CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217064Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 217064
Drug Name:	Ryzumvi (phentolamine mesylate ophthalmic solution) 0.75%
Indication(s):	Treatment of pharmacologically induced mydriasis produced by adrenergic agonists or parasympatholytic agents, or a combination thereof
Applicant:	Ocuphire Pharma, Inc.
Date(s):	Letter/Receipt date: November 23, 2022 60-Day Filing date: January 27, 2023 74-Day Letter date: February 10, 2023 PDUFA date: September 28, 2023
Review Priority:	Standard
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Keywords: NDA Review, logistic regression**,** subgroup analysis, randomization, odd ratio	

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1 EXECUTIVE SUMMARY

This is a statistical review of the New Drug Application (NDA) submitted by Ocuphire Pharma, Inc. (Applicant) for Ryzumvi (phentolamine mesylate ophthalmic solution) 0.75% (POS). The proposed indication is for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (phenylephrine) or parasympatholytic (tropicamide) agents, or a combination (Paremyd). The primary objective of this review is to evaluate whether the safety and efficacy results in the two pivotal studies, MIRA-2, and MIRA-3, support the proposed indication.

Both MIRA-2 and MIRA-3 were randomized, parallel-arm, double-masked, placebo-controlled studies. In MIRA-2, 185 eligible subjects (171 adults and 14 adolescents ≥ age 12) were randomly assigned to one of the two treatment arms (POS vs Placebo) in 1:1 ratio. MIRA-3 randomized 368 subjects (337 adults and 31 adolescents ≥ age 12) to the two treatment arms in a 2:1 ratio. In both studies, randomization was stratified by irides type (Dark and light) and mydriatic agents (2.5% phenylephrine, 1% tropicamide, or Paremyd). Subjects in both studies received 1 drop of mydriatic agent in each eye. One hour after mydriatic drug instillation, adult subjects in both studies received 2 drops of study treatment 5 minutes apart in the study eye, and 1 drop in the fellow eye (non-study eye). The two studies provided different doses for pediatric patients. For the MIRA-2, pediatric subjects received 1 drop of study treatment in both eyes, while in MIRA-3, pediatric subjects received 2 drops in the study eye and 1 drop in the fellow eye.

The primary clinical outcome of interest was pupil's diameter (PD) measured using a pupillometer in both studies. In each study, PD measurements were taken 1 hour before mydriatic agent instillation (baseline) and 60 min after mydriatic agent instillation, i.e., immediately before the study treatment was administered to each eye. Additional measurements were taken at 30 min, 60 min, 90 min, 2-hour, 3-hour, 4-hour, and 6-hour after study treatment dosing. The primary efficacy endpoint of the studies was the percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline PD at 90 min after study treatment dosing. The primary efficacy analysis was conducted based on the modified-intent-to-treat (mITT) population which consisted of all randomized subjects who received at least one dose of their assigned treatment and have at least one post baseline measurement. It is not generally recommended to consider the mITT population which excludes patients requiring one post-baseline measurement, as it can bias the study findings. However, in this submission, the mITT population was similar to the ITT, all randomized patients.

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 presented. 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 (See Appendix for details).

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

	Treatments		
Study	**POS**	**Placebo**	**ODDS Ratio (95% CI)**
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

	Treatments		
Study	**POS**	**Placebo**	**ODDS Ratio (95% CI)**
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.

2 INTRODUCTION

This is a statistical review of the New Drug Application (NDA) submitted by Ocuphire Pharma, Inc., referred to as the Applicant, for Ryzumvi (phentolamine mesylate ophthalmic solution) 0.75% (POS). The Applicant is submitting this NDA pursuant to section 505(b)(2) of the Food, Drug and Cosmetic Act (FD&C Act).

The proposed indication is for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (phenylephrine) or parasympatholytic (tropicamide) agents, or a combination (Paremyd). The primary evidence of efficacy and safety for this 505 b (2) NDA comes from two pivotal Phase 3 studies (MIRA-2 and MIRA-3). The two studies were conducted across multiple sites. Study MIRA-2 enrolled 185 subjects in 12 study sites while Study MIRA-3 enrolled 330 subjects in 16 sites. In addition to their completed studies and information available in the published literature, the Applicant 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 008278) and OraVerse® (NDA 022159).

The Applicant proposes to include findings from MIRA-2 and MIRA-3 and the two supportive studies MIRA-1 and MIRA-4 into the "Clinical Studies" (Section 14) of the US Prescribing Information (USPI) to describe the efficacy of Ryzumvi (phentolamine mesylate ophthalmic solution) 0.75% for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (phenylephrine) or parasympatholytic (tropicamide) agents, or a combination (Paremyd). This review investigates whether the findings from these studies support the proposed indication and provides recommendations for the USPI to be considered by the Division of Ophthalmology (DO) if the product is approved.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the Applicant's summary of the specific studies reviewed.

2.1.1 Drug Class and Indication

Per the Applicant, POS is a sterile, preservative-free ophthalmic solution for topical ocular administration that reduces PD moderately via inhibition of α-1 adrenergic receptors on the dilator muscle of the iris. The proposed indication is for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof.

2.1.2 History of Drug Development

The protocols (original and amendments) and the statistical analysis plans (SAPs) for Studies MIRA-2 and MIRA-3 were reviewed under IND70499. The Applicant had a series of discussions with the DO to reach agreement on the development program for POS. The summary of the relevant interactions between the Applicant and the DO are provided below:

- On 05/11/2020, the Applicant had an end-of-phase 2 (EOP 2) meeting with the Division. As POS had been evaluated for other indications, this meeting was specifically centered on the Applicant's intention to evaluate POS for the indication "the treatment of pharmacologically- induced mydriasis produced by adrenergic (phenylephrine) or parasympatholytic (tropicamide) agents, or a combination thereof" in pivotal clinical studies. During this meeting, the Applicant discussed the design of the two pivotal studies, MIRA-2 and MIRA-3 to support the indication of reversal of mydriasis. The following recommendations were communicated with the Applicant:

  - Allow subjects as young as 12 years of age into studies for reversal of mydriasis.

  - The pediatric dosing in MIRA-2 should be changed FROM "two drops in study eye/one drop in non-study eye" TO "one drop in each eye". If one drop is well tolerated in the MIRA-2 study, the Applicant could plan to increase the dose in MIRA-3 in subjects aged 12-17 years TO "two drops in study eye/one drop in non-study eye" FROM "one drop in each eye"; the same dose as used in adults in the MIRA-2/ MIRA-3 studies.

  - The design of the two studies to be double-masked, placebo-controlled, parallel arm.

  - The statistical plan to be designed to allow for stratification of safety and efficacy analysis, if appropriate, for adult vs. pediatric subjects.

  - The treatment group should demonstrate a statistically significant difference in the number of patients who have a pupillary diameter that returns to its baseline (within 0.2 millimeters of baseline) under defined and controlled lighting conditions as compared to the vehicle group.

  - Efficacy in reversing pupillary dilation be demonstrated within 60 minutes of product administration and that duration of the treatment effect be evaluated. Note, in the two pivotal studies, the Applicant evaluated the primary endpoint at 90 minutes.

  - The inclusion of adult as well as pediatric population in the safety evaluation was agreed up on. The discussion concluded on an agreement to consider phenylephrine/tropicamide agents as the two are the commonly used mydriatic product in practice. A consideration of two mydriatic combined was suggested.

- On 06/24/2022, the Applicant had a Type B Pre-NDA meeting with the DO to discuss the format and content of their planned NDA. In addition to the format and content of the NDA submission, the Applicant also submitted questions regarding the planned integrated safety (ISS) and integrated efficacy (ISE) analyses. The Division stated that analysis of the pooled data is acceptable provided the study reports, data and relevant SAS codes are presented for each individual study separately.

  The Applicant also requested (b) (4) (b) (4)

(b) (4)

The Applicant stated that many secondary endpoints were found to be statistically significant with a p<0.0001 in the MIRA-3 study, which included a hierarchical analysis plan of primary and secondary endpoints; the findings in the MIRA-2 study was of a similar magnitude, but this study had no prespecified hierarchical analysis plan. The Applicant asked if the Division agreed (b) (4)

(b) (4)

(b) (4) Additionally, the Division provided further clarity stating that the appropriateness of pooling study data was based on comparable study designs; it may be better to see treatment effects independently from 2 separate studies. The Applicant noted that both pivotal studies were similarly designed and indicated that they plan to provide both separate study and pooled study data/analysis in the NDA.

2.1.3 Studies Reviewed

The Applicant's overall efficacy summary for the primary efficacy endpoint in the two pivotal studies is presented in Table 3. For the summary of the additional studies, please see Appendix.

Table 3: Efficacy Summaries of MIRA-2 and MIRA-3

Design	Treatment (Sample size)	Endpoint/Analysis	Applicant's findings
MIRA-2 [1] RD, DM, PC	• POS (N=94) • Placebo: (N=91)	**Primary Endpoint**: The percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline PD at 90 min after study treatment dosing. The primary efficacy analysis provided the percentage of subjects whose study eyes returned to ≤ 0.2 mm from baseline PD at 90 min after study treatment, the Odds ratio and a 2-sided 95% CI using a logistic regression model based on the modified intent to treat population (mITT).	The study **met** its primary objective of demonstrating the statistical superiority of POS against placebo. The percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline PD at 90 min after study treatment dosing was 48.9% in the POS arm compared to 6.6% in the placebo arm resulting in an odds ratio of 25.93 (95% CI: 9.37, 71.79).

MIRA-3 [1] RD, DM, PC	• POS (N=244) • Placebo: (N=124)	**Primary Endpoint**: The percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline PD at 90 min after study treatment dosing. The primary efficacy analysis provided the percentage of subjects whose study eyes returned to ≤ 0.2 mm from baseline PD at 90 min after study treatment, the Odds ratio and a 2-sided 95% CI using a logistic regression model based on the modified intent to treat population (mITT).	The study **met** its primary objective of demonstrating the statistical superiority of POS against placebo. The percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline PD at 90 min after study treatment dosing was 58.2% in the POS arm compared to 5.6% in the placebo arm resulting in an odds ratio of 55.64 (95% CI: 23.04, 134.39).

Source: Applicant's study reports. [1]RD: Randomized, DB: Double-Masked, PC: Placebo-controlled.

Review comments: *Note, the Applicant has conducted a total of 11 studies. Of the 11 studies submitted by the Applicant, only 4 studies support this application. The remaining 7 studies focus on other indications:* (b) (4) (b) (4)

2.2 Data Sources

The data source for this review included the clinical study reports, the analysis and tabulation datasets, study protocols and corresponding statistical analysis plans, and the integrated summary of safety and efficacy datasets. These are provided in an electronic submission located at \\CDSESUB1\evsprod\NDA217064\0001.

