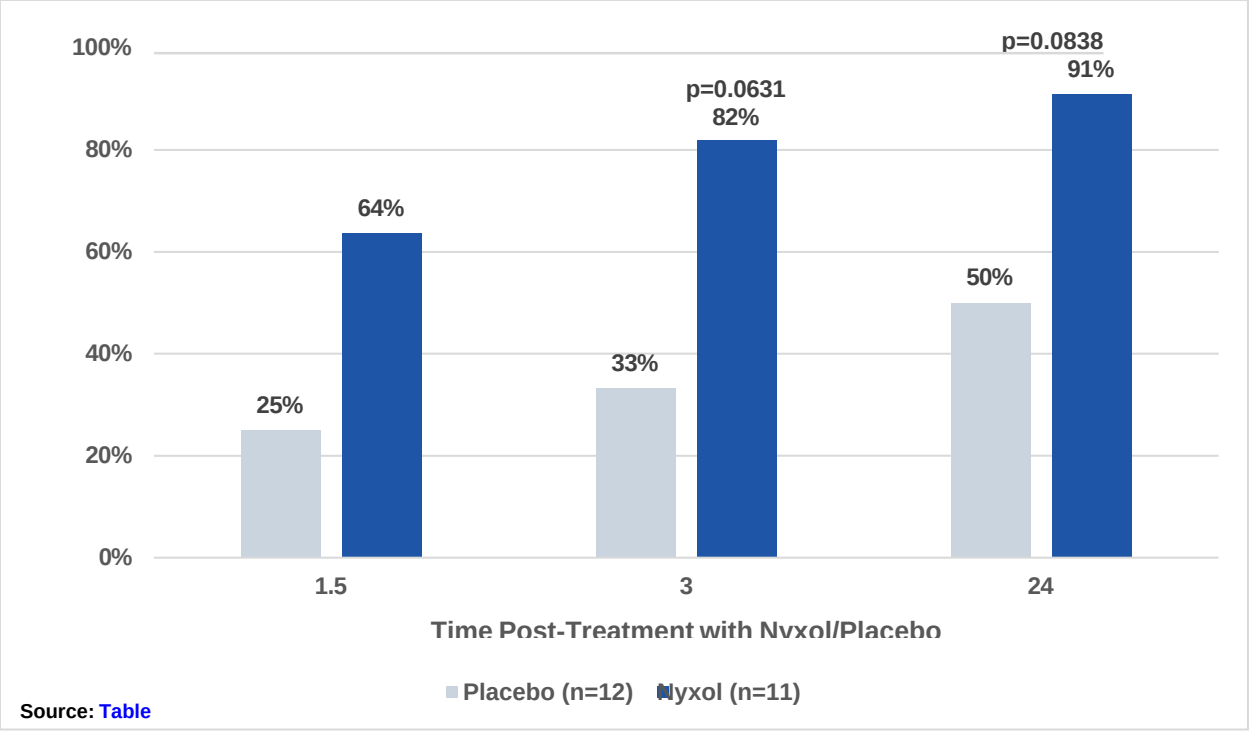
Minimum, maximum	49, 60	49, 64
BCDVA (-1 hr) in the fellow eye, letters [b] Mean (SD) Median Minimum, maximum	55.0 (3.71) 55.0 49, 60	52.9 (4.21) 52.5 49, 60
BCDVA (0 min) in the study eye, letters [b] Mean (SD) Median Minimum, maximum	53.9 (3.73) 55.0 48, 59	53.5 (4.30) 54.0 49, 60
BCDVA (0 min) in the fellow eye, letters [b] Mean (SD) Median Minimum, maximum	54.7 (4.20) 55.0 49, 60	52.6 (4.64) 50.5 47, 60

Sources: Table 14.1.2.1 and Table 14.2.1.5 generated 26 Apr 2022.
BCDVA, best-corrected distance visual acuity; OD, right eye; PD, pupil diameter; SD, standard deviation.
d. Subjects can be included in more than 1 category, so the sum of the percentages may be greater than 100%.
e. For BCDVA, the number of letters read is from the 4-m distance only, so that 55 letters read is equivalent to a Snellen acuity of 20/20.

