Cross-Discipline Team Leader, Deputy Division Director, Division Director Summary Review of NDA 217064

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, M.D., William Boyd, M.D., Wiley Chambers, M.D.
Subject	Summary Review
NDA #	217064
Applicant	OcuPhire Pharma, Inc.
Date of Submission	November 28, 2022
PDUFA Goal Date	September 28, 2023
Proprietary Name	Ryzumvi
Established or Proper Name	Phentolamine ophthalmic solution, 0.75%
Dosage Form(s)	Topical
Indication	To reverse mydriasis
Dosing Regimen	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.
Regulatory Action	**APPROVAL**

NDA 217603 Review Team Role	**Reviewer**
OND RPM	Lois Almoza
CDTL	Rhea Lloyd
Clinical Reviewer	Shilpa Rose
Nonclinical Reviewer	Maria Rivera/ Mukesh Summan
ATL	Chunchun Zhang
Drug Substance	Joseph Leginus/ Sithamalli Chandramouli
Drug Product	Anne Marie Russell/ Danae Christodolou
Manufacturing/ Facilities/ Process	Kejun Cheng/ Nallaperumal Chidambaram
OPQ Microbiology	David Bateman / Laura Wasil
Statistical Reviewer	Epiphanie Nyirabahizi / Abel Eshete
Regulatory Business Process Manager	Shazma Aftab
Clinical Pharmacology Reviewer	Sanjida Mahjabeen/ Ji Ping
OND Labeling Reviewer	Derek Alberding
OSE RPM	Oyinlola Fashina
DMEPA Team Lead	Valerie Vaughan
DMEPA Reviewer	Sofanit Getahun
OSI Lead	Michelle Fedowitz
OSI CSO	Roy Blay
OPDP Reviewer	Carrie Newcomer

Administrative Background

Phentolamine Ophthalmic Solution, 0.75% (POS) is a sterile, solution of phentolamine mesylate, USP (1%) 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% (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.

The Applicant relies on the Agency's previous findings of nonclinical systemic safety for the approved listed drug (LD), OraVerse® (NDA 022159), in addition to Applicant-conducted studies, and information available in the published literature. The clinical development program for phentolamine ophthalmic solution, 0.75% in support of this application included 4 clinical studies, including one Phase 2 study MIRA-1, two Phase 3 studies (OPI-NYXRM-301 (MIRA-2), OPI-NYXRM-302 (MIRA-3)), and one pediatric Study OPI-NYXRM-303 (MIRA-4). PK of phentolamine ophthalmic solution, 0.75% was assessed in a subset of adult participants in Study OPI-NYXRM-302 (MIRA-3).

OcuPhire Pharma LLC submitted a New Drug Application (NDA) for Ryzumvi (phentolamine ophthalmic solution) 0.75% through the 505(b)(2) pathway for approval. Ryzumvi is indicated for the reversal of mydriasis.

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.

The benefits of treating pharmacologically induced mydriasis outweigh the risks associated with the use of Ryzumvi (phentolamine ophthalmic solution) 0.75%

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 ability to focus on near objects, read, or drive for up to 24 hours.	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 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	• Rev-Eyes is approved, but not marketed for this indication.	This product, if approved would provide an alternative 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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.

Product Quality

From the Integrated Quality Assessment finalized on August 11, 2023:

Qualitative and Quantitative Composition of Phentolamine Ophthalmic Solution, 0.75%

Ingredient and Quality Reference	Purpose	Composition (% w/v)	Amount per mL (mg/mL)
		0.75% Phentolamine	
Phentolamine Mesylate, cUSP	Drug substance	1.0	10.00
Mannitol, cUSP	(b) (4)		
Sodium Acetate Trihydrate, cUSP	(b) (4)		
(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	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 ** Adjustment pH

Drug Product Release and Stability Specifications for Phentolamine Ophthalmic Solution, 0.75%

Test	Acceptance Criteria	Test Method (b) (4)	Test Method (b) (4)	Stability
Appearance of Solution (including color and clarity)	Clear, colorless to slightly brown solution, essentially free of visible particles	Visual examination	Visual/ TP25481/ cUSP <771>	Yes
Appearance of Container	Container intact, no leakage observed	Visual examination	Visual/ TP25481	Yes
Appearance of Packaging (foil pouch)	Foil free of damage, scuffs, and discoloration	Visual examination	Visual/ TP25481	Yes
Foil Pouch Leak Detection[1]	No Leaks	ASTM F1140	ASTMF1140	Yes
Identification by HPLC	Retention time of peak in samples is ± (b) (4)% of retention time of peak in standard	PDR-ATM-ODV-0001 (HPLC)	TP80413	No
Identification by UV	UV spectra of the sample solution and of the Standard solution exhibit maxima and minima at the same wavelengths (± (b) (4) run)	PDR-ATM-ODV-0001 (HPLC)	TP80413	No
Assay	(b) (4)% of label claim	PDR-ATM-ODV-0001 (HPLC)	TP80413	Yes
Related substances	Specified Impurity (b) (4) Individual Unspecified Impurities ≤ (b) (4)% (Report all unspecified impurities ≥ %) Total impurities ≤ (b) (4)%	PDR-ATM-ODV-0001 (HPLC)	TP80413	Yes
Uniformity of Dosage by Weight	According to cUSP	cUSP <905>	cUSP <905>/ TP80788	No
pH	(b) (4)	cUSP <791>	cUSP <791>/ TP80525	Yes
Osmolality	(b) (4) mOsm/kg	cUSP <785>	cUSP <785>/ TP80527	Yes
Sterility[2]	No growth	cUSP <71>	cUSP <71>/ TP80545	Yes
Particulate Matter	≤ 10 µm NMT (b) (4) particles per mL ≥ 25 µm NMT (b) (4) particles per mL ≥ 50 µm NMT particles per mL	cUSP <789>	cUSP <789>/ TP80526	Yes
Container Closure Integrity[1]	According to cUSP	cUSP <1207> Dye immersion with UVNIS + microbial/bacterial immersion including sterility		No

1 Foil Pouch Leak Detection and Container Closure Integrity performed at (b) (4)

2 Sterility is performed at release, annually, and at the end of the study

Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History

OPQ Recommendations and Conclusion on Approvability

NDA 217064, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Phentolamine Ophthalmic Solution, 0.75%. All information requests and review issues have been addressed. The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on July 29, 2023.

The drug product is regulated as a drug/device combination product per the Genus decision. CDRH confirmed that no CDRH GMP/QS consults were necessary as the single dose BFS vial is considered a low risk on December 6, 2022.