For each study, the following datasets submitted by the Applicant are used in this statistical review:

- adsl.xpt: contains the demographic and disposition data.
- adeff.xpt: contains the PD efficacy data.
- adae.xpt: contains the adverse event data.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets and analyses conducted by the Applicant are acceptable. The data definition files, and reviewer's guide submitted in the NDAs were sufficiently detailed to facilitate replication of the findings from the Applicant's primary analysis and other major analyses using the submitted datasets.

3.2 Evaluation of Efficacy

This section summarizes the design of the two pivotal studies MIRA-2 and MIRA-3 and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Both studies were randomized, parallel-arm, double-masked, placebo-controlled Phase 3 studies. The primary objective of these studies was to evaluate the safety and efficacy of POS compared to placebo. To be eligible for these studies, patients had to meet the following inclusion criteria:

- Males or females ≥ 12 years of age
- Ability to comply with all protocol-mandated procedures independently and to attend all scheduled office visits
- 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

In addition to the inclusion criteria listed above, MIRA-2 listed an additional inclusion criterion which is specified in the protocol as "subjects needed to be healthy and well-controlled."

MIRA-2 enrolled a total of 185 eligible subjects (171 adults and 14 adolescents ≥ age 12) with pharmacologically induced mydriasis. Eligible subjects were randomized to POS or placebo in a 1:1 ratio. Similarly, MIRA-3 enrolled a total of 368 subjects (337 adults and 31 adolescents ≥ age 12) with pharmacologically induced mydriasis. Eligible subjects were randomized to the two treatment arms in 2:1 ratio. In both studies, randomization was stratified by irides type and mydriatic agent. Note the composition of the mydriatic agents was 3:1:1; 2.5% phenylephrine, 1% tropicamide, or Paremyd, respectively.

Subjects in both studies received 1 drop of mydriatic agent in each eye. One hour after mydriatic drug instillation, adult subjects had 2 drops of study treatment (POS or placebo) administered in the study eye (right eye [OD]). Drops were instilled 5 min apart. Subjects received only 1 drop of study treatment in the fellow eye (left eye [OS]) 1 hour after mydriatic drug instillation. The two studies used different dosing for pediatric patients. For MIRA-2, pediatric subjects received 1 drop of study treatment in both eyes (OU), while in MIRA-3, pediatric subjects received 2 drops in the study eye and 1 drop in the fellow eye.

The primary clinical outcome of interest was pupil's diameter (PD) measured using a pupillometer (VIP-300) in both MIRA-2 and MIRA-3 studies. In each study, PD measurements were taken 1 hour before mydriatic agent installation (baseline) and 60 min after mydriatic agent instillation, i.e., immediately before the study treatment was administered to each eye. Additional

measurements were taken at 30 min, 60 min, 90 min, 2-hour, 3-hour, 4-hour, and 6-hour after study treatment dosing.

3.2.1.2 Study Endpoints

The primary efficacy endpoint of the studies was the percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline PD at 90 min after study treatment dosing. For both MIRA-2 and MIRA-3, secondary efficacy endpoints include:

- Percentage of subjects returning to ≤ 0.2 mm from baseline (-1 hour) photopic PD at each remaining time point (0 minutes, 30 minutes, 60 minutes, 90 minutes [fellow eye], 2 hours, 3 hours, 4 hours, 6 hours, and 24 hours)

- Change (in mm) in photopic PD from max pupil dilation (0 minutes) at each time point (30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, and 24 hours)

- Time (hours) to return to ≤ 0.2 mm from baseline (-1 hour) photopic pupil diameter (time-savings analysis)

- Percentage of subjects with unchanged accommodation from baseline (-1 hour) at 0 minutes, 90 minutes, 2 hours, 3 hours, and 6 hours Change (in diopters) in accommodation from max pupil dilation (0 minutes) at 90 minutes, 2 hours, 3 hours, and 6 hours

- Change (in letters) in photopic BCDVA (best-corrected distance visual acuity) from baseline (-1 hour) at 0 minutes, 60 minutes, 2 hours, and 6 hours

- Change (in letters) in photopic DCNVA (distance-corrected near visual acuity) from baseline (-1 hour) at 0 minutes, 90 minutes, 3 hours, and 6 hours

3.2.2 Statistical Methods

This section describes the statistical hypotheses, sample size calculations, and efficacy analyses presented in this review that are performed by the Applicant, as described in the SAPs for Study MIRA-2 and MIRA-3, as well as independent analyses performed by the statistical reviewer for the objective clinical response.

3.2.2.1 Hypotheses testing, Type-1 error Control and Sample Size

- ❑ Hypothesis Testing

The Sponsor claimed a superiority of POS over placebo which would imply a one-sided hypothesis testing. However, to see both side of the story, based on the Agency's position, the primary null and alternative hypotheses related to the primary efficacy endpoint for the comparison of POS against placebo can be mathematically stated as follows:

$$H_{o1}: Ppos = Pplacebo$$

$$H_{a1}: Ppos \neq Pplacebo$$

where *Ppos*, and *Pplacebo* respectively represent the percentage of success (returning PD to <0.2mm) POS and placebo arms, respectively.

- ❑ Type-1 error Control

In MIRA-3, the Applicant implemented a fixed-sequence testing procedure to control the family-wise type-I error due to the testing of the primary and secondary efficacy endpoints (Table 39). However, for MIRA-2, no adjustments for multiplicity due to the comparison of the two treatment arms with respect to secondary efficacy endpoints was implemented. (b) (4)

(b) (4)

(b) (4)

- ❑ Sample Size

– MIRA-2: A sample size of 160 subjects was planned. This sample size was calculated based an estimated 12% placebo effect and a 30% POS treatment effect, a significant level of 5%. This sample size was meant to provide 80% power to detect a treatment difference of 18% between the POS and placebo arms in percentage of subjects returning to ≤ 0.2 mm from baseline PD at 90 min.

– MIRA-3: A sample seize of 330 subjects was planned. The sample size calculation was done to achieve a >90% power to detect a difference of 25% between the POS and placebo arms in percentage of subjects returning to ≤ 0.2 mm from baseline PD at 90 min.

3.2.2.2 Analysis Populations

The two studies defined the analysis populations as follows:

– Modified Intention-to-Treat Population (mITT): The mITT population included all randomized subjects who received 2 drops of study medication in the study eye and then had at least 1 subsequent PD measurement during Visit 1 (Day 1). The mITT population was used for the primary endpoint analysis and to analyze selected secondary efficacy endpoints. Subjects were included in the treatment group to which they were randomized, regardless of the treatment they received.

– Per Protocol Population (PP): The PP included all subjects in the mITT population who had 2 drops of study medication in their study eye, completed all scheduled PD measurements during Visit 1, had an increase of > 0.2 mm in PD in the study eye at 0 min compared to baseline (-1 hour) PD, and had no major protocol deviations considered to have significant impact on treatment outcome. The PP population was used to analyze selected secondary efficacy endpoints, and subjects were included in the treatment group to which they were randomized, regardless of the treatment they received.

– All Randomized Population (ARP): The ARP included all randomized subjects. This population was an intention-to-treat (ITT) population. The ARP was used in confirmatory efficacy analyses. Subjects were included in the treatment group to which they were randomized, regardless of the treatment they received.

– The Safety Population: The safety population included all randomized subjects who received at least 1 drop of study medication. The safety population was used to summarize safety variables, using the treatment they actually received.

Reviewer comment*: As shown above, per definition, the mITT population excludes subjects with no post baseline measurements. However, because all subjects in both studies had at least one-post baseline measurement, the mITT population included all randomized subjects. Therefore, the results based on the mITT population are acceptable.*

3.2.2.3 Analysis Methods

The primary efficacy analysis for both studies was conducted based on the mITT population using a logistic regression. The model included treatment, mydriatic agent, and light/dark irides as factors and the baseline PD as a covariate. From the model, the percentage of subjects in each treatment group meeting the criteria (an increase of > 0.2 mm in PD in the study eye), the odds ratio (OR) with 95% confidence interval (CI), and p-value are provided.

Per the SAP, if 5% or fewer data are missing, the last observation forward (LOCF) approach would be used. However, if the missing data exceeds 5%, a multiple imputation approach under the missing at random (MAR) assumption was to be implemented. Note, single imputation approaches such as LOCF are not generally recommended. Likely due to the study's short duration (one day), measurements for the primary endpoint were complete with no missing values, and hence, no imputation was done.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

As can be seen from Table 4, in both studies, none of the randomized subjects discontinued the study. This is to be expected given the short duration of the study. Consequently, the safety and modified-intent-to-treat populations are identical to all randomized subjects. The proportion of subjects excluded from the per-protocol population is comparable between the two arms in both studies.

Table 4: Patient Disposition

	MIRA-2		**MIRA-3**	
	POS N (%)	**Placebo N (%)**	**POS N (%)**	**Placebo N (%)**
All randomized (ARP)	94	91	244	124
mITT Population	94 (100)	91 (100)	244 (100)	124 (100)
PP Population	84 (89.4)	81 (89.0)	230 (94.3)	115 (92.7)

Safety Population	94(100)	91(100)	185(100)	244(100)
Completed study	94 (100)	91 (100)	244 (100)	124 (100)
Completed study medication dosing	94 (100)	91 (100)	244 (100)	124 (100)

Source: Table 14.1.1 of the Applicant's study reports

3.2.3.2 Demographic and Baseline Characteristics

Within each study, there is no notable difference in demographics and baseline characteristics between treatments (Table 5 and Table 6). In all arms, there were more female participants than male participants, and most of the study participants were White with a median age of around 31 years.