Reviewer's Comment: *Sixty percent of study subjects received one drop of phenylephrine 2.5% , 17% received one drop of tropicamide 1% and 22% received one drop of Paremyd as their mydriatic agent.*

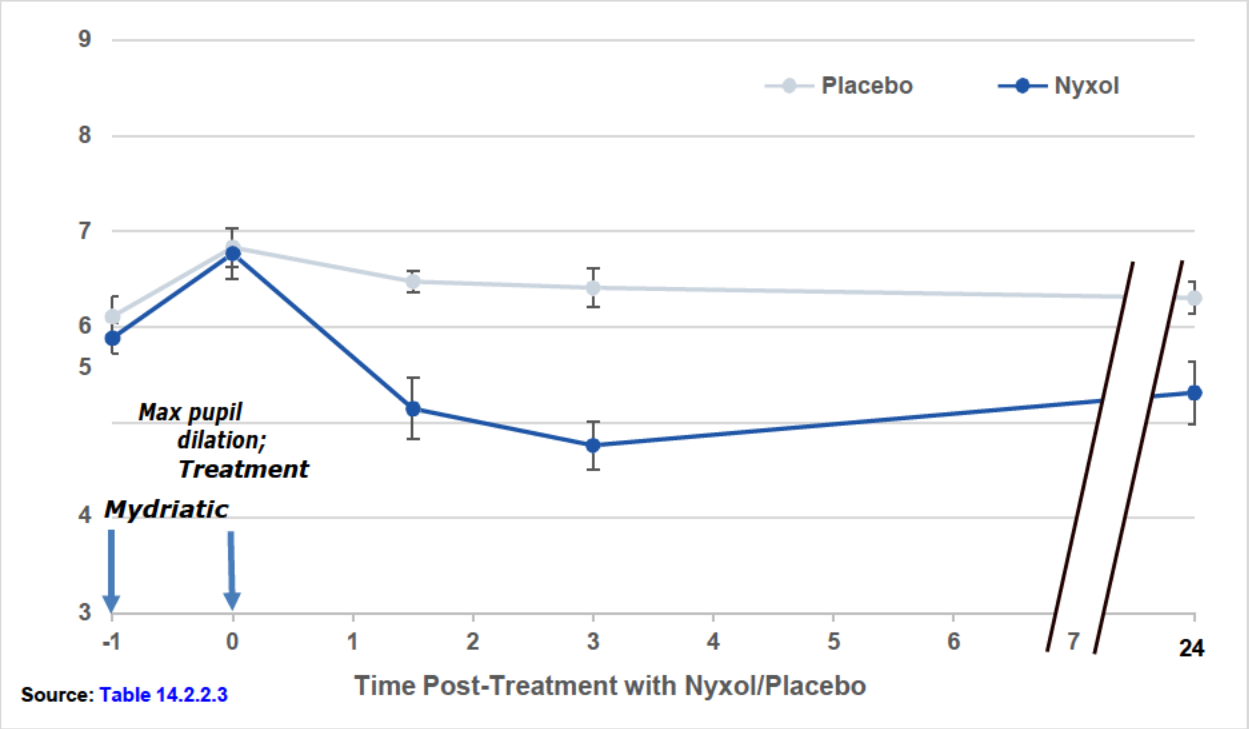
Efficacy Results – Primary Endpoint

Percent of Pediatric Subjects With Study Eye Returning to ≤ 0.2 mm From Baseline, mITT