Therefore, NDA 217064 is recommended for approval from Product Quality perspective.

Nonclinical Pharmacology/Toxicology

From the Nonclinical review dated 8/7/23: The nonclinical studies conducted by the Applicant support the approval the NDA. The NDA is approvable from nonclinical pharmacology/toxicology standpoint.

Brief Discussion of Nonclinical Findings
Based on the intended dosing regimen of a total of 1 to 2 drops, the rabbit 5- day non-GLP and 28-day GLP studies were reviewed to support this NDA. The 6-month rabbit ocular toxicity study was not reviewed. The drug product concentration intended for marketing is 0.75% based on phentolamine, equivalent to 1% based on the mesylate salt. The concentrations below refer to the mesylate salt.

In the 5-day ocular tolerability study, no adverse findings were observed after treatment with phentolamine mesylate up to 1.5% BID for 4 days or 1.5% QID for 1 day (NOAEL). Slight conjunctival redness, swelling and discharge were observed at 2% QID administered for 3 days (NOAEL). Severe ocular irritation was observed at 5% QID. Animals displayed head shaking, partial palpebral closure, rubbing/pawing of the treated eyes, slight to moderate discharge, redness, and swelling, iritis, sloughing of the nictating membrane, and slight dulling of the normal luster of the cornea.

In the 28-day ocular toxicity study, isolated occurrences of conjunctival redness and discharge, and corneal opacity (involving < 25% of the cornea) were observed at ≤1% QID (NOAEL). Conjunctivitis (redness, swelling and discharge), ocular surface hyperemia (slight), and corneal opacities (involving <25 to 75% of the cornea) were observed mainly at 2% QID. No adverse systemic effects were observed. As noted by the Applicant, the conjunctival redness could be associated with the pharmacological activity of phentolamine as an alpha-adrenergic antagonist (vasodilation).

The 2% QID NOAEL from the 5-day ocular tolerability study provides ocular exposure margins of 6.7X (adults) and 13X (children). The 2% NOAEL from the 28-day ocular toxicity study provides ocular exposure margins of 2.7X (adults) and 5.3X (children). Based on the intended total dose of 1 or 2 drops per eye and longer treatment duration in these nonclinical studies, the exposure margins are expected to be higher.

Systemic safety is supported by the lower systemic phentolamine exposure observed in the clinic after treatment with 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. In addition, the systemic exposure in the clinical trials (Cmax ≤ 0.71 ng/mL and AUC ≤ 1.31 ng*hr/mL) was lower than that observed in the 28-day ocular toxicity study (Cmax ≤ 46.8 ng/mL and AUC≤ 67 ng*hr/mL), at which no adverse systemic effects were observed.

The nonclinical data support the ocular and systemic safety of Phentolamine Ophthalmic Solution, 0.75% (or 1% as the mesylate salt) at the intended dosing regimen for marketing.

Clinical Pharmacology

From the Clinical Pharmacology review dated 8/4/23:

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of NDA 217064 and finds the application acceptable to support approval from a clinical pharmacology perspective.

The focus of the Clinical Pharmacology review is to evaluate the systemic exposure of phentolamine ophthalmic solution, 0.75% from the Study OPI-NYXRM-302 (MIRA-3).

Review Issue	Recommendations and Comments
Labeling	See Section 2.4
Bridge between the to-be- marketed and clinical trial Formulations	Not applicable. The to-be-marketed formulation was used in 2 pivotal clinical efficacy studies (MIRA-2, MIRA-3); and two other key supportive studies: MIRA-1 and MIRA-4 study.

Clinical Efficacy

Efficacy Results – Primary Endpoint

MIRA-1 and MIRA-2 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**. MIRA-4 was a pediatric safety study with consistent findings.

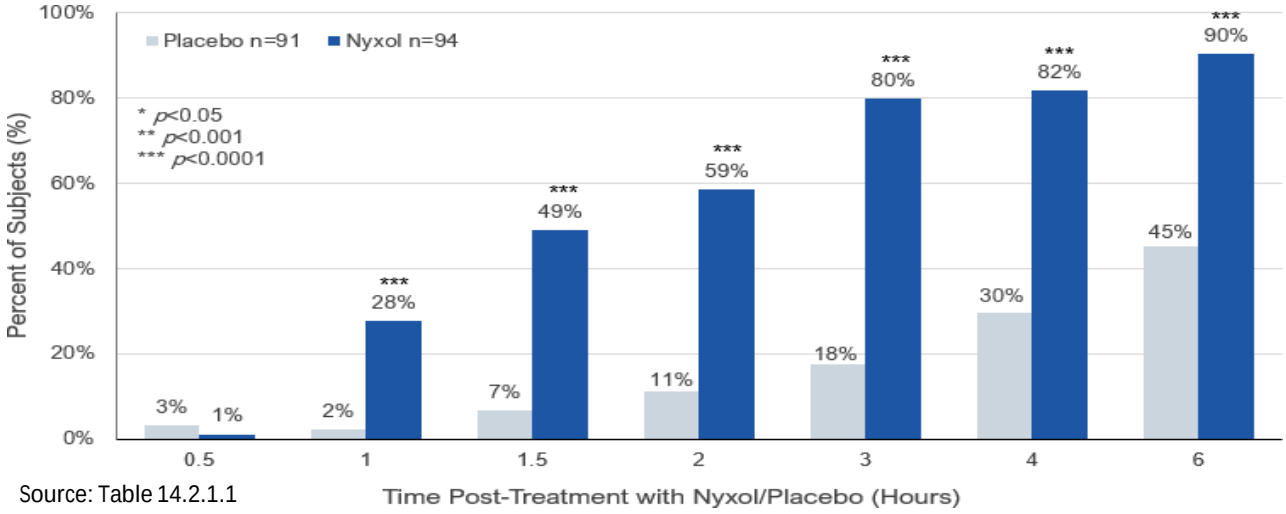
MIRA-1: Percent of Subject Study Eyes Returning to ≤ 0.2 mm From Baseline (-1 Hour) Pupil Diameter by Time Point (mITT Population)

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 hours	55 (58.5)	10 (11.0)	22.99 (8.92, 59.27)	<0.0001
3 hours	75 (79.8)	16 (17.6)	23.85 (10.25, 55.49)	<0.0001
4 hours	77 (81.9)	27 (29.7)	14.04 (6.41, 30.72)	<0.0001
6 hours	85 (90.4)	41 (45.1)	12.03 (5.29, 27.34)	<0.0001
24 hours	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.*