Table 5: Demographics and Baseline Characteristics (mITT Population) in MIRA-2

	POS (n=94)	**Placebo (n=91)**	**Total (N=185)**
Age, years			
n	94	91	185
Mean (SD)	33.9 (14.04)	32.8 (13.55)	33.4 (13.77)
Median	31.0	30.0	31.0
Min, max	12, 70	13, 73	12, 73
Sex, n (%)			
Male	36 (38.3)	36 (39.6)	72 (38.9)
Female	58 (61.7)	55 (60.4)	113 (61.1)
Race, n (%) [a]			
White	70 (74.5)	74 (81.3)	144 (77.8)
American Indian or Alaska Native	1 (1.1)	1 (1.1)	2 (1.1)
Native Hawaiian or Other Pacific Islander	1 (1.1)	0	1 (0.5)
Black or African American	17 (18.1)	16 (17.6)	33 (17.8)
Asia	6 (6.4)	3 (3.3)	9 (4.9)
Study eye, n (%)			
OD	94 (100)	91 (100)	185 (100)
Irides type, n (%)			
Light	45 (47.9)	45 (49.5)	90 (48.6)
Dark	49 (52.1)	46 (50.5)	95 (51.4)
Distance vision/Near vision correction needed, n (%)			
Yes	59 (62.8)	53 (58.2)	112 (60.5)
No	35 (37.2)	38 (41.8)	73 (39.5)
Mydriatic agent, n (%)			
Phenylephrine	56 (59.6)	55 (60.4)	111 (60.0)
Tropicamide	19 (20.2)	18 (19.8)	37 (20.0)
Paremyd	19 (20.2)	18 (19.8)	37 (20.0)
PD (-1 hr) in the study eye, mm			
n	94	91	185
Mean (SD)	5.085 (0.9295)	5.177 (0.9678)	5.130 (0.9471)
Median	5.020	5.190	5.140
Minimum, maximum	2.91, 7.88	3.07, 7.68	2.91, 7.88
PD (-1 hr) in the fellow eye, mm			
n	94	91	185
Mean (SD)	5.049 (0.9707)	5.220 (0.9633)	5.133 (0.9682)
Median	4.980	5.230	5.150

Minimum, maximum	2.90, 7.30	2.89, 7.33	2.89, 7.33
Maximum PD (0 min) in the study eye, mm			
n	94	91	185
Mean (SD)	7.207 (1.0240)	7.197 (1.1717)	7.202 (1.0961)
Median	7.245	7.370	7.340
Minimum, maximum	4.04, 9.28	4.50, 9.14	4.04, 9.28
Maximum PD (0 min) in the fellow eye, mm			
n	94	91	185
Mean (SD)	7.169 (1.1117)	7.241 (1.1099)	7.204 (1.1084)
Median	7.230	7.330	7.270
Minimum, maximum	3.67, 9.53	4.56, 9.12	3.67, 9.53
DCNVA (-1 hr) in the study eye, letters			
n	94	91	185
Mean (SD)	65.6(10.63)	67.0 (9.74)	66.3 (10.20)
Median	70.0	70.0	70.0
Minimum, maximum	24, 80	27, 80	24, 80
DCNVA (-1 hr) in the fellow eye, letters			
n	94	91	185
Mean (SD)	65.7 (10.34)	67.4 (9.70)	66.6 (10.04)
Median	70.0	70	70.0
Minimum, maximum	30, 79	31, 80	30, 80

Source: Table 14.1.2.2 of the Applicant's study reports. DCNVA, distance-corrected near visual acuity; OD, right eye; PD, pupil diameter; SD, standard deviation. [a]Subjects can be included in more than 1 category, so the sum of the percentages may be greater than 100%.

Table 6: Demographics and Baseline Characteristics (mITT Population) in MIRA-3

	POS (n=24)	**Placebo (n=124)**	**Total (N=368)**
Age, years			
n	244	124	368
Mean (SD)	34.2 (15.61)	35.6 (17.58)	34.6 (16.29)
Median	31.0	30.0	30.0
Min, max	12, 80	12, 80	12, 80
Sex, n (%)			
Male	92 (37.7)	59 (47.6)	151 (41.0)
Female	152 (62.3)	65 (52.4)	217 (59.0)
Race, n (%) [a]			
White	182 (74.6)	93 (75.0)	275 (74.7)
American Indian or Alaska Native	1 (0.4)	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	4 (1.6)	0	4 (1.1)
Black or African American	38 (15.6)	21 (16.9)	59 (16.0)
Asia	22 (9.0)	9 (7.3)	31 (8.4)
Other	0	1 (0.8)	1 (0.3)
Study eye, n (%)			
OD	244 (100)	124 (100)	368 (100)
Irides type, n (%)			
Light	113 (46.3)	58 (46.8)	171 (46.5)
Dark	131 (53.7)	66 (53.2)	197 (53.5)
Distance vision/Near vision correction needed, n (%)			
Yes	156 (63.9)	78 (62.9)	234 (63.6)
No	88 (36.1)	46 (37.1)	134 (36.4)
Mydriatic agent, n (%)			

Phenylephrine	146 (59.8)	74 (59.7)	220 (59.8)
Tropicamide	50 (20.5)	26 (21.0)	76 (20.7)
Paremyd	48 (19.7)	24 (19.4)	72 (19.6)
PD (-1 hr) in the study eye, mm			
n	244	124	368
Mean (SD)	5.141 (1.2558)	4.932 (1.1682)	5.070 (1.2294)
Median	5.265	4.885	5.145
Minimum, maximum	2.06, 7.97	2.12, 7.56	2.06, 7.97
PD (-1 hr) in the fellow eye, mm			
n	244	124	368
Mean (SD)	5.131 (1.2665)	4.828 (1.2283)	5.029 (1.2603)
Median	5.145	4.750	5.095
Minimum, maximum	2.03, 8.02	2.20, 7.34	2.03, 8.02
Maximum PD (0 min) in the study eye, mm			
n	244	124	368
Mean (SD)	7.214 (1.3165)	7.082 (1.2749)	7.170 (1.3024)
Median	7.475	7.275	7.415
Minimum, maximum	2.22, 9.49	4.12, 9.43	2.22, 9.49
Maximum PD (0 min) in the fellow eye, mm			
n	244	124	368
Mean (SD)	7.176 (1.3524)	7.057 (1.3360)	7.136 (1.3462)
Median	7.385	7.265	7.320
Minimum, maximum	2.32, 9.85	3.25, 9.38	2.32, 9.85
DCNVA (-1 hr) in the study eye, letters			
n	244	124	368
Mean (SD)	64.9 (11.19)	65.0 (11.89)	65.0 (11.42)
Median	70.0	70.0	70.0
Minimum, maximum	23, 83	30, 83	23, 83
DCNVA (-1 hr) in the fellow eye, letters			
n	244	124	368
Mean (SD)	65.5 (10.99)	64.8 (11.87)	65.3 (11.29)
Median	70.0	69.5	70.0
Minimum, maximum	29, 85	30, 80	29, 85

Source: Table 14.1.2.2 of the Applicant's study reports. DCNVA, distance-corrected near visual acuity; OD, right eye; PD, pupil diameter; SD, standard deviation. [a]Subjects can be included in more than 1 category, so the sum of the percentages may be greater than 100%.

Reviewer comments*: A subject's age in years was calculated using the date of the informed consent and date of birth. Other demographic characteristics not tabulated includes iris color (light blue, dark blue, blue with peripupillary brown, uniform green, green with brown iris ring, central brown and peripheral green, brown with some peripheral green, or brown), eyeglasses-wearing status (yes or no; distance vision or near vision), and accommodation, best-corrected distance visual acuity (BCDVA).*

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

A. Results for the Primary Efficacy Endpoint

This section summarizes the findings from the analyses of the primary endpoint for the two pivotal studies MIRA-2 and MIRA-3. Recall, the primary efficacy endpoint of the studies was the percentage of subjects' study eyes returning to ≤ 0.2 mm from baseline PD at 90 min after study treatment dosing.

In both studies, the primary efficacy analysis conducted based on the mITT population using a logistic regression model provided statistically significant results in favor of POS (Table 7). Per the observed results, compared to a subject randomized to placebo, the odds of a subject treated with POS to return to ≤ 0.2 mm PD from baseline were 26 and 56 times higher in MIRA-2 and MIRA-3, respectively.

Table 7: Percent of Subjects Returning to ≤ 0.2 mm From Baseline Pupil Diameter at 90 Minute Post Treatment (mITT Population) – Study Eye

	Treatments		
Study	**POS**	**Placebo**	**ODDS Ratio (95% CI)**
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.

The Applicant also provided the analysis of the primary efficacy endpoint for the fellow eye. The results are consistent with the results for the study eye. Note, the fellow eyes for adult subjects received one drop of the study drug while the study eye was dosed with two drops.

Table 8: Percent of Subjects Returning to ≤ 0.2 mm From Baseline Pupil Diameter at 90 Minute Post Treatment (mITT Population) – Fellow Eye

	Treatments		
Study	**POS**	**Placebo**	**ODDS Ratio (95% CI)**
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.

B. Sensitivity analysis for the Primary Efficacy Endpoint

As sensitivity analysis, the Applicant conducted the analysis of the primary efficacy endpoint using a logistic regression with treatment as a factor and the baseline PD as a covariate. Unlike the primary analysis, this analysis did not adjust for the stratifying factors, mydriatic agent and irides type. The results of the sensitivity analysis are consistent with the results of the primary efficacy analysis (Table 13 and Table 14).

C. Analysis of Secondary Efficacy Endpoints

This section presents the results of the secondary efficacy endpoints evaluated in the two studies. For binary endpoints, the analysis was conducted using a similar logistic model that was used for the protocol defined primary efficacy endpoints based on the mITT population. Overall, in both studies, the treatment differences were consistently favorable to the POS arm reaching statistical significance 60 minutes after treatment. Note, as discussed earlier, because no multiplicity adjustment was planned in MIRA-2, no formal inferential claim could be made for the secondary efficacy endpoints in this study (Table 15 and Table 16).

3.3 Evaluation of Safety

This section presents descriptive summaries of the percentages of treatment-emergent adverse events (TEAEs), from Study MIRA-2 and Study MIRA-3. These summaries are provided for the safety analysis population, which is defined in the SAPs as all randomized patients who receive at least 1 dose of study medication. The safety analysis population is comprised of 185 subjects in Study MIRA-2 [POS (94); placebo (91)], and 368 subjects in Study MIRA-3 [POS (244) and Placebo (124)].

3.3.1 Adverse Event Summary

This section presents the overall adverse event summary and treatment emergent adverse event (TEAE) reported for each study separately. In both studies, a higher percentage of subjects in the POS arm reported at least one TEAE compared to subjects in the placebo arm.

MIRA-2

A total of 113 treatment emergent adverse events (TEAEs) were reported in 50 subjects (53%) treated with POS and 31 TEAEs were reported in 15 subjects (17%) treated with placebo. All subjects experienced mild TEAEs, except for 3 subjects in the POS group (1 TEAE each of instillation site discomfort, instillation site pain, and dysgeusia), who experienced TEAEs that were moderate in severity and considered related to study medication per the Investigator. Four subjects (2 in the POS group [2%] and 2 in the placebo group [2%]) had TEAEs that were considered possibly related to study medication per the Investigator; 23 (17 in the POS group [18%] and 6 in the placebo group [7%]) had TEAEs that were considered probably related, and 36 (30 in the POS group [32%] and 6 in the placebo group [7%]) had TEAEs that were considered definitely related. Most of the treatment related TEAEs in the POS group were general disorders and administration site conditions (most common preferred term was instillation site discomfort; 38%) or eye disorders (most common preferred term was conjunctival hyperemia; 13%; Table 9 and Table 10).

MIRA-3

A total of 101 TEAEs were reported in 48 subjects (20%) treated with POS and 7 TEAEs were reported in 6 subjects (5%) treated with placebo. All TEAEs were mild, except for 1 in the POS group, in which the subject experienced a TEAE that was moderate in severity and considered unlikely related to study medication per the Investigator. Three subjects (1 in the POS group [0.4%] and 2 in the placebo group [1.6%]) had TEAEs that were considered unlikely related to study medication per the Investigator; 8 subjects (6 in the POS group [2.5%] and 2 in the placebo group [1.6%]) had TEAEs that were considered possibly related to study medication per the Investigator; 3 subjects (all in the POS group [1.2%]) had TEAEs that were considered probably related, and 40 subjects (38 in the POS group [15.6%] and 2 in the placebo group [1.6%]) had TEAEs that were considered definitely related to study medication per the Investigator. Most of the treatment related TEAEs in the POS group were eye disorders (most common preferred term was conjunctival hyperemia; 10.7%; Table 11 and Table 12).