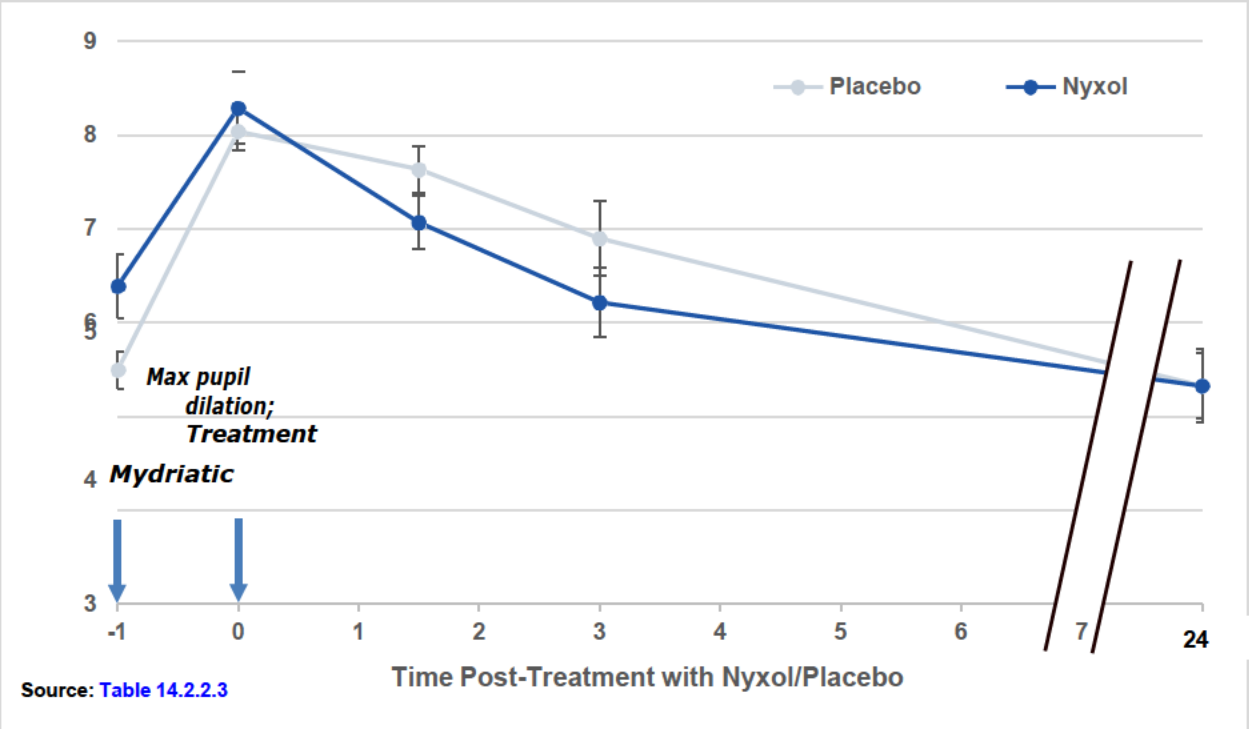
Source: Table

Mean Pupil Diameter in Study Eyes receiving Phenylephrine - mIT



Source: Table 14.2.2.3

Mean Pupil Diameter in Study Eyes Receiving Tropicamide or Paremyd



Source: Table 14.2.2.3

7. Integrated Review of Effectivenes

7.1.1. Primary Endpoints

Two trials (OPI-NYXRM-301 (MIRA-2) and OPI-NYXRM-302 (MIRA-3) studied the same endpoint and demonstrated a statistically significant increase in the percentage of POS-treated subjects returning to ≤ 0.2 mm from baseline PD compared to placebo at 90 minutes post-treatment. OPI-NYXRMP-303 (MIRA-4) was a pediatric safety study with consistent findings.

7.1.2. Primary Efficacy by Mydriatic Agent

Reviewer's Comments: *The effectiveness of Ryzumvi in reversing mydriasis is dependent on the agent used to induce the mydriasis. Ryzumvi was significantly more effective by 1-2 hours in subjects dilated with phenylephrine than with either Tropicamide or Paramyd. It is also notable that in the Ryzumvi group, the pupil constricts to a position more miotic (1 mm less) than baseline.*

8. Review of Safety

8.1. Safety Review Approach

A total of 11 trials were included in this NDA to support the safety of Phentolamine Ophthalmic Solution. A total of 647 subjects were exposed to at least 1 dose up to including 0.75% Phentolamine Ophthalmic Solution in each eye. 593 subjects received the to be marketed dose of 0.75% solution and higher. Three studies, MIRA-2, MIRA-3 and MIRA-4 were completed in healthy pediatric and adult subjects.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Phentolamine Mesylate Clinical Exposure in Applicant-conducted Studies

Study	Dose	1 Day	**4–5** Days	14 Days
OP-NYX-001	0.2% PMOS	30		
OP-NYX-002	0.2% PMOS 0.4% PMOS 0.8% PMOS	16		
OP-NYX-SNV	1% PMOS	16		
OP-NYX-01a2	0.5% PMOS			20
OP-NYX-01a2	1% PMOS			20
OPI-NYXG-201	1% PMOS			19
OPI-NYXRM-201	1% PMOS	31		
OPI-NYXRM-301	0.75% POS	94		
OPI NYXP-201	0.75% POS + 0.4% LDP		74	
OPI-NYXRM-302	0.75% POS	244		
OPI-NYXRM-303	0.75% POS	11		
OPI-NYXDLD-301	0.75% POS			72
Total		442	74	131

Demographic Profile of Patients (Integrated Safety Population)