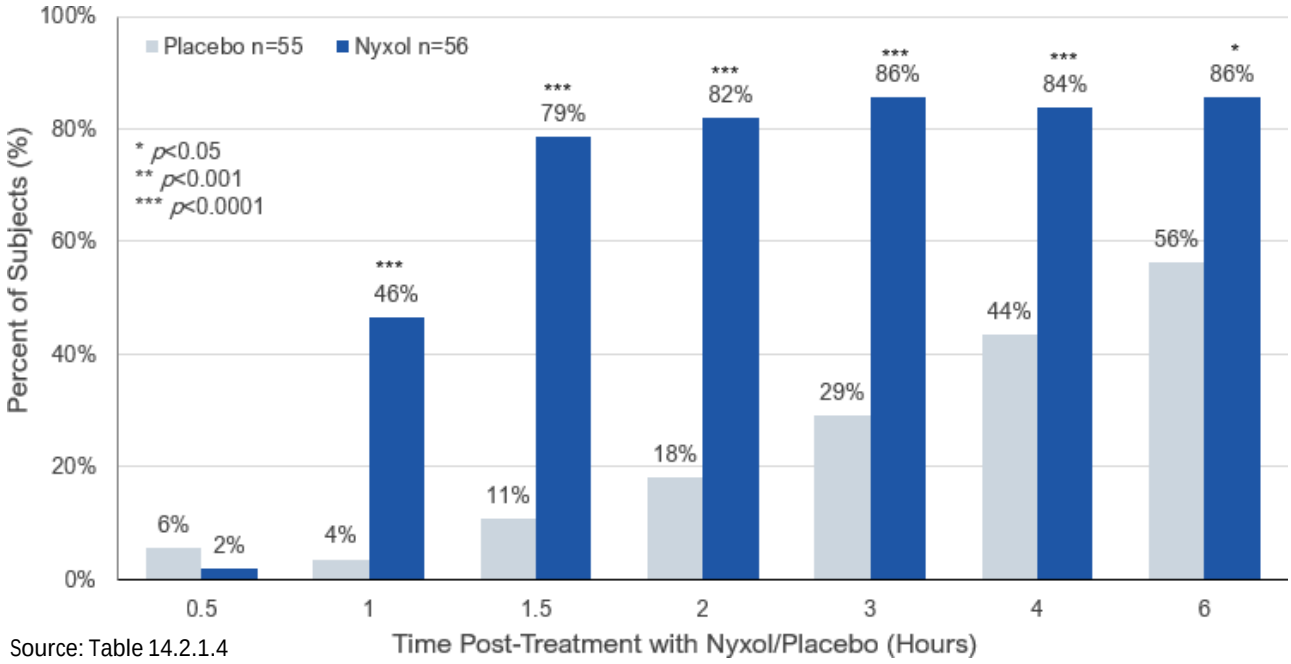
Sensitivity Analyses

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



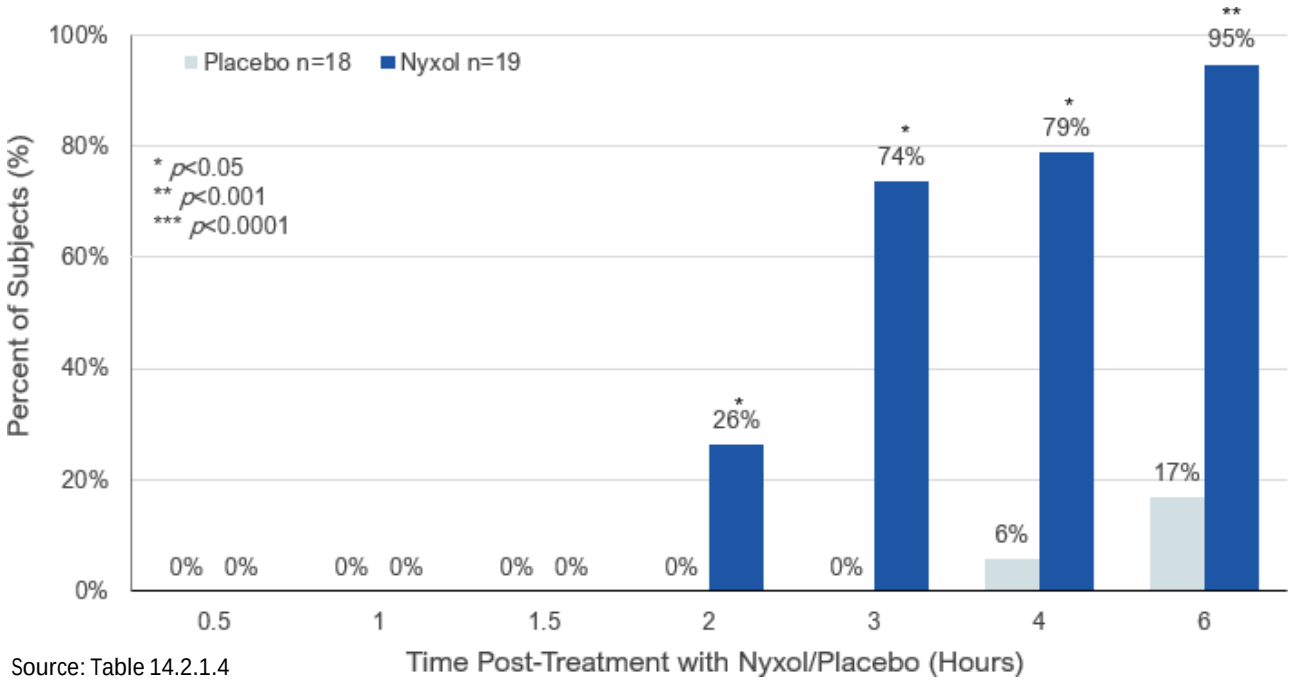
Source: Table 14.2.1.1

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



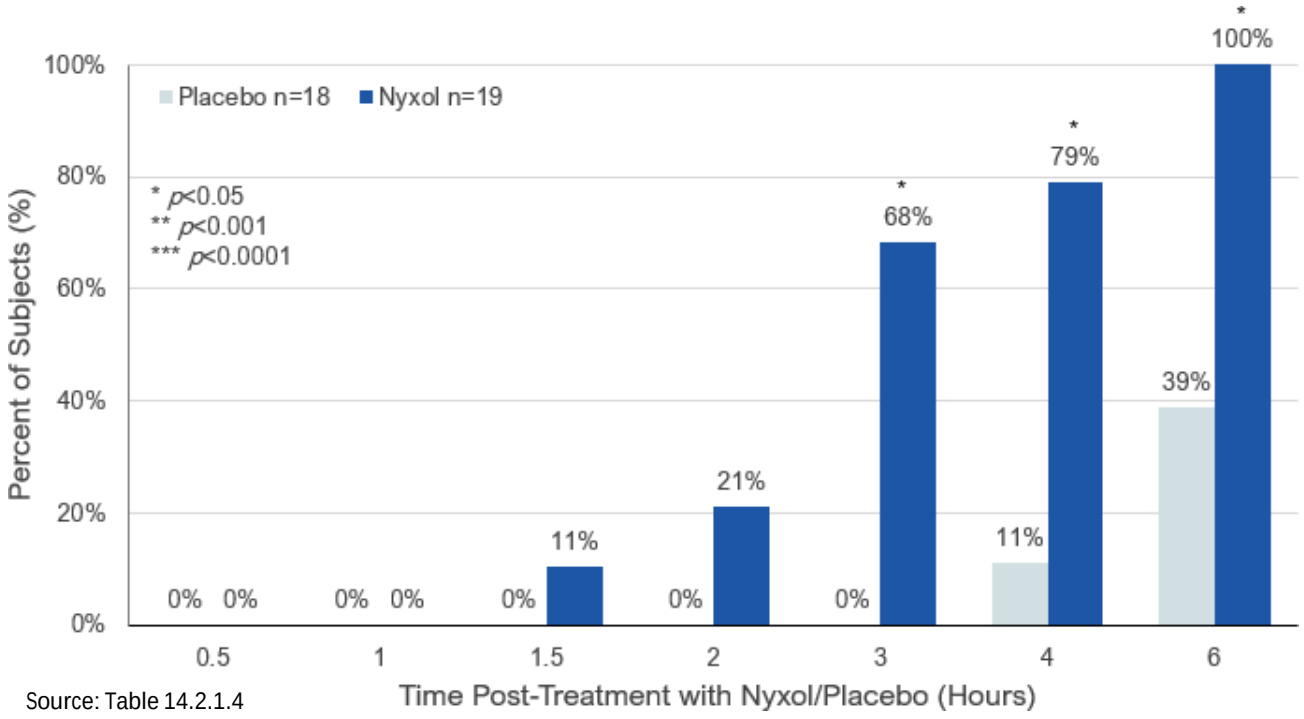
Source: Table 14.2.1.4

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



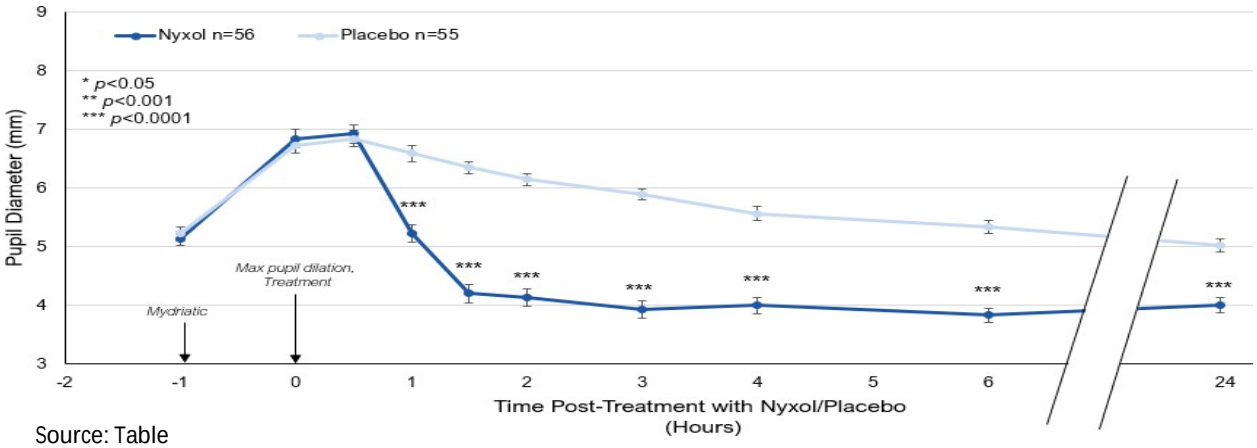
Source: Table 14.2.1.4

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



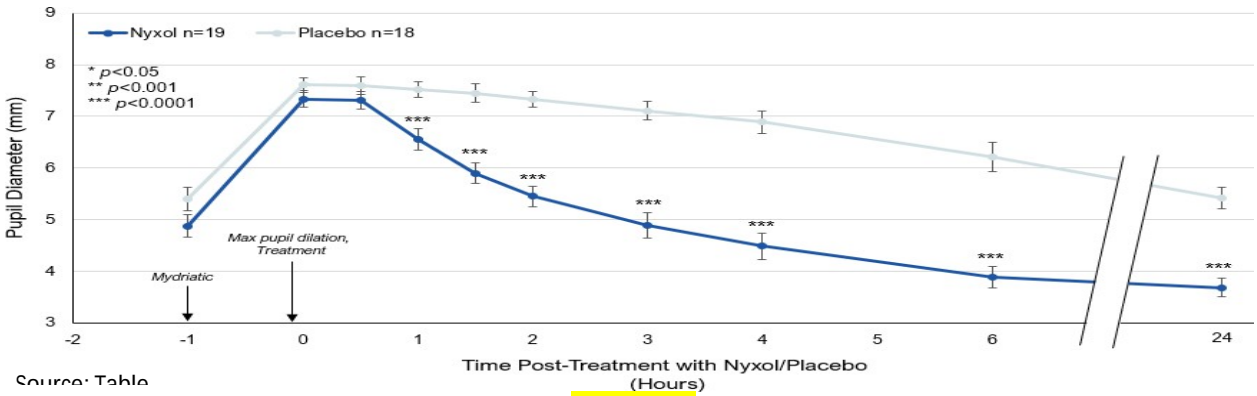