Table 9: Overall Summary of Adverse Events (Up to Month 18: MIRA-2)

Adverse Events	POS (n=94) n (%)	Placebo (n=91) n (%)	Total (N=185) n (%)
Total number of TEAEs, n [a]	113	31	144
Subjects reporting any TEAEs	50 (53.2)	15 (16.5)	65 (35.1)
Subjects reporting TEAE by maximum severity			
Mild	47 (50.0)	15 (16.5)	62 (33.5)
Moderate	3 (3.2)	0	3 (1.6)
Severe	0	0	0
Subjects reporting TEAE by greatest relationship			
Not related	0	1 (1.1)	1 (0.5)
Unlikely related Possibly related	1 (1.1)	0	1 (0.5)
Probably related	2 (2.1)	2 (2.2)	4 (2.2)
Definitely related	17 (18.1)	6 (6.6)	23 (12.4)
	30 (31.9)	6 (6.6)	36 (19.5)
Subjects reporting any serious TEAE	0	0	0
Subjects reporting any TEAE leading to withdrawal from the study	0	0	0
Subjects reporting any TEAE leading to study medication discontinuation	0	0	0
Subject deaths	0	0	0

Source: Table 14.3.1.1 of the Applicant's study reports. AE, adverse event; TEAE, treatment-emergent adverse event. [a] In counting the number of AEs reported, an AE is defined as an event with a unique subject identification number, system organ class, preferred term, and site. Bilateral ocular events are counted twice (i.e., once for each eye).

Table 10: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population) Study MIRA-2)

System Organ Class Preferred Term	POS (n=94) n (%)	Placebo (n=91) n (%)	Total (N=185) n (%)
Total number of TEAEs [a]	113	31	144
Subjects reporting any TEAEs	50 (53.2)	15 (16.5)	65 (35.1)
General disorders and administration site conditions	40 (42.6)	12 (13.2)	52 (28.1)
Instillation site coldness	0	1 (1.1)	1 (0.5)
Instillation site discomfort	36 (38.3)	8 (8.8)	44 (23.8)
Instillation site erythema	4 (4.3)	0	4 (2.2)
Instillation site pain	3 (3.2)	4 (4.4)	7 (3.8)
Eye disorders	14 (14.9)	2 (2.2)	16 (8.6)
Conjunctival hyperaemia	12 (12.8)	0	12 (6.5)
Dry eye	0	1 (1.1)	1 (0.5)
Eye irritation	0	1 (1.1)	1 (0.5)
Swelling of eyelid	1 (1.1)	0	1 (0.5)
Visual impairment	1 (1.1)	1 (1.1)	2 (1.1)
Nervous system disorders	5 (5.3)	1 (1.1)	6 (3.2)
Dysgeusia	4 (4.3)	0	4 (2.2)
Headache	1 (1.1)	1 (1.1)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	2 (2.1)	0	2 (1.1)
Nasal congestion	1 (1.1)	0	1 (0.5)

Sinus disorder	1 (1.1)	0	1 (0.5)
Throat irritation	1 (1.1)	0	1 (0.5)
Investigations	1 (1.1)	1 (1.1)	2 (1.1)
Intraocular pressure increased	1 (1.1)	1 (1.1)	2 (1.1)
Vascular disorders	1 (1.1)	0	1 (0.5)
Hypertension	1 (1.1)	0	1 (0.5)

Source: Table 14.3.1.2.1 of the Applicant's study reports. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event. [a] In counting the number of AEs reported, an AE is defined as an event with a unique subject identification number, system organ class, preferred term, and site. Bilateral ocular events are counted twice (ie, once for each eye). NOTE: A subject reporting >1 TEAE (preferred term) is only counted once within the system organ class and once within the preferred term. Adverse events are coded with MedDRA Version 22.0

Table 11: Overall Summary of Adverse Events (Up to Month 12: MIRA-3)

Adverse Events	**POS (n=244) n (%)**	**Placebo (n=124) n (%)**	**Total (N=368) n (%)**
Total number of TEAEs, n [a]	101	7	108
Subjects reporting any TEAEs	48 (19.7)	6 (4.8)	54 (14.7)
Subjects reporting TEAE by maximum severity			
Mild	47 (19.3)	6 (4.8)	53 (14.4)
Moderate	1 (0.4)	0	1 (0.3)
Severe	0	0	0
Subjects reporting TEAE by greatest relationship			
Not related	0	0	0
Unlikely related	1 (0.4)	2(1.6)	3 (0.8)
Possibly related	6 (2.5)	2.(1.6)	8 (2.2)
Probably related	3 (1.2)	0	3 (0.8)
Definitely related	38 (15.6)	2 (1.6)	40 (10.9)
Subjects reporting any serious TEAE	0	0	0
Subjects reporting any TEAE leading to withdrawal from the study	0	0	0
Subjects reporting any TEAE leading to study medication discontinuation	0	0	0
Subject deaths	0	0	0

Source: Table 14.3.1.1 of the Applicant's study reports. AE, adverse event; TEAE, treatment-emergent adverse event. [a] In counting the number of AEs reported, an AE is defined as an event with a unique subject identification number, system organ class, preferred term, and site. Bilateral ocular events are counted twice (i.e., once for each eye).

Table 12: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population) Study MIRA-3)

System Organ Class Preferred Term	**POS (n=244) n (%)**	**Placebo (n=124) n (%)**	**Total (N=368) n (%)**
Total number of TEAEs [a]	101	7	108
Subjects reporting any TEAEs	48 (19.7)	6 (4.8)	54 (14.7)
General disorders and administration site conditions Instillation site erythema	14 (5.7) 9 (3.7)	1 (0.8) 0	15 (4.1) 9 (2.4)
Instillation site pain	5 (2.0)	1 (0.8)	6 (1.6)
Eye disorders	30 (12.3)	3 (2.4)	33 (9.0)
Conjunctival hyperaemia	26 (10.7)	0	26 (7.1)
Eye irritation	1 (0.4)	0	1 (0.3)
Eye pain	0	1 (0.8)	1 (0.3)

Eyelid disorder	1 (0.4)	0	1 (0.3)
Ocular discomfort	1 (0.4)	0	1 (0.3)
Visual acuity reduced	1 (0.4)	1 (0.8)	2 (0.5)
Vitreous floaters	0	1 (0.8)	1 (0.3)
Nervous system disorders	14 (5.7)	2 (1.6)	16 (4.3)
Dysgeusia	8 (3.3)	0	8 (2.2)
Headache	6 (2.5)	2 (1.6)	8 (2.2)
Tremor	1 (0.4)	0	1 (0.3)
Investigations	1 (0.4)	0	1 (0.3)
Heart rate increased	1 (0.4)	0	1 (0.3)

Source: Table 14.3.1.2.1 of the Applicant's study reports. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event. [a] In counting the number of Aes reported, an AE is defined as an event with a unique subject identification number, system organ class, preferred term, and site. Bilateral ocular events are counted twice (ie, once for each eye). NOTE: A subject reporting >1 TEAE (preferred term) is only counted once within the system organ class and once within the preferred term. Adverse events are coded with MedDRA Version 22.0

Reviewer comment: *For both MIRA-2 and MIRA-3, the prevalence of TEAEs was higher with POS treatment compared with placebo treatment, but almost all the POS related TEAEs were mild in severity. Note that there were no severe TEAEs, serious TEAEs, or TEAEs leading to withdrawal or study medication discontinuation. This may be an indication that the treatment was tolerated.*

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In MIRA-2 and MIRA-3, the Applicant conducted subgroup analysis of the primary efficacy endpoint for subgroups formed based on mydriatic agent and by light/dark irides. The subgroup analyses were conducted using the same logistic regression model used for the primary efficacy analysis. However, the logistic model was fitted without mydriatic agent or irides as a factor as appropriate. In addition, missing data was not imputed. Note, in MIRA-3, treatment comparisons in subgroups based on mydriatic agent and irides color were listed as alpha-adjusted comparisons

This reviewer also provided subgroup summaries for subgroups based on gender, race, and age group (<18, >=18 years). Overall, the subgroup results are generally consistent with the Applicant's primary efficacy analysis results (Table 17-Table 38).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

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 formal inferential claims for the nominally significant treatment (b) (4)

(b) (4)

(b) (4)

5.2 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.

5.3 Conclusions and Recommendations

Overall, the results in this review provide evidence to support the efficacy of POS for the treatment of pharmacologically induced mydriasis. Safety wise, 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.

5.4 Labeling Recommendations

After the review of this NDA including the draft labeling and different communication between the Agency and the Applicant, this reviewer recommends the following:

1) As family-wise type I error rate for the primary and secondary endpoints was only controlled in study MIRA-3, it is recommended that the odds ratios and their corresponding 95 % CI be presented without the p-values. Besides, (b) (4) (b) (4)