Demographics and Baseline Characteristics	POS (N =642)	Placebo (N = 393)
Age (Years)		
N	642	393
Mean (SD)	37.5 (15.83)	39.5 (17.39)
Median	36.0	40.0
Min, Max	0, 80	3, 81
Gender [n (%)]		
Male	226 (35.2)	148 (37.7)
Female	415 (64.6)	245 (62.3)
Race [n (%)]*		
White	511 (79.6)	318 (80.9)
American Indian or Alaska Native	5 (0.8)	3 (0.8)
Native Hawaiian or Other Pacific Islander	5 (0.8)	0
Black or African American	82 (12.8)	57 (14.5)
Asian	31 (4.8)	17 (4.3)
Other	12 (1.9)	2 (0.5)
Ethnicity [n (%)]		
Hispanic or Latino	57 (8.9)	38 (9.7)
Not Hispanic or Latino	528 (82.2)	347 (88.3)
Iris Color [n (%)]		
Light blue	82 (12.8)	61 (15.5)
Dark blue	18 (2.8)	16 (4.1)
Blue with peri-pupillary brown	65 (10.1)	37 (9.4)
Uniform green	45 (7.0)	31 (7.9)
Green with brown iris ring	46 (7.2)	35 (8.9)
Central brown and peripheral green	47 (7.3)	26 (6.6)
Brown with some peripheral green	62 (9.7)	35 (8.9)
Brown	221 (34.4)	123 (31.3)
Other	33 (5.1)	9 (2.3)
Unknown	23 (3.6)	20 (5.1)
Irides Type [n (%)]		
Light	277 (43.1)	185 (47.1)
Dark	342 (53.3)	188 (47.8)
Unknown	23 (3.6)	20 (5.1)
Mydriatic Agent [n (%)]		
Phenylephrine	225 (35.0)	136 (34.6)
Tropicamide	87 (13.6)	46 (11.7)
Paremyd®	69 (10.7)	45 (11.5)
Not Applicable	261 (40.7)	166 (42.2)

8.2.2. Adequacy of the safety database

The overall exposure to the Phentolamine ophthalmic solution 0.75% and the size of the database and clinical evaluations conducted during development were adequate to assess the safety profile of this drug product.

8.3. Adequacy of Applicant's Clinical Safety Assessments Issues Regarding Data Integrity and Submission Quality

No issues with data integrity were identified. The application was of sufficient quality to allow a substantive review.

8.3.1. Categorization of Adverse Events

Adverse events for all studies were coded according to the MedDRA dictionary. A treatment emergent adverse event (TEAE) was defined as any AE that was new or worsened in severity after the first dose of study drug. Treatment-emergent AEs were categorized by system organ class (SOC) and preferred term (PT), seriousness, severity, and relationship to study drug.

8.3.2. Routine Clinical Tests

The routine clinical testing to evaluate the safety concerns associated with the treatment of ophthalmic conditions were adequately addressed in the design and conduct of the trials.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in any of the applicant-conducted clinical studies.

8.4.2. Serious Adverse Events

No SAEs occurred in any of the applicant-conducted clinical studies.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations during this study.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Ocular and Non-ocular TEAEs Occurring in ≥ 3% of POS-Treated Subjects by Frequency (Integrated Safety Population)

OCULAR TEAEs	POS (N = 642) n (%)	Placebo (N = 393) n (%)
Conjunctival hyperemia	75 (12)	3 (0.8)
Instillation site pain/stinging/burning	111 (16)	8 (2.0)
NON-OCULAR TEAEs		
Dysgeusia	36 (6.0)	4 (1.0)

Reviewer's Comments: *The most common adverse events occurring in POS treated patients were instillation site pain/burning/discomfort (16%) and conjunctival hyperemia (12%), and dysgeusia (6%).*

8.4.5. Laboratory Findings

No clinical laboratory evaluations were performed during the Applicant-conducted clinical studies.

8.4.6. Vital Signs

No clinical changes were observed with systolic blood pressure or diastolic blood pressure in subjects treated with POS. No clinical changes were observed with heart rate in subjects treated with POS. Respiration as a safety parameter was not evaluated in Applicant-conducted clinical studies.

8.4.7. Electrocardiograms (ECGs)

Electrocardiograms were not assessed during this development program.

8.5. Safety Analyses by Demographic Subgroups

No difference in safety was observed between pediatric and adult subjects. In POS-treated subjects, TEAEs reported in the studies did not significantly differ between males (21%) and females (24%) in the clinical studies. In POS-treated subjects, TEAEs reported by subject in the pooled studies did not significantly differ between the races (White [32%], Black/African American [27%], Asian [20%], Other [13%]).

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

No carcinogenicity studies have been conducted with phentolamine for this NDA.

8.6.2. Human Reproduction and Pregnancy

No adequate and well-controlled trials of phentolamine have been conducted in pregnant or lactating women for this NDA.