Source: Table 14.2.1.4

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



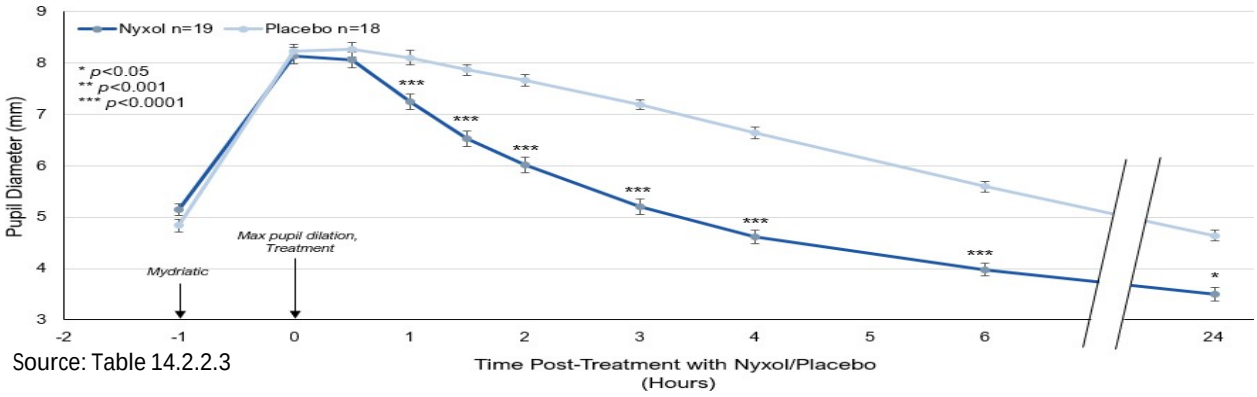
Source: Table

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.*

MIRA-2

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

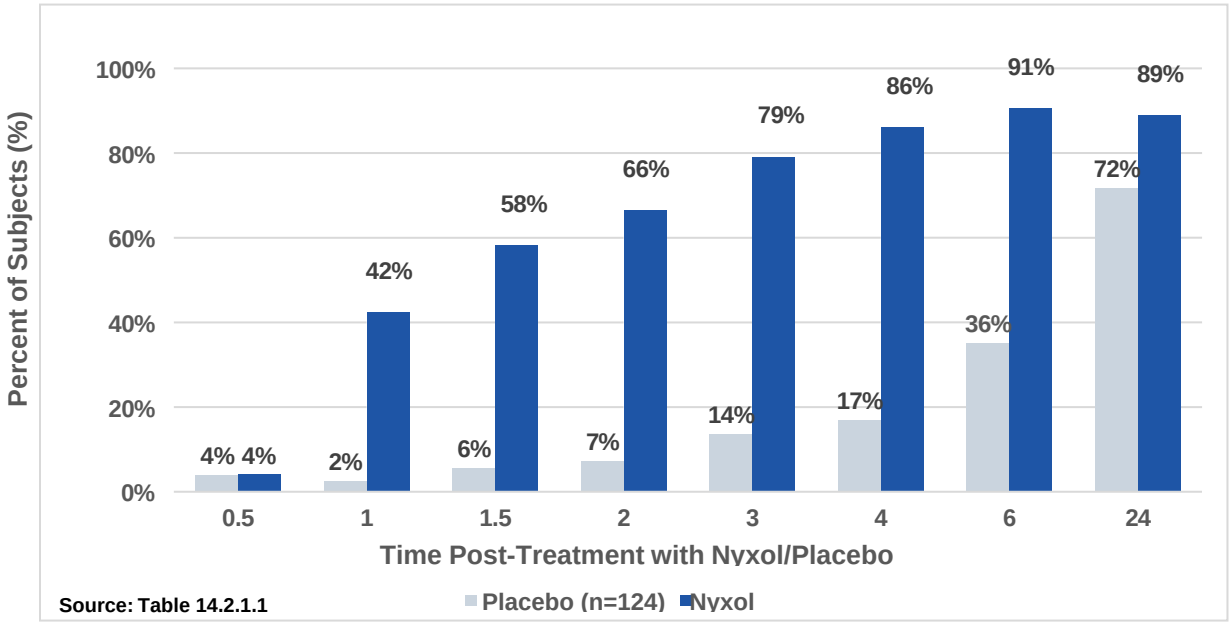
Study Eye Time point	POS (n=244) n (%)	Placebo (n=124) n (%)	POS vs placebo [a]	
			Odds ratio (95% CI)	p-value
30 min	10 (4.1)	5 (4.0)	0.95 (0.33, 2.72)	0.9264
60 min	103 (42.2)	3 (2.4)	24.92 (8.34, 74.42)	<0.0001