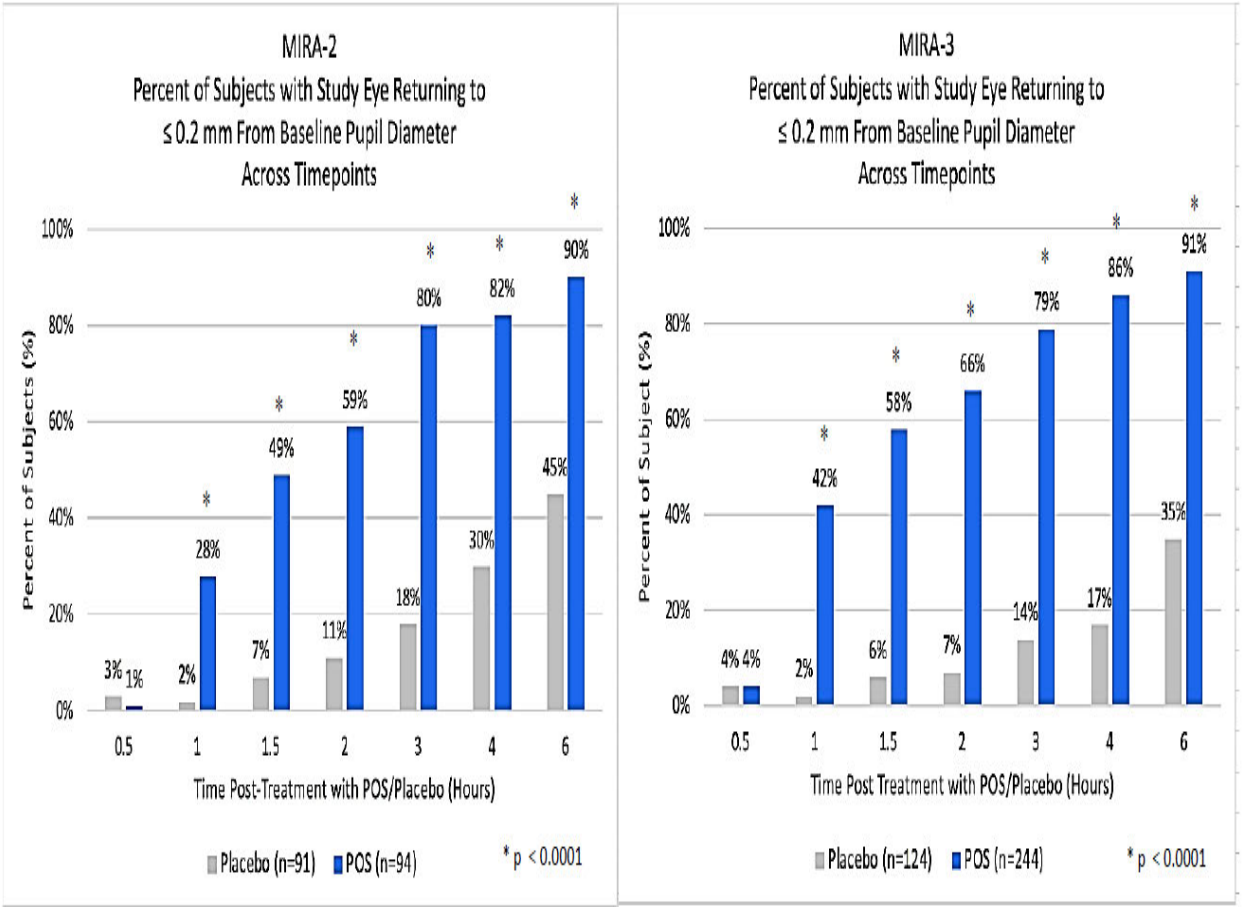
2) (b) (4) (b) (4) As the Agency has previously recommended, results for each study should be presented instead.

Applicant's summary in Section 14 of the Drug Label

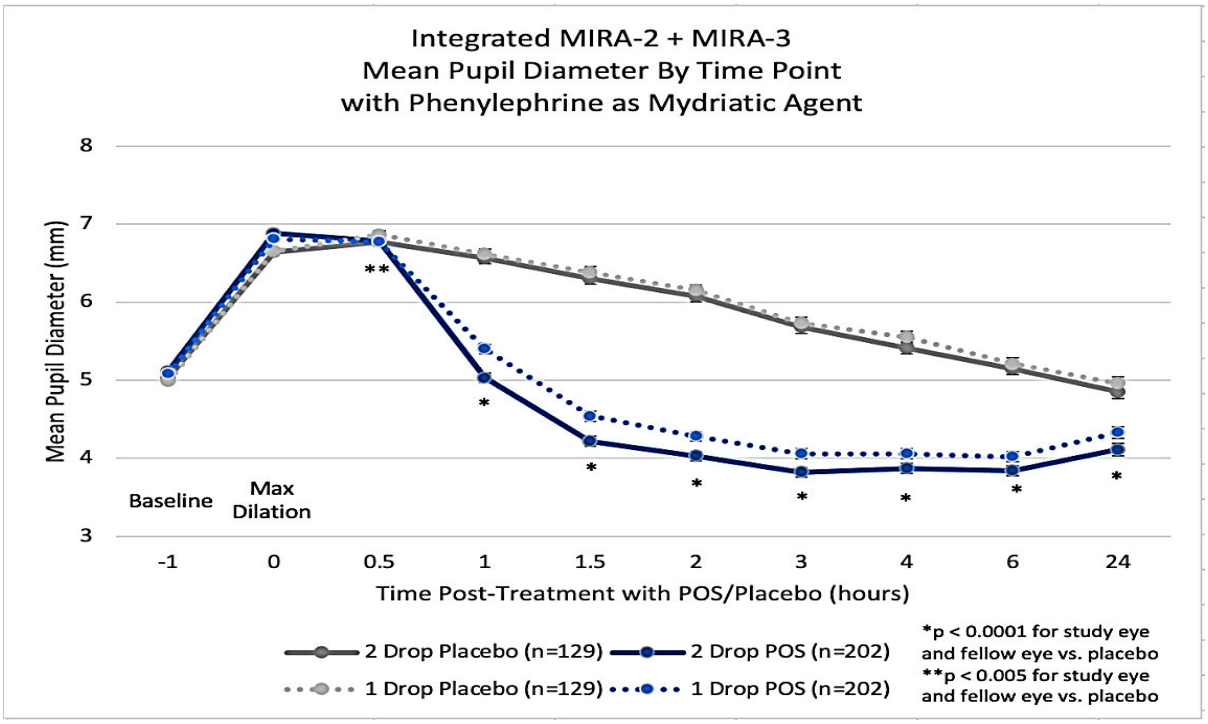
The efficacy of Phentolamine Ophthalmic Solution 0.75% (POS) for the reversal of mydriasis was demonstrated in two, randomized, double-masked, vehicle-controlled trials; MIRA-2 (NCT#04620213) and MIRA-3 (NCT#05134974). A total of 553 subjects aged 12 to 81 years old who had mydriasis induced by instillation of phenylephrine or tropicamide or a combination

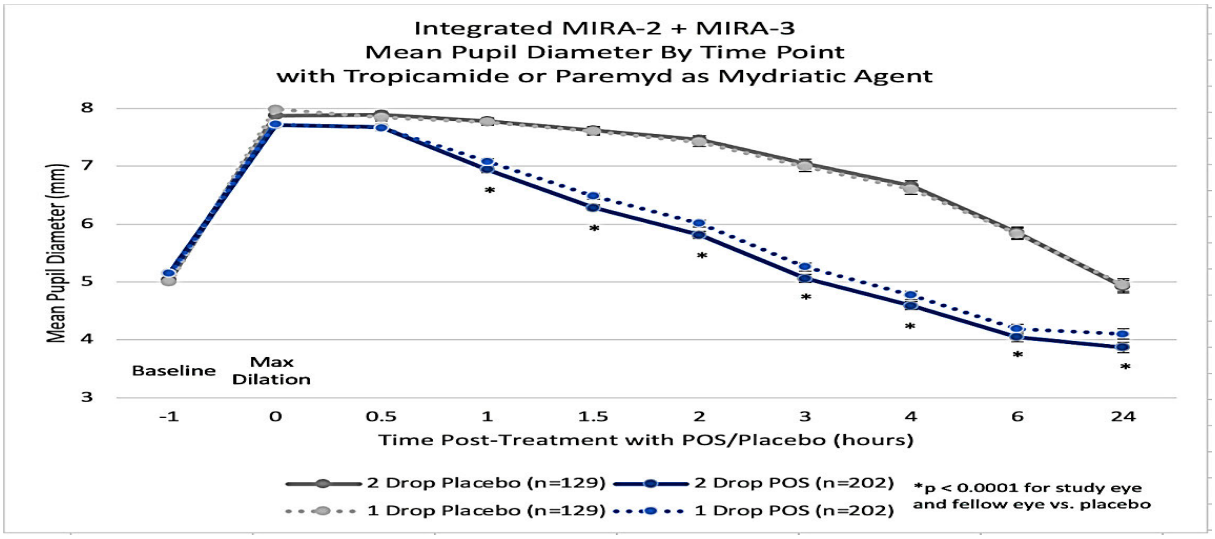
of hydroxyamphetamine hydrobromide and tropicamide (Paremyd) were randomized. Two drops (study eye) or one drop (fellow eye) of Phentolamine Ophthalmic Solution 0.75% or placebo (vehicle) were administered one hour after instillation of the mydriatic agent. The percentage of subjects with study eyes returning to ≤0.2 mm from baseline pupil diameter was statistically significantly greater (p<0.0001) at all time points measured from 60 minutes through 24 hours in the Phentolamine Ophthalmic Solution 0.75% group compared with the placebo (vehicle) group across both of the MIRA-2 and MIRA-3 studies (see Figure 1). In an integrated efficacy analysis of MIRA-2 and MIRA-3, a statistically significantly greater percentage of subjects with study eyes in the POS- treated group versus the placebo-treated group returned to ≤0.2 mm from their baseline pupil diameter at 60 minutes (38% vs. 2%, respectively; p<0.0001), at 90 vs. 6%, respectively; p<0.0001), and at 6 hours (91% vs. 40%, respectively; p<0.0001*). Similar statistically significant results were also seen in the fellow eye (Table 1).*

	At 60 Minutes			At 90 Minutes			At 6 hours		
	POS (n=338)	**Placebo (n=215)**	**p-value**	**POS (n=338)**	**Placebo (n=215)**	**p-value**	**POS (n=338)**	**Placebo (n=215)**	**p-value**
2 drop (Study Eye)	38%	2%	p<0.0001	56%	6%	p<0.0001	91%	40%	p<0.0001
1 drop (Fellow Eye	27%	5%	p<0.0001	51%	5%	p<0.0001	89%	37%	p<0.0001



The integrated efficacy of MIRA-2 and MIRA-3 also showed that the change from maximum pupil dilation in study eyes and fellow eyes was statistically significantly different between the POS-treated group and the placebo-treated group at all time points from 60 minutes through 24 hours post-treatment ($p<0.0001$). These results were consistent regardless of whether phenylephrine or tropicamide/Paremyd were used as mydriatic agents (Figure 2, Figure 3; respectively).





Across all subjects, the mean time to return to ≤0.2 mm from baseline pupil diameter in study eyes (2 drops) was statistically significantly shorter in POS-treated group compared to the placebo-treated group, with an average time savings of 3.9 hours (p<0.0001). In light and dark irides, the time to return to ≤0.2 mm from baseline pupil diameter in study eyes was statistically significantly shorter for the POS-treated group relative to the placebo-treated group (4.8 hours versus 3.1 hours; respectively; p<0.0001). Regardless of whether phenylephrine, tropicamide, or Paremyd were used as mydriatic agents, the time to return to ≤ 0.2 mm from baseline pupil diameter in study eyes was statistically significantly shorter for the POS-treated group relative to the placebo-treated group (3.9 hours, 3.7 hours, and 4.2 hours, respectively; p<0.0001). Additionally, fellow eyes treated with one drop showed similar results with a statistically significant time savings across all subjects, light/dark irides, and mydriatic agents (p<0.0001) (Table 2).