8.6.3. Pediatrics and Assessment of Effects on Growth

The Applicant has requested a partial waiver for ages 0 to 3 years. A pediatric assessment for ages > or equal to 3 -18 years. The PeRC meeting was held on August 8, 2023. The PeRC agreed with the partial waiver of pediatric studies.

8.6.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Phentolamine does not have any abuse potential.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

There have been no previous approvals for this topical product.

8.7.2. Additional Safety Issues From Other Disciplines

None.

8.8. Integrated Assessment of Safety

The data from MIRA-2, MIRA-3 and MIRA-4 support the use of Ryzumvi (phentolamine mesylate ophthalmic solution) 0.75% for adults and pediatric patients aged (b)(4) or older for the proposed indication. See Section 8.9.2 of this review.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for the NDA. There were no issues that were felt to benefit from discussion at an Advisory Committee Meeting.

10. Risk Evaluation and Mitigation Strategies (REMS)

There are no recommended Risk Evaluation or Mitigation strategies for this NDA.

11. Appendices

11.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

11.2. Financial Disclosure

Covered Clinical Study (MIRA-2, MIRA-3, and MIRA-4)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 21		
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): 4		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 4		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
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) 21		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

11.3. List of Investigators

OPI-NYXRM-301 (MIRA-2)
List and Description of Investigators and Participants in the Study

SITE ID#	Principal Investigators	Affiliation	Phone and Email	Number of Subjects Randomized/Completed
01	Marc Abrams, MD	Abrams Eye Center 2322 East 22nd St., Suite 102 Cleveland, OH 44115	PH 216-937-2020 Email: marc.a.abrams@gmail.com	18 / 18
02	Douglas Day, MD	Coastal Research Associates 11205 Alpharetta Highway, Suite J-3 Roswell, GA 30076	PH 770-777-1928 Email: dday@coastalresearch associates.com	19 / 19
03	Brenda Edwards, OD	Heart of America Eye Care, P.A. 8800 West 7th St., Suite 140/141 Shawnee Mission, KS 66204	PH 913-362-3210 Email: bedwards317@gmail.com	9 / 9
04	David Evans, OD	Total Eye Care 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	PH 901-761-4620 Email: tneyedoc@mac.com	23 / 23
05	Shane Foster, OD	Athens Eye Care 416 West Union Street Athens, OH 45701	PH 740-594-2721 Email: foster@athenseyecare.com	12 / 12
06	Bradley Giedd, OD	Kindred Optics @ Maitland Vision 668 North Orlando Ave., Suite 1700 Maitland, FL 32751	PH 407-647-2020 Email: bgiedd@mvc2020.com	14 /14
07	Shane Kannarr, OD	Kannarr Eye Care 2521 N Broadway St Pittsbug, KS 66762	PH 620-235-1737 Email:skannarr@kannarrey e care.com	12 / 12
08	Stephen Montaquila, OD	West Bay Eye Associates 222 Jefferson Blvd. Warwick, RI 02888	PH 401-732-2350 Email:drmontaquila@westb a yeye.com	13 / 13
09	Christopher Pearson, OD	Sabal Eye Care 105 E. Lake Brantley Dr. Longwood, FL 32772	PH 407-889-4733 Email: sabaleyedoc@gmail.c om	15 / 15
10	Eric M. White, OD	Eric M. White, O.D. Inc. 5075 Ruffin Rd., Suite B San Diego, CA 92123	PH 858-278-4770 Email: ericwhiteod@gmail.com	7 / 7
11	David Wirta, MD	Eye Research Foundation 520 Superior Ave., Suite 235 Newport Beach, CA 92663	PH 949-650-1863 Email David.wirta@drwirta. com	40 / 40
12	Robert Benza, MD	Apex Eye Clinical Research 10615 Montgomery Road, Suite 202 Cincinnati, OH 45242	PH 513-290-0443 Email: Rbenza@CVPHealth.c om	3 / 3

OPI-NYXRM-302 (MIRA-3)
List and Description of Investigators and Participants in the Study