90 min	**142 (58.2)**	**7 (5.6)**	**21.38 (9.78, 46.73)**	**<0.0001**
2 hr	162 (66.4)	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.

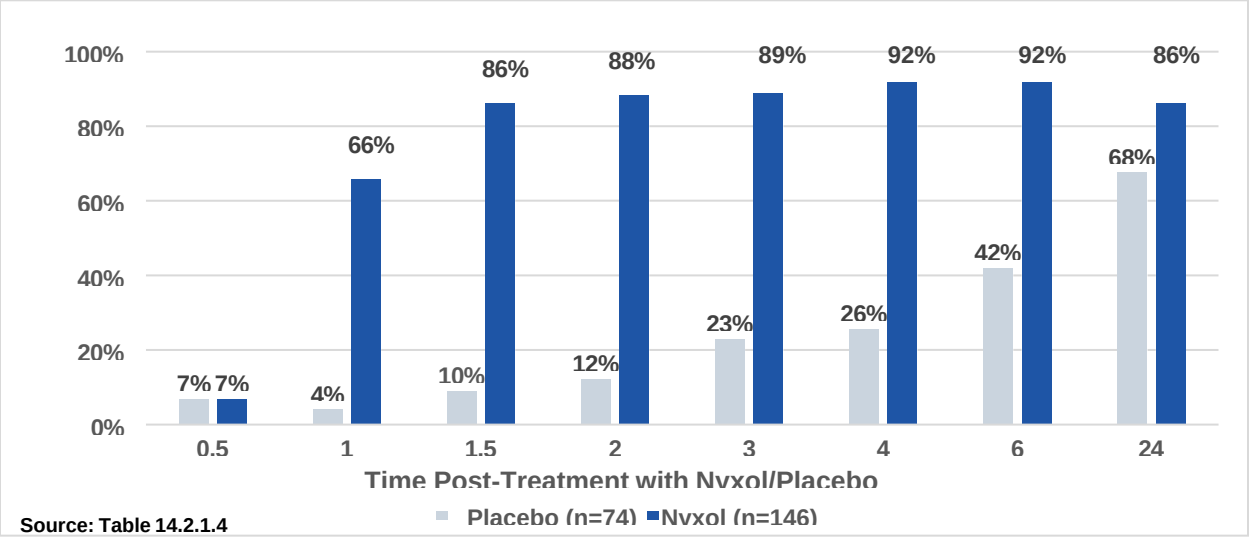
Reviewer's comment: *In the mITT Population, a statistically significant greater percent of subjects treated with POS had study eyes that showed reversal of mydriasis, using a PD threshold of ≤ 0.2 mm from baseline at 90 min (primary endpoint) compared with the placebo treatment (58% vs 6%, respectively;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