	2 Drop (Study Eye)				1 Drop (Fellow Eye)			
	POS n=314 (hours)	Placebo n=196 (hours)	POS Time Savings (hours)	p-value	POS n=314 (hours)	Placebo n=196 (hours)	POS Time Savings (hours)	p-value
Overall	2.2	6.1	3.9	p<0.0001	2.6	6.3	3.7	p<0.0001
Phenylephrine	1.3	5.2	3.9	p<0.0001	1.7	5.6	3.9	p<0.0001
Tropicamide	3.9	7.6	3.7	p<0.0001	4.2	7.3	3.1	p<0.0001
Paremyd	3.0	7.2	4.2	p<0.0001	3.5	7.4	3.9	p<0.0001
Light Irides	1.9	6.7	4.8	p<0.0001	2.3	6.7	4.4	p<0.0001
Dark Irides	2.4	5.5	3.1	p<0.0001	2.9	5.8	2.9	p<0.0001

Across all subjects, a statistically significantly greater percentage of study eyes treated with Phentolamine Ophthalmic Solution 0.75% returned to unchanged accommodation from baseline compared with placebo treatment at 90 min (63% vs 54%, respectively; p=0.0193), 2 hours (68% vs 56%, respectively; p=0.0012), and 6 hours (82% vs 73%, respectively; p=0.0109). Dilation with tropicamide or Paremyd (cycloplegic agents) caused an approximately 3.0 D reduction in accommodative power and the effect was more pronounced in these subjects. Among eyes receiving tropicamide or Paremyd, Phentolamine Ophthalmic Solution 0.75% treatment enabled a statistically significantly greater percentage of subjects to return to baseline accommodation in the study eye compared with placebo treatment at 2 hours (56% vs 40%, respectively; p=0.0407) 3 hours (69% vs 53%, respectively; p=0.0416), and 6 hours (81% vs 63%, respectively; p=0.0081).

Similar statistically significant effects on accommodation were seen in fellow eyes treated with one drop of Phentolamine Ophthalmic Solution 0.75%. Pharmacologically induced mydriasis reduced Distance-Corrected Near Visual Acuity (DCNVA) by least squares (LS) mean change of 9.4 letters from baseline. At 90 minutes, study eyes treated with Phentolamine Ophthalmic Solution 0.75% had returned to within 1 letter of baseline DCNVA. The difference between Phentolamine Ophthalmic Solution 0.75% and placebo DNCVA at 90 minutes was statistically significant (LS mean difference: 1.9 letters p<0.0001), as was the difference at 3 hours (LS mean difference 1.4 letters, p=0.0086). Similar significant effects of Phentolamine Ophthalmic Solution 0.75% on DCNVA were seen in fellow eyes, treated with 1 drop, and with binocular viewing. The efficacy of Phentolamine Ophthalmic Solution 0.75% was similar for all age ranges including pediatric subjects aged 3 to 17 years. Pediatric subjects aged 12 to 17 (n=27) were treated in MIRA-2 and MIRA-3 and pediatric subjects, aged 3 to 11 (n= 11) were treated in MIRA-4, (NCT#05223478).

6 APPENDIX

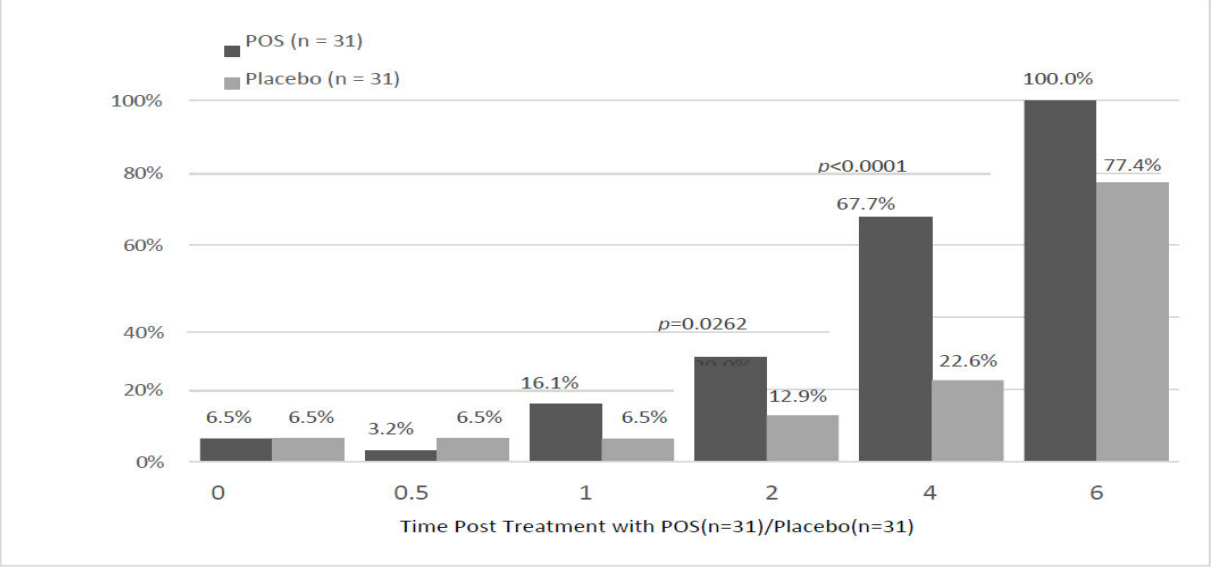
6.1 Summary of Addition Studies

MIRA-1

MIRA-1 was designed as a randomized, cross-over, multicenter, double-masked, placebo-controlled study. This study enrolled 32 normal healthy subjects. The objective of this study was to evaluate the safety and efficacy of 1% POS to reverse pharmacologically induced mydriasis by a parasympathetic (tropicamide) or adrenergic (phenylephrine) mydriatic agent. The average age of the subjects in this study was 28 years. In the study eye, mean (SD) PD at baseline (-1 hour) was 4.54 (0.785) mm within the POS treatment group and 4.45 (0.722) mm within the placebo treatment group. At max timepoint (0 minutes), mean (SD) PD was 7.20 (1.128) mm within the POS treatment group and 6.97 (1.304) mm within the placebo treatment group.

Compared to placebo, a statistically significant percent of subjects in the POS arm had study eyes that showed reversal of mydriasis at 2 hours (29% vs 13%, p=0.0262) and 4 hours (68% vs 23%, p<0.0001), with a trend towards significance at 1 hour (16% vs 7%, p=0.1094 (Figure 1). With respect to safety, no serious TEAEs or TEAEs leading to withdrawal or study medication discontinuation were reported. Overall, the analysis of the data resulting from MIRA-2 study support the POS effect of mydriatic reversal.

Figure 1: Percent of Subjects Achieving Study Eye Pupil Diameter No More Than 0.2 mm Above Baseline by Timepoint



Source: Table 14.2.3.1.5 of the Applicant's study reports.

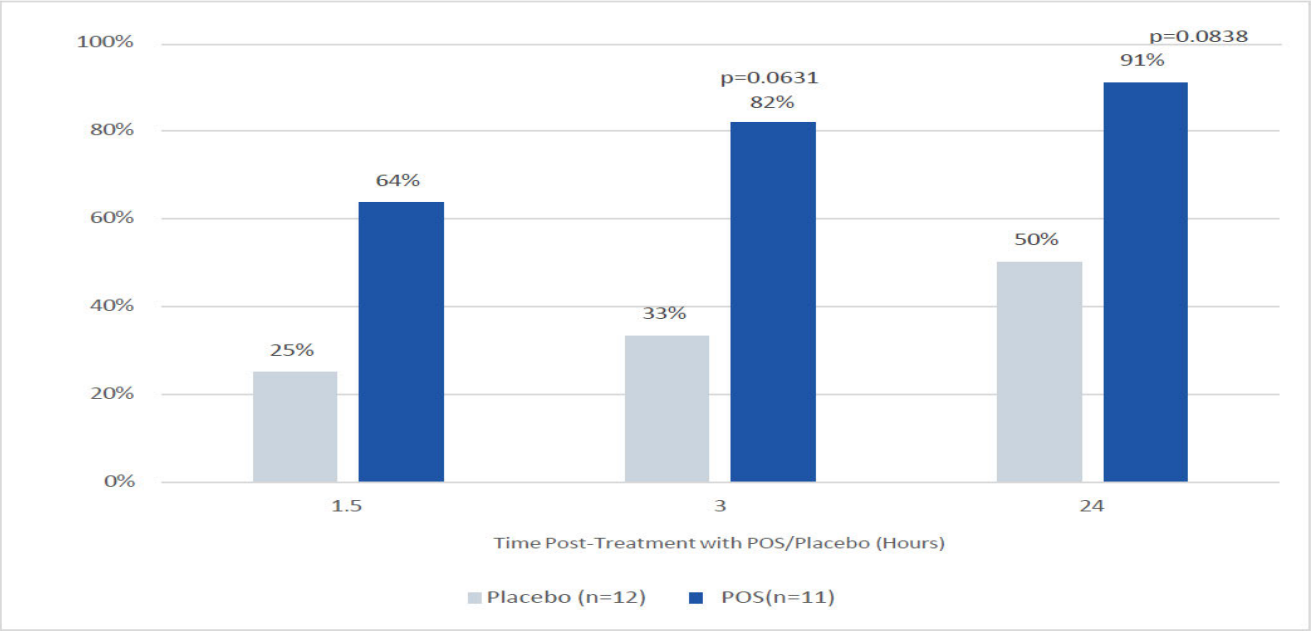
Reviewer comment: *In this crossover study, one subject tested positive for pregnancy after randomization and was excluded from the study.*

MIRA-4

MIRA-4 study was a Randomized, Parallel-Arm, Double-Masked, Placebo-Controlled Study designed to assess the safety of POS in pediatric subjects 3 to 11 years of age. The primary efficacy endpoint was defined as an increase in the percent of study eyes returning to baseline PD (defined as PD ≤ 0.2 mm above baseline) at 90 min after POS dosing compared to placebo in subjects who were pharmacologically dilated. Among the pediatric subjects treated with POS, 64% had PD returned to ≤ 0.2 mm from baseline PD at 90 min compared to 17% of study eyes treated with placebo. This effect is fairly consistent to those seen in the adult pivotal studies (49% vs 7% in MIRA-2 and 58% vs 6% in MIRA-3)