SITE ID#	Principal Investigators	Affiliation	Phone and Email	Number of Subjects Randomized / Completed
01	Ralph Chu, MD	Chu Vision Institute 9117 Lyndale Avenue South Bloomington, MN 55420	PH 952-835-1235 Email vrchu@chuvision.com	9 / 9
02	Douglas Day, MD	Coastal Research Associates 11205 Alpharetta Highway, Suite J-3 Roswell, GA 30076	PH 770-777-1928 Email: dday@coastalresearch associates.com	25 / 25
03	David Evans, OD	Total Eye Care 6060 Primacy Parkway, #200 Memphis, TN 38119	PH 901-761-4620 FAX Email: tneyedoc@mac.com	59 / 59
04	Shane Foster, OD	Athens Eye Care 416 West Union Street Athens, OH 45701	PH 740-594-2721 Email: foster@athenseyecare. com	15 / 15
05	Shane Kannarr, OD	Kannarr Eye Care 2521 N Broadway St Pittsbug, KS 66762	PH 620-235-1737 Email: skannarr@kannarreye care.com	21 / 21
06	Jennifer Kim, MD	Clayton Eye Center 1000 Corporate Center Drive, Suites 100, 120 Morrow, GA 30260	PH 77-968-8888 Email: jenniferkim@claytone ye.net	33 / 33
07	Stephen Montaquila, OD	West Bay Eye Associates 222 Jefferson Blvd. Warwick, RI 02888	PH 401-732-2350 Email:drmontaquila@westba yeye.com	24 / 24
08	Christopher Pearson, OD	Sabal Eye Care 105 E. Lake Brantley Dr. Longwood, FL 32772	PH 407-889-4733 Email: sabaleyedoc@gmail.c om	25 / 25
09	Bruce A. Segal, MD	Segal Drug Trials, Inc. 5258 Linton Blvd, #302 Delray Beach, FL 33484	PH 561-498-3664 Email: segalmd@bellsouth.net	27 / 27
10	David Wirta, MD	Eye Research Foundation 520 Superior Ave., Suite 235 Newport Beach, CA 92663	PH 949-650-1863 Email David.wirta@drwirta. Com	50 / 50
11	Vance Thompson, MD	Vance Thompson Vision 8101 W 57th St Sioux Falls, SD 57108	PH 605-361-3937 Email vance.thompson@van cethompsonvision.com	29 / 29
12	Michael K. Tran, MD	Michael K. Tran, MD, Inc. 15355 Brookhurst St., #104 Westminster, CA 92683	PH 704-839-2077 Email mtran.md@gmail.com	10 / 10
13	Robert Smyth-Medina, MD	North Valley Eye Medical Group, Inc. 11550 Indian Hills Rd #341 Mission Hills, CA 91342	PH 818-365-0606 Email rsmyth@ucla.edu	6 / 6
14	Mitchell Jackson, MD	Jackson Eye 300 N Milwaukee Ave, Ste L Lake Villa, IL 60046	PH 847-356-0700 Email Mjlaserdoc@msn.com	7 / 7

15	Leslie E. O'Dell, OD	Medical Optometry America 781 Fair Hills Dr., Suite 100 Shrewsbury, PA 17349	PH 717-748-5263 Email drodell@medodamerica.com	20 / 20
16	Carol Aune, OD	Oculus Research, Inc. 958 Vandora Springs Road Garner, NC 27529	PH 919-346-6945 Email carol.aune.oculusresearch@gmail.com	8 / 8

OPI-NYXRMP-303 (MIRA-4)
List and Description of Investigators and Participants in the Study

SITE ID#	Principal Investigators	Affiliation	Phone and Email	Number of Subjects Randomized / Completed
01	Christopher Pearson, OD	Sabal Eye Care 105 E. Lake Brantley Dr. Longwood, FL 32772	PH 407-889-4733 Email: sabaleyedoc@gmail.com	20 / 20
02	Shane Foster, OD	Athens Eye Care 416 West Union Street Athens, OH 45701	PH 740-594-2721 Email: foster@athenseyecare.com	3 / 3

11.4. Recommended Labeling

NDA 217064 for Ryzumvi (phentolamine ophthalmic solution) 0.75% is recommended for approval for the reversal of pharmacologically-induced mydriasis produced by adrenergic agonists or parasympathetic agents with the following revisions to the labeling. See the CDTL memo for the final labeling.

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.