Sensitivity Analyses

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

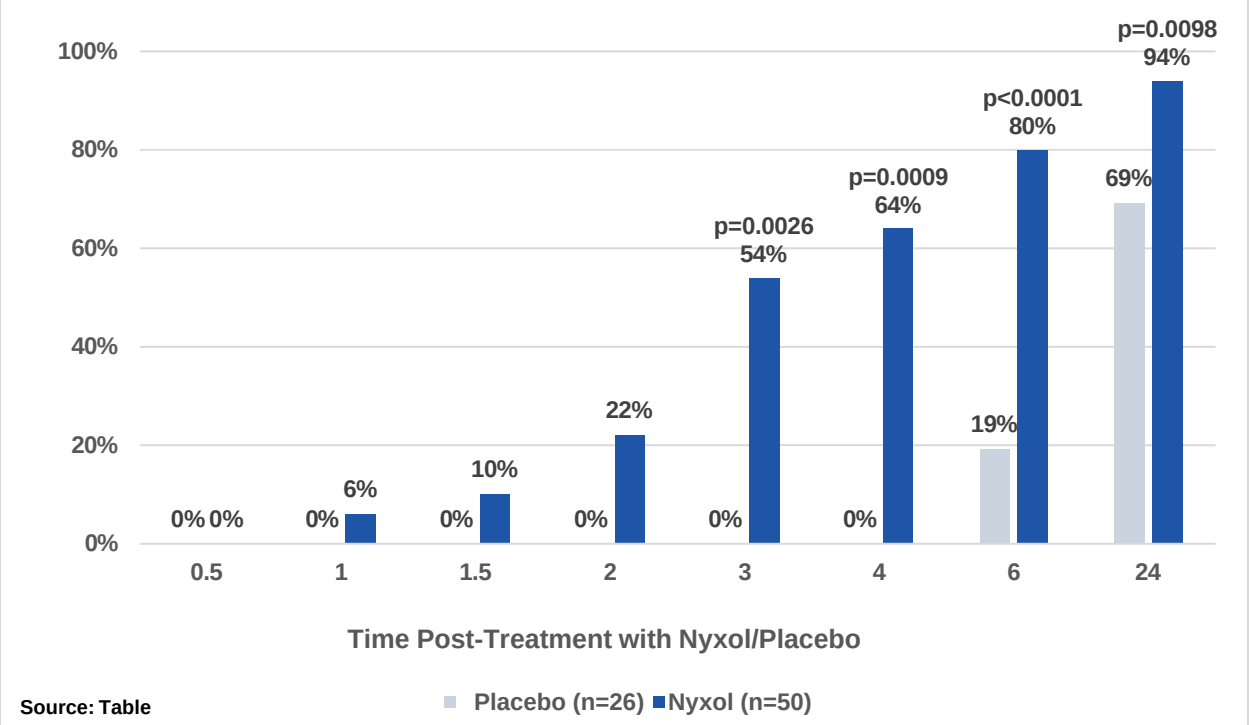


Percent of Subjects Receiving Phenylephrine With Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hour) Pupil Diameter by Time Point (mITT Population)