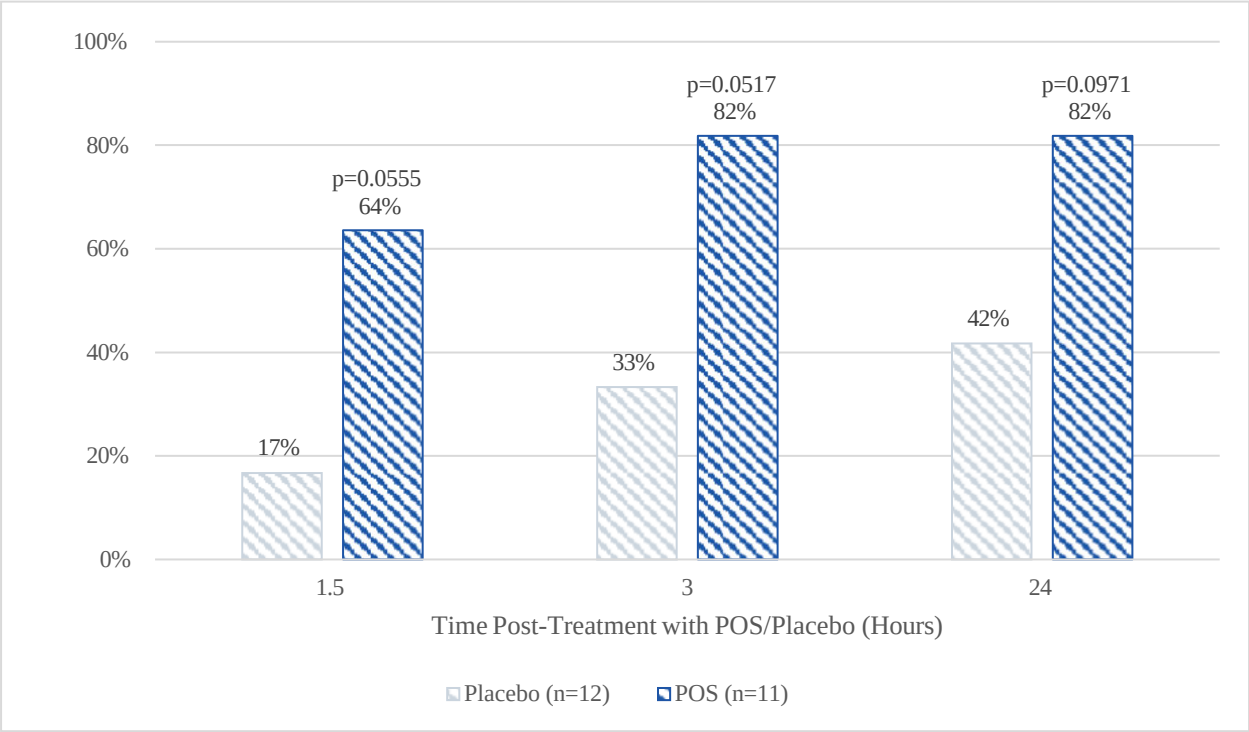
Note that MIRA-4 main goal was to prove POS tolerance in pediatric population. As in the adult studies, POS treatment was well tolerated with a favorable safety profile in this pediatric study, with no adverse effects reported. There were no reports of burning, stinging, irritation, or ptosis with POS treatment. In summary, the results of MIRA-4 study show that POS is well tolerated in pediatric subjects aged 3 to 11 years with an efficacy profile that is similar to that observed in subjects aged 12 to 17 year and aged 18 years and older in 2 pivotal MIRA-2 and MIRA-3 Phase 3 studies. No adverse effects of POS were observed following a single drop of POS in each eye 1 hour after pharmacological mydriasis of the pupil. POS was well tolerated, with the only drug-related effect of a mild to moderate transient conjunctival hyperemia that peaked at 90 min post-dose.

Figure 2: Percent of Pediatric 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 and Figure 2 of the Applicant's study reports.

Figure 3: Percent of Pediatric 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 and Figure 3 of the Applicant's study reports.

6.2 Summary of Selected Efficacy Results

Table 13: Sensitivity Analysis of Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Eye ***Time point***	**POS (N=244) n (%)**	**Placebo (n=124) n (%)**	**POS vs Placebo Odd Ratios (95% CI)**
Study eye 30 min Returning to ≤ 0.2 mm from baseline (-1 hr)	94 1 (1.1)	91 3 (3.3)	0.44 (0.07, 2.94)
60 min Returning to ≤ 0.2 mm from baseline (-1 hr)	94 26 (27.7)	91 2 (2.2)	14.22 (3.75, 54.01)
90 min Returning to ≤ 0.2 mm from baseline (-1 hr)	94 46 (48.9)	91 6 (6.6)	12.62 (5.15, 30.95)

2 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 55 (58.5)	91 10 (11.0)	11.36 (5.23, 24.67)
3 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 75 (79.8)	91 16 (17.6)	17.67 (8.46, 36.89)
4 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 77 (81.9)	91 27 (29.7)	11.59 (5.65, 23.77)
6 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 85 (90.4)	91 41 (45.1)	11.19 (5.05, 24.78)
24 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 86 (91.5)	91 60 (65.9)	5.31 (2.32, 12.15)
Fellow eye 30 min Returning to ≤ 0.2 mm from baseline (-1 hr)	94 2 (2.1)	91 2 (2.2)	1.07 (0.19, 6.03)
60 min Returning to ≤ 0.2 mm from baseline (-1 hr)	94 23 (24.5)	91 5 (5.5)	5.62 (2.08, 15.19)
90 min Returning to ≤ 0.2 mm from baseline (-1 hr)	94 46 (48.9)	91 5 (5.5)	16.43 (6.23, 43.34)
2 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 48 (51.1)	91 9 (9.9)	10.68 (4.70, 24.27)
3 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 64 (68.1)	91 13 (14.3)	14.13 (6.60, 30.23)
4 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 71 (75.5)	91 22 (24.2)	10.43 (5.19, 20.96)
6 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 81 (86.2)	91 41 (45.1)	8.86 (4.17, 18.84)
24 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	94 83 (88.3)	91 62 (68.1)	3.43 (1.60, 7.33)

Source: Table 14.2.1.10 of the Applicant's study reports.

Table 14: Sensitivity Analysis of Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Eye ***Time point***	**POS (N=244) n (%)**	**Placebo (n=124) n (%)**	**POS vs Placebo Odd Ratios (95% CI)**
Study eye 30 min Returning to ≤ 0.2 mm from baseline (-1 hr)	10 (4.1)	5 (4.0)	0.95 (0.33, 2.72)
60 min Returning to ≤ 0.2 mm from baseline (-1 hr)	103 (42.2)	3 (2.4)	24.92 (8.34, 74.42)
90 min Returning to ≤ 0.2 mm from baseline (-1 hr)	142 (58.2)	7 (5.6)	21.38 (9.78, 46.73)
2 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	162 (66.4)	9 (7.3)	23.54 (11.50, 48.17)
3 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	193 (79.1)	17 (13.7)	23.03 (12.66, 41.92)
4 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	210 (86.1)	21 (16.9)	29.06 (16.05, 52.60)
6 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	221 (90.6)	44 (35.5)	16.69 (9.49, 29.32)
24 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	218 (89.3)	89 (71.8)	3.36 (1.91, 5.91)
Fellow eye 30 min Returning to ≤ 0.2 mm from baseline (-1 hr)	9 (3.7)	5 (4.0)	0.78 (0.27, 2.29)
60 min Returning to ≤ 0.2 mm from baseline (-1 hr)	67 (27.5)	6 (4.8)	6.71 (2.89, 15.54)
90 min Returning to ≤ 0.2 mm from baseline (-1 hr)	127 (52.0)	6 (4.8)	19.69 (8.57, 45.21)
2 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	158 (64.8)	9 (7.3)	21.54 (10.55, 43.98)
3 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	182 (74.6)	18 (14.5)	16.47 (9.23, 29.39)

4 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	206 (84.4)	13 (10.5)	44.83 (22.79, 88.19)
6 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	220 (90.2)	38 (30.6)	19.49 (11.07, 34.34)
24 hr Returning to ≤ 0.2 mm from baseline (-1 hr)	221(90.6)	80 (64.5)	5.04 (2.86, 8.85)

Source: Table 14.2.1.10 of the Applicant's study reports.

Table 15: Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-Study eye

	MIRA-2			**MIRA-3**		
Eye Time Point	**POS (N=94) n/m (%)**	**Placebo (N=91) n/m (%)**	**POS vs Placebo [a] Odds Ratio (95% CI) p-value**	**POS (N=244) n/m (%)**	**Placebo (N=124) n/m (%)**	**POS vs Placebo [a] Odds Ratio (95% CI) p-value**
Study eye						
30 min	1/94 (1.1)	3/91 (3.3)	0.53	10/244 (4.1)	5/124 (4.0)	0.95
			(0.09, 2.98)			(0.34, 2.66)
			0.4688			0.9243
60 min	26/94 (27.7)	2/91 (2.2)	18.27	103/244 (42.2)	3/124 (2.4)	39.53
			(4.75, 70.19)			(12.88, 121.28)
			<0.0001			<0.0001
90 min	**46/94 (48.9)**	**6/91 (6.6)**	**25.93**	**142/244 (58.2)**	**7/124 (5.6)**	**55.64**
			(9.37, 71.79)			**(23.04, 134.39)**
			<0.0001			**<0.0001**
2 hr	55/94 (58.5)	10/91 (11.0)	22.99	162/244 (66.4)	9/124 (7.3)	56.63
			(8.92, 59.27)			(24.46, 131.15)
			<0.0001			<0.0001
3 hr	75/94 (79.8)	16/91 (17.6)	23.85	193/244 (79.1)	17/124 (13.7)	36.24
			(10.25, 55.49)			(18.11, 72.53)
			<0.0001			<0.0001
4 hr	77/94 (81.9)	27/91 (29.7)	14.04	210/244 (86.1)	21/124 (16.9)	44.56
			(6.41, 30.72)			(22.29, 89.06)
			<0.0001			<0.0001
6 hr	85/94 (90.4)	41/91 (45.1)	12.03	221/244 (90.6)	44/124 (35.5)	18.37
			(5.29, 27.34)			(10.16, 33.21)
			<0.0001			<0.0001
24 hr	86/94 (91.5)	60/91 (65.9)	5.37	218/244 (89.3)	89/124 (71.8)	3.39
			(2.35, 12.28)			(1.92, 5.98)
			<0.0001			<0.0001

Source: Table 14.2.1.1 of the Applicant's study reports. CI, confidence interval; m, number of subjects with an assessment at the time point; n, number of subjects returning to ≤ 0.2 mm from baseline (-1 hr); PD, pupil diameter; POS, phentolamine ophthalmic solution 0.75%. Baseline is

defined as -1 hr prior to treatment on Day 1, prior to the administration of mydriatic agent, when the PD measurement is considered normal. [a] From a logistic regression model with study ID, treatment, mydriatic agent, and light/dark irides as factors and the baseline PD as a covariate.