/s/

SHILPA D ROSE
09/14/2023 02:26:17 PM

RHEA A LLOYD
09/15/2023 03:31:56 PM

Clinical Inspection Summary

Date	August 04, 2023
From	Roy Blay, Ph.D. Michele Fedowitz, M.D. Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Deputy Division Director Rhea Lloyd, M.D., Clinical Team Leader Shilpa Rose, M.D., Reviewing M.O. Lois Almoza, P.M. Division of Ophthalmology
NDA	217064
Applicant	Ocuphire Pharma, Inc
Drug	Ryzumvi (phentolamine)
NME	No
Therapeutic Classification	Long-acting, adrenergic, alpha-receptor blocking agent
Proposed Indication(s)	Reversal of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof
Consultation Request Date	22 Jan 2023
Summary Goal Date	18 Aug 2023
Action Goal Date	23 Sep 2023
PDUFA Date	23 Sep 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Protocols OPI-NYXRM-301 (MIRA-2) and OPI-NYXRM-302 (MIRA-3) were submitted to the Agency in support of NDA 217064 for the use of Ryzumvi (phentolamine) for the reversal of pharmacologically induced mydriasis. The clinical investigators, Drs. Day and Foster, and the sponsor, Ocuphire Pharma, Inc., were inspected in support of this NDA.

Based on the results of these inspections, the data generated by these clinical sites and submitted by the sponsor and the sponsor's oversight of these studies appear to be acceptable.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Ryzumvi, a long-acting, adrenergic, alpha-receptor blocking agent, for the reversal of pharmacologically induced mydriasis.

Inspections were requested of the following protocols in support of this application:

Protocol Numbers: OPI-NYXRM-301 (MIRA-2) and OPI-NYXRM-302 (MIRA-3)

Title: Both protocols are titled, "Randomized, Parallel Arm, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) to Reverse Pharmacologically Induced Mydriasis in Healthy Subjects"

OPI-NYXRM-301 (MIRA-2)

This protocol had a randomized, parallel arm, double-masked, placebo-controlled, multi-center design whose objectives were to evaluate:

- The efficacy of phentolamine in expediting the reversal of pharmacologically induced mydriasis across multiple mydriatic agents with an emphasis on phenylephrine
- The efficacy of phentolamine in returning subjects to baseline accommodation after worsening (with cycloplegic agents such as tropicamide and Paremyd®)
- The safety of phentolamine
- Any additional benefits of the reversal of pharmacologically induced mydriasis

Qualifying subjects were randomized in a 1:1 ratio to phentolamine or placebo. Mydriatic agent randomization was 3:1:1 to 2.5% phenylephrine: 1% tropicamide: Paremyd. Subjects received one drop of the mydriatic agent in both eyes (OU) an hour prior to treatment with phentolamine or placebo (OU). The study eye was defined as the right eye (OD) and the non-study eye as the left eye (OS). The study and non-study eyes were both evaluated at all assessments. The study is of two days duration with Day 1 being Screening and Treatment and Day 2 being Follow-up.

The primary efficacy endpoint was the percentage of subjects' study eyes returning to ≤0.2 mm from baseline pupil diameter at 90 minutes.

The study period was from 18 Nov 2020 (first enrollment) to 22 Dec 2020 (last completion). The study was conducted at 12 sites with a resulting database of 185 subjects.

OPI-NYXRM-302 (MIRA-3)

This protocol is very similar to MIRA-2 above other than some PK sampling considerations.

The primary efficacy endpoint is the percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline (-1 hour) photopic pupil diameter at 90 minutes.

The study period was from 19 Nov 2021 (date of first enrollment) to 03 Feb 2022 (date of last completion). The study was conducted at 16 sites with a resulting database of 368 subjects.

III. RESULTS:

1. **Douglas Day, M.D.**
   Coastal Research Associates
   11205 Alpharetta Highway, Suite 1-3
   Roswell, GA 30076

   Site: 02 (Protocol OPI-NYXRM-301 (MIRA-2**)**
   Site: 02 (Protocol OPI-NYXRM-302 (MIRA-3**)**

   Inspection Dates: 05-08 Jun 2023

   Dr. Day was inspected for the conduct of both Protocols **OPI-NYXRM-301 (MIRA-2)** and **OPI-NYXRM-302 (MIRA-3)**. Dr. Day was previously inspected in 2011. For Protocol OPI-NYXRM-301 (MIRA-2), 20 subjects were screened, and 19 subjects completed the study. For Protocol OPI-NYXRM-302 (MIRA-3), 25 subjects were screened and enrolled, and all 25 subjects completed the study.

   For both studies, the primary efficacy data (the return of subjects' study eyes returning to 0.2 mm from baseline pupil diameter at 90 minutes) and adverse event reporting were verified. Subject records reviewed for both protocols OPI-NYXRM-301 (MIRA-2) and OPI-NYXRM-302 (MIRA-3) included inclusion/exclusion criteria, protocol adherence and assessments, protocol deviations, informed consent, medical histories, and concomitant medications.