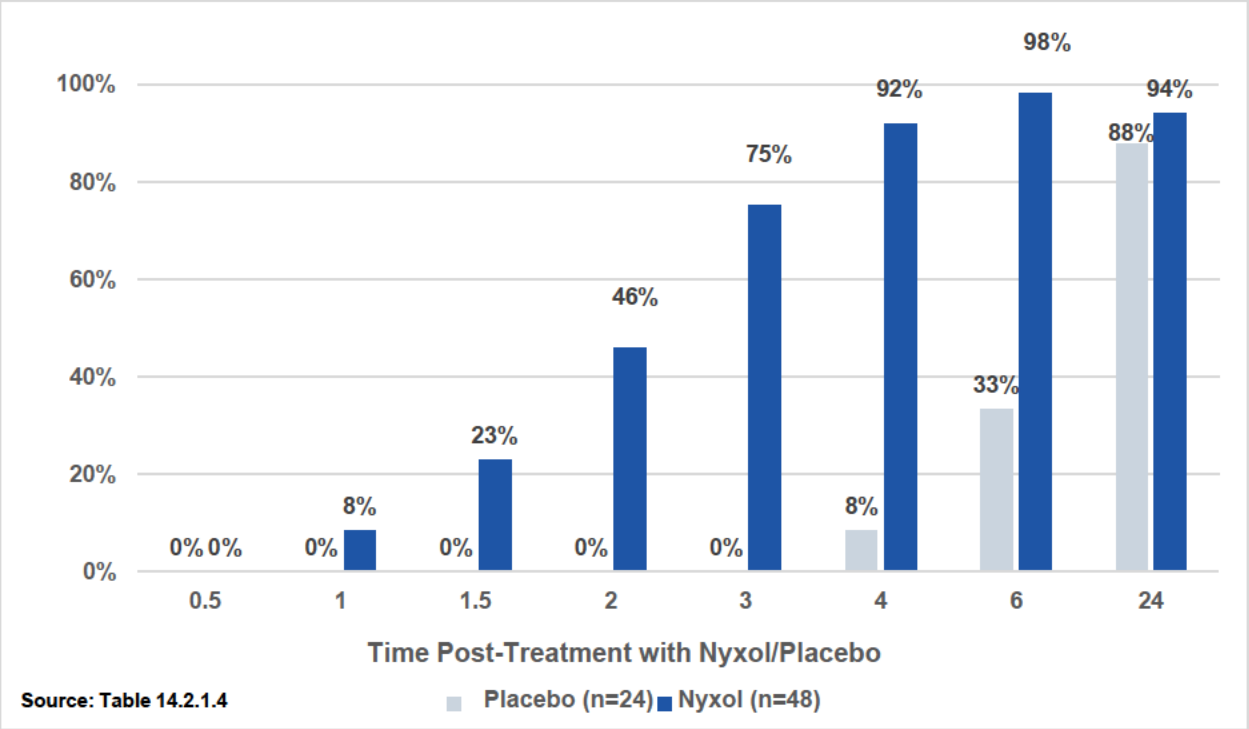
Source: Table 14.2.1.4

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



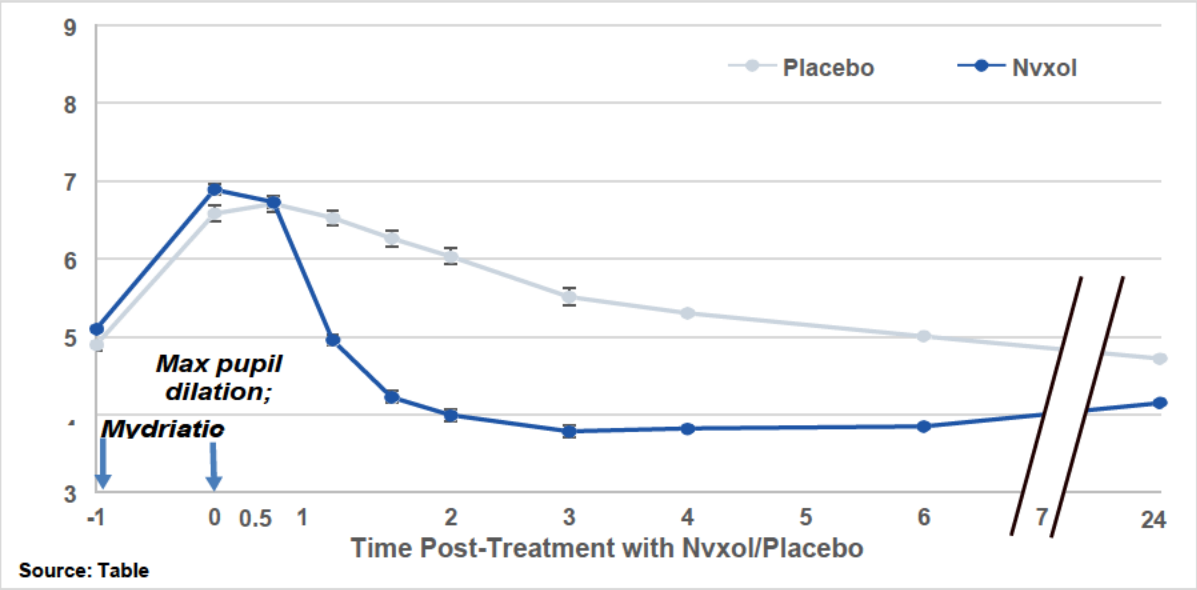
Source: Table

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



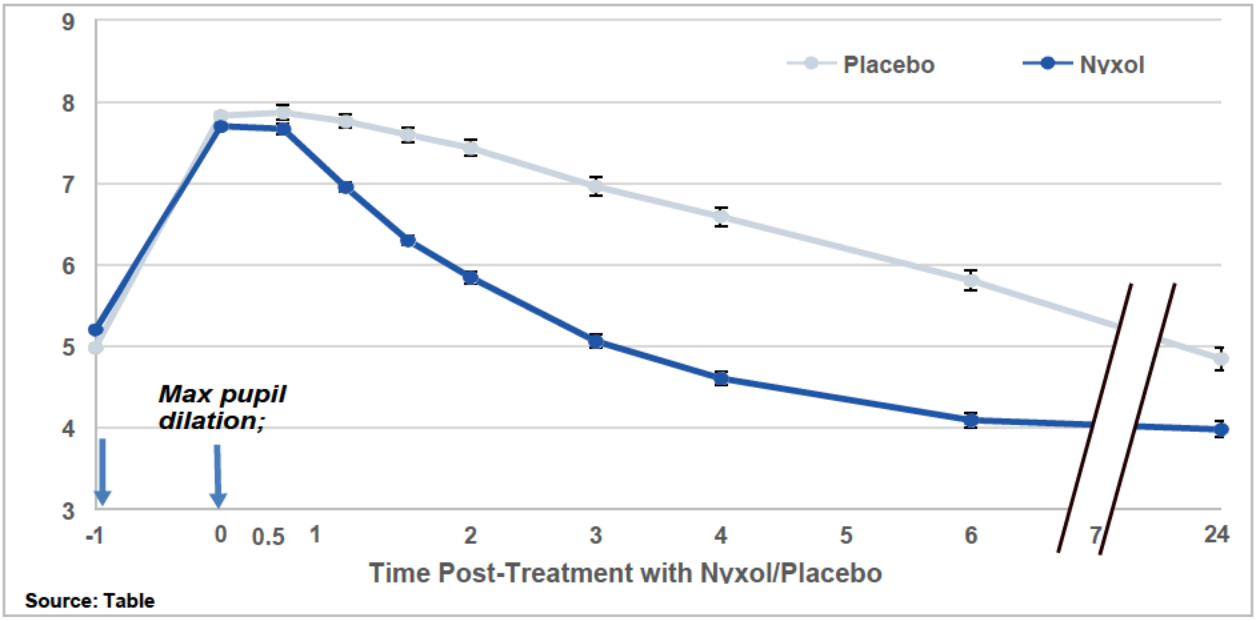
Source: Table 14.2.1.4

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.*

Safety

Safety Database

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.

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

Reviewer's comments:
There was adequate exposure for this indication.

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

Serious Adverse Events
No serious adverse events occurred in in any of the applicant-conducted clinical studies.

Dropouts and/or Discontinuations Due to Adverse Events
No dropouts and/or discontinuations due to adverse events occurred in in any of the applicant-conducted clinical studies.

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 (11.7)	3 (0.8)
Instillation site discomfort	36 (5.6)	8 (2.0)
Instillation site erythema	28 (4.4)	0
Instillation site pain	28 (4.4)	6 (1.5)
Instillation site burn	19 (3.0)	7 (1.8)
NON-OCULAR TEAEs		
Dysgeusia	36 (5.6)	4 (1.0)

Reviewer's Comments: *The most common adverse events occurring in POS treated patients were instillation site pain/burning/discomfort (16%), conjunctival hyperemia (12%), dysgeusia and instillation site erythema (4%).*

Biomicroscopy and Fundus Exam
There were no clinically relevant changes in the fundus exam that occurred in either treatment group during the clinical trials.

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.

Subgroup Analyses by Demographic Group
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%]).

Advisory Committee Meeting

There were no issues raised during the review of this application that were thought to benefit from an Advisory Committee meeting.

Pediatrics

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

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 findings in MIRA-4 were consistent with those of MIRA-1 and MIRA-2.