   For both studies, study related documents reviewed included Form 1572s, IRB correspondence and approvals, training documentation, delegation logs, IP accountability, sponsor and monitor correspondence, electronic records and access control and audit trails, and financial disclosure.

   The inspection compared the source records and eCRFs with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

2. **Shane Foster, O.D.**
   Athens Eye Care
   416 West Union Street
   Athens, OH 45701

   Site: 05 (Protocol OPI-NYXRM-301 (MIRA-2**)**
   Site: 04 (Protocol OPI-NYXRM-302 (MIRA-3**)**

   Inspection Dates: 06-15 Jun 2023

Dr. Foster was inspected for the conduct of both Protocols **OPI-NYXRM-301 (MIRA-2)** and **OPI-NYXRM-302 (MIRA-3).** This was the first inspection of Dr. Foster. For Protocol OPI-NYXRM-301 (MIRA-2**),** 13 subjects were screened, 12 subjects were enrolled, one subject failed screening, and 12 subjects completed the study. For Protocol OPI-NYXRM-302 (MIRA-3), 15 subjects were screened and enrolled, and all 15 subjects completed the study.

For both studies, the primary efficacy data (the return of subjects' study eyes returning to 0.2 mm from baseline pupil diameter at 90 minutes) and adverse event reporting were verified. Subject records were reviewed in their entirety for protocol adherence, informed consent, medical histories, physical examinations, assessments, questionnaires, and protocol deviations.

For both studies, study related documents reviewed included Form 1572s, IRB correspondence and approvals, training documentation, delegation logs, investigational product (IP) accountability, sponsor and monitor correspondence, electronic records and access control and audit trails, and financial disclosure.

The inspection compared the source records and eCRFs with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

3. Ocuphire Pharma, Inc. (Sponsor)
37000 Grand River Ave, Suite 120
Farmington Hills, MI 48835

Protocols: OPI-NYXRM-301 (MIRA-2) and OPI-NYXRM-302 (MIRA-3)
Inspection Dates: 26-29 May 2023

This is the first inspection of Ocuphire and covered sponsor oversight of Protocols **OPI-NYXRM-301 (MIRA-2)** and **OPI-NYXRM-302 (MIRA-3)**.

Documents reviewed included paper source worksheets documenting inclusion/exclusion criteria, informed consent, visual acuity, questionnaires, adverse events, and protocol deviations. Typically, data were captured on paper source documents and then transcribed to an electronic data capture (EDC) system, first Datatrak, then Fountayn. However, some sites used a hybrid approach of using paper source documents and EDC to capture source data. Only the clinical investigators and delegated authorized personnel were authorized to make changes to source data. Other documents reviewed included standard operating procedures (SOPs), service agreements with providers, clinicaltrials.gov reporting requirements, transfer of responsibilities and obligations (TOROs) to (b) (4) the contract research organization (CRO) which was then responsible for most study functions, selection of clinical investigators, Form FDA 1572s, validation of electronic records, training documentation, quality assurance audits, safety oversight including the CRO's medical monitoring plan,

safety and adverse event reporting, monitoring plans and procedures, electronic records including access controls, audit trails, user training, and system validation, investigational product (IP) accountability, and financial disclosure.

Senior staff personnel were interviewed regarding the conduct of the studies. Those study responsibilities transferred to the CRO, (b) (4) included protocol development, selection of investigators, clinical data management, monitoring, quality assurance, and evaluations of adverse event reports and safety information. The sponsor retained responsibility for development of the Investigator's Brochure, site selection, approval of the clinical data management plan, and oversight of the CRO and the IP. Other specific tasks including statistical analysis, clinical supply distribution, laboratory analysis, regulatory strategy, and publishing submission and repository functions were delegated to specific vendors as needed.

The sponsor appears to have conducted its responsibilities adequately with regards to oversight of the CRO, (b) (4) which was in turn responsible for most of the study activities. The sponsor/CRO also appeared to have adequate oversight of those responsibilities delegated to specific vendors. Overall, the sponsor appears to have met its study responsibilities adequately.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.
DO/Division Director/Wiley Chambers
DO/Deputy Director/William Boyd
DO/Medical Team Leader/Rhea Lloyd
DO/MO/Shilpa Rose
DO/Project Manager/Lois Almoza
OSI/Office Director/David Burrow
OSI/Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Michele Fedowitz
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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.

/s/

ROY A BLAY
08/07/2023 09:54:34 AM

MICHELE B FEDOWITZ
08/07/2023 10:51:07 AM

JENN W SELLERS
08/07/2023 10:55:30 AM