BIOSTATISTICS

From the Statistical Review finalized on 7/31/2023:

Efficacy Results

The Applicant's findings for the study and fellow eyes are presented in Table 1 and Table 2, respectively. Both studies met the primary objective of demonstrating the efficacy of POS compared to placebo. Sensitivity analyses and analyses across various patient subgroups are also reviewed. Results from these analyses are generally consistent with the primary analysis findings. Note, the Applicant has also submitted study reports and data for two additional studies, a Phase 2b study (MIRA-1), and pediatric study (MIRA-4), as supportive evidence. The results from these studies are supportive of the results observed in the two pivotal studies.

Regarding safety, a higher percentage of subjects in the POS arm of both studies reported at least one treatment emergent adverse event (TEAE) compared to the corresponding subjects in the placebo arms. The most frequently reported ocular adverse event in subjects randomized to the POS arms was conjunctival hyperemia. None of the subjects randomized to POS or placebo discontinued the study due to TEAE, and no deaths or serious TEAEs were reported in either study.

In conclusion, the results of the primary efficacy analyses based on pupil's diameter (PD) measure in the two pivotal studies demonstrated the efficacy of POS for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (phenylephrine) or parasympatholytic (tropicamide) agents, or a combination (Paremyd). The incidence of TEAE was higher in the POS arm compared to placebo. This reviewer recommends the final determination for the approval of this drug to be made based on the totality of evidence taking the potential safety issues into account.

Table 1: Percent of Subjects Returning to ≤ 0.2 mm From Baseline Pupil Diameter at 90 Minute Post Treatment (mITT Population) – Study Eye

Study	Treatments		ODDS Ratio (95% CI)
	POS	Placebo	
MIRA-2	46/94 (48.9%)	6/91 (6.6%)	25.93 (9.37, 71.79)
MIRA-3	142/244 (58.2%)	7/124 (5.6%)	55.64 (23.04, 134.39)

Source: Table 8 of the Applicant's study reports.

Table 2: Percent of Subjects Returning to ≤ 0.2 mm From Baseline Pupil Diameter at 90 Minute Post Treatment (mITT Population) – Fellow Eye

Study	Treatments		ODDS Ratio (95% CI)
	POS	Placebo	
MIRA-2	46/94 (48.9%)	5/91 (5.5%)	38.03 (12.4, 116.67)
MIRA-3	127/244 (52.0%)	6/124 (4.8%)	36.54 (15.05, 88.68)

Source: Table 9 of the Applicant's study reports.

No major statistical issues were identified in the review of the two pivotal studies. As noted, in MIRA-2, the Applicant has not specified a testing procedure to control the type-I error rate due to the comparison of the two treatment arms with respect to multiple secondary efficacy endpoints. However, they have made (b) (4) and presented the results in Section 14 of the drug label. The Applicant was informed during the pre-NDA meeting that the decision to include (b) (4) is a review issue. It is the recommendation of this reviewer not to present (b) (4).

Collective Evidence

The efficacy of POS to rapidly return PD to baseline PD following pharmacologically induced mydriasis was demonstrated in two Phase 3 studies enrolling a total of 553 subjects 12 to 81 years of age. Both studies demonstrated robust and similar effects of POS on PD. Robust effect of POS was found regardless of which mydriatic agent was used, subject's irides color (light or dark). The additional Phase 2 study MIRA-1 and younger pediatric subjects study MIRA-4 further supported the efficacy findings for POS to rapidly reverse mydriasis.

The incidence of adverse events was higher in the POS arm compared to the placebo arm. The most frequently reported ocular adverse events in subjects randomized to the POS arms in the two studies was conjunctival hyperemia. Overall, the safety results in Studies MIRA-2 and MIRA-3 provide evidence that POS was well tolerated in both adults as well as pediatrics populations. No subjects had any serious TEAEs or any TEAEs leading to withdrawal from the study or study medication discontinuation, and no subjects died during the study.

Conclusions and Recommendations

Overall, the results in this review provide evidence to support the efficacy of POS for the treatment of pharmacologically induced mydriasis. Adverse events, including some ocular adverse events were higher in the POS arm. Therefore, the final determination for the approval of this drug should be made based on the totality of evidence, taking the potential safety issues into account.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators in the original NDA submission.

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)

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 Clinical Efficacy
		☐	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.			

Office of Scientific Investigations (OSI)

From the OSI Clinical Inspections Summary dated August 7, 2023:

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 ophthalmic solution) 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.

OPDP and DMEPA

The Division of Medication Error Prevention and Analysis 1 (DMEPA) completed a review dated July 14, 2023. Revisions were proposed for the draft prescribing information (PI), professional sample and trade container labels and carton labeling. The Division did not agree with transmitting the following comment regarding vial labeling:

> *As currently presented, we note important information such as the proprietary name, established name, strength, and route of administration is proposed to be embossed on the clear plastic container (vial). Important information embossed on clear plastic such as Low-density polyethylene (LDPE) containers without color is "generally illegible" making it difficult to read, which can lead to medication errors. See FDA guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*
>
> *Our OPQ colleagues confirmed that CMC data "demonstrated the product is stable when stored in the foil pouch and it is not stable only in the vial." Storing the vial in the foil pouch until ready for use, may help mitigate risk of medication error due to difficulty reading the product information embossed on clear plastic.*
>
> *We recommend including the statement "store in foil pouch until ready for use" in the pouch and carton labeling. Additionally, we recommend this storage information be included in Section 16 How Supplied/Storage and Handling of the PI.*

The proposed embossed vial labeling is not illegible. It contains both the proprietary and established name of the product and lot number and expiration date. Ryzumvi is not dispensed to the patient. The product is administered only by health care professionals in their office. The foil pouch is not resealable. After opening the foil pouch, the product is labeled to be stored at 25ºC (68°F to 77ºF) outside the pouch and is labeled to be used within 14 days, not to exceed the expiration date printed on the vial. The single patient-use vial once opened is to be discarded immediately after use. The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete package insert and draft carton/ container labeling on September 19, 2023.

Post-marking Risk Management

There are no proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

Regulatory Action

NDA 217064 Ryzumvi (phentolamine ophthalmic solution) 0.75% will be approved for the reversal of mydriasis.

Labeling

Attached is the agreed-upon labeling for NDA 217064 Ryzumvi (phentolamine ophthalmic solution) 0.75% for the reversal of mydriasis. Vial labeling was summitted on 9/15/23. All other labeling was submitted on 9/21/23.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

RHEA A LLOYD
09/25/2023 12:06:55 PM

WILLIAM M BOYD
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WILEY A CHAMBERS
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