Table 16 : Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point for MIRA-2 and MIRA-3 Studies (mITT Population) – Fellow Eye

	MIRA-2		POS vs Placebo[a]		MIRA-3	POS vs Placebo [a]
Eye Time Point	POS (N=94) n/m (%)	Placebo (N=91) n/m (%)	Odds Ratio (95% CI) p-value	POS (N=244) n/m (%)	Placebo (N=124) n/m (%)	Odds Ratio (95% CI) p-value
Fellow eye						
30 min	2/94 (2.1)	2/91 (2.2)	0.96	9/244 (3.7)	5/124 (4.0)	0.79
			(0.20, 4.59)			(0.27, 2.25)
			0.9554			0.6538
60 min	23/94 (24.5)	5/91 (5.5)	6.74	67/244 (27.5)	6/124 (4.8)	8.15
			(2.42, 18.82)			(3.44, 19.30)
			0.0003			<0.0001
90 min	**46/94 (48.9)**	**5/91 (5.5)**	**38.03**	**127/244 (52.0)**	**6/124 (4.8)**	**36.54**
			(12.40, 116.67)			**(15.05, 88.68)**
			<0.0001			**<0.0001**
2 hr	48/94 (51.1)	9/91 (9.9)	22.18	158/244 (64.8)	9/124 (7.3)	48.26
			(8.21, 59.87)			(21.20, 109.86)
			<0.0001			<0.0001
3 hr	64/94 (68.1)	13/91 (14.3)	27.53	182/244 (74.6)	18/124 (14.5)	31.88
			(10.57, 71.71)			(15.63, 65.02)
			<0.0001			<0.0001
4 hr	71/94 (75.5)	22/91 (24.2)	14.16	206/244 (84.4)	13/124 (10.5)	52.40
			(6.38, 31.42)			(25.60, 107.27)
			<0.0001			<0.0001
6 hr	81/94 (86.2)	41/91 (45.1)	10.66	220/244 (90.2)	38/124 (30.6)	19.77
			(4.71, 24.12)			(11.12, 35.13)
			<0.0001			<0.0001
24 hr	83/94 (88.3)	62/91 (68.1)	3.59	221/244 (90.6)	80/124 (64.5)	5.29
			(1.65, 7.79)			(2.98, 9.38)
			0.0012			<0.0001

Source: Table 14.2.1.1 of the Applicant's study reports. CI, confidence interval; m, number of subjects with an assessment at the time point; n, number of subjects returning to ≤ 0.2 mm from baseline (-1 hr); PD, pupil diameter; POS, phentolamine ophthalmic solution 0.75%. Baseline is defined as -1 hr prior to treatment on Day 1, prior to the administration of mydriatic agent, when the PD measurement is considered normal. [a] From a logistic regression model with study ID, treatment, mydriatic agent, and light/dark irides as factors and the baseline PD as a covariate

Table 17: Percent of Subjects Receiving Phenylephrine with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Mydriatic Agent *Eye* *Time Point*	POS(N=56) n/m (%)	Placebo(N=55) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Phenylephrine *Study eye*			
30 Minutes			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	1 (1.8)	3 (5.5)	0.53 (0.08, 3.47)
60 Minutes			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	26 (46.4)	2 (3.6)	18.28 (4.68, 71.39)
90 Minutes			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	44 (78.6)	6 (10.9)	24.93 (8.94, 69.50)
2 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	46 (82.1)	10 (18.2)	18.02 (6.97, 46.62)
3 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	48 (85.7)	16 (29.1)	12.91 (5.10, 32.73)
4 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	47 (83.9)	24 (43.6)	6.49 (2.67, 15.80)
6 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	48 (85.7)	31 (56.4)	4.64 (1.84, 11.66)
24 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	48 (85.7)	37 (67.3)	2.76 (1.10, 6.91)

Source: Table 14.2.1.5

Table 18: Percent of Subjects Receiving Phenylephrine with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Mydriatic Agent *Eye* *Time Point*	POS(N=56) n/m (%)	Placebo(N=55) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Phenylephrine *Fellow eye*			
30 Minutes			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	2 (3.6)	2 (3.6)	0.95 (0.17, 5.29)
60 Minutes			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	23 (41.1)	5 (9.1)	6.76 (2.38, 19.19)
90 Minutes			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	45 (80.4)	5 (9.1)	36.06 (11.80, 110.22)
2 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	44 (78.6)	9 (16.4)	18.63 (6.96, 49.90)
3 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	49 (87.5)	13 (23.6)	29.24 (9.24, 92.55)
4 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	48 (85.7)	20 (36.4)	10.54 (4.09, 27.13)
6 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	50 (89.3)	31 (56.4)	6.58 (2.41, 17.99)
24 Hours			
n	56	55	
Returning to <=0.2 mm of Baseline (-1 hour)	49 (87.5)	38 (69.1)	2.91 (1.12, 7.55)

Source: Table 14.2.1.5

Table 19: Percent of Subjects Receiving Phenylephrine with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Mydriatic agent *Eye* *Time Point*	POS(N=146) n/m (%)	Placebo(N=74) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Phenylephrine			
Study eye			
30 Minutes			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	10 (6.8)	5 (6.8)	0.95 (0.33, 2.75)
60 Minutes			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	96 (65.8)	3 (4.1)	37.68 (12.24, 115.95)
90 Minutes			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	126 (86.3)	7 (9.5)	54.49 (22.25, 133.44)
2 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	129 (88.4)	9 (12.2)	50.93 (21.55, 120.33)
3 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	130 (89.0)	17 (23.0)	25.82 (12.17, 54.78)
4 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	134 (91.8)	19 (25.7)	30.35 (13.82, 66.64)
6 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	134 (91.8)	31 (41.9)	15.21 (7.17, 32.27)
24 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	126 (86.3)	50 (67.6)	3.21 (1.62, 6.39)

Source: Table 14.2.1.5

Table 20: Percent of Subjects Receiving Phenylephrine with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Mydriatic agent *Eye* *Time Point*	POS(=146) n/m (%)	Placebo(N=46) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Phenylephrine *Fellow eye*			
30 Minutes			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	9 (6.2)	5 (6.8)	0.79 (0.26, 2.34)
60 Minutes			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	64 (43.8)	6 (8.1)	7.86 (3.28, 18.82)
90 Minutes			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	113 (77.4)	6 (8.1)	34.94 (14.24, 85.71)
2 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	128 (87.7)	8 (10.8)	53.79 (22.33, 129.59)
3 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	130 (89.0)	18 (24.3)	22.78 (10.93, 47.46)
4 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	130 (89.0)	11 (14.9)	41.09 (18.27, 92.43)
6 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	131 (89.7)	28 (37.8)	13.36 (6.59, 27.07)
24 Hours			
n	146	74	
Returning to <=0.2 mm of Baseline (-1 hour)	129 (88.4)	40 (54.1)	6.37 (3.21, 12.63)

Source: Table 14.2.1.5

Table 21: Percent of Subjects Receiving Tropicamide or Paremyd with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Mydriatic Agent *Eye* *Time Point*	POS(N=38) n/m (%)	Placebo(N=36) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Tropicamide or Paremyd *Study eye*			
30 Minutes			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	0	0	-
60 Minutes			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	0	0	-
90 Minutes			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	2 (5.3)	0	4.74 (0.33, 68.46)
2 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	9 (23.7)	0	38.35 (1.93, 761.16)
3 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	27 (71.1)	0	277.71 (14.43,>999.99)
4 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	30 (78.9)	3 (8.3)	121.50 (14.80, 997.45)
6 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	37 (97.4)	10 (27.8)	61.91 (10.33, 371.02)
24 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	38 (100)	23 (63.9)	47.52 (2.85, 791.19)

Source: Table 14.2.1.5

Table 22: Percent of Subjects Receiving Tropicamide or Paremyd with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Mydriatic Agent *Eye* *Time Point*	POS(N=38) n/m (%)	Placebo(N=36) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Tropicamide or Paremyd *Fellow eye*			
30 Minutes			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	0	0	-
60 Minutes			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	0	0	-
90 Minutes			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	1 (2.6)	0	3.02 (0.20, 46.10)
2 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	4 (10.5)	0	14.03 (0.77, 254.83)
3 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	15 (39.5)	0	71.50 (3.96, >999.99)
4 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	23 (60.5)	2 (5.6)	92.03 (10.66, 794.93)
6 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	31 (81.6)	10 (27.8)	21.50 (5.21, 88.74)
24 Hours			
n	38	36	
Returning to <=0.2 mm of Baseline (-1 hour)	34 (89.5)	24 (66.7)	4.18 (1.23, 14.24)

Source: Table 14.2.1.5

Table 23: Percent of Subjects Receiving Tropicamide or Paremyd with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Mydriatic Agent *Eye* *Time Point*	POS(N=56) n/m (%)	Placebo(N=55) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Tropicamide or Paremyd *Study eye*			
30 Minutes			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	0	0	-
60 Minutes			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	7 (7.1)	0	6.44 (0.40, 103.52)
90 Minutes			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	16 (16.3)	0	17.24 (1.03, 289.83)
2 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	33 (33.7)	0	64.89 (3.64, >999.99)
3 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	63 (64.3)	0	284.06 (15.98, >999.99)
4 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	76 (77.6)	2 (4.0)	121.16 (26.04, 563.69)
6 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	87 (88.8)	13 (26.0)	29.85 (10.54, 84.49)
24 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	92 (93.9)	39 (78.0)	3.89 (1.39, 10.84)

Source: Table 14.2.1.5

Table 24: Percent of Subjects Receiving Tropicamide or Paremyd with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Mydriatic Agent *Eye* *Time Point*	POS(N=98) n/m (%)	Placebo(N=50) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Tropicamide or Paremyd *Fellow eye*			
30 Minutes			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	0	0	-
60 Minutes			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	3 (3.1)	0	4.33 (0.27, 68.27)
90 Minutes			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	14 (14.3)	0	14.97 (0.93, 241.59)
2 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	30 (30.6)	1 (2.0)	14.52 (2.54, 82.94)
3 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	52 (53.1)	0	147.10 (8.35, >999.99)
4 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	76 (77.6)	2 (4.0)	117.23 (24.67, 556.96)
6 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	89 (90.8)	10 (20.0)	40.42 (14.22, 114.91)
24 Hours			
n	98	50	
Returning to <=0.2 mm of Baseline (-1 hour)	92 (93.9)	40 (80.0)	3.25 (1.12, 9.37)

Source: Table 14.2.1.5

Table 25: Percent of Subjects with Light Iride with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Iride Color *Eye* *Time Point*	POS(N=45) n/m (%)	Placebo(N=45) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Light Iride *Study eye*			
30 Minutes			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	0	0	-
60 Minutes			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	14 (31.1)	0	56.38 (3.26, 973.89)
90 Minutes			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	25 (55.6)	1 (2.2)	114.61 (15.23, 862.50)
2 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	32 (71.1)	3 (6.7)	69.60 (13.46, 359.90)
3 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	40 (88.9)	6 (13.3)	60.46 (14.12, 258.86)
4 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	43 (95.6)	11 (24.4)	44.99 (10.98, 184.44)
6 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	42 (93.3)	22 (48.9)	12.19 (3.55, 41.90)
24 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	42 (93.3)	31 (68.9)	5.50 (1.58, 19.06)

Source: Table 14.2.1.6

Table 26 : Percent of Subjects with Light Iride with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Iride Type *Eye* *Time Point*	POS(N=45) n/m (%)	Placebo(N=45) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Light Iride *Fellow eye*			
30 Minutes			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	2 (4.4)	1 (2.2)	1.26 (0.19, 8.49)
60 Minutes			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	12 (26.7)	1 (2.2)	13.44 (2.29, 78.94)
90 Minutes			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	24 (53.3)	2 (4.4)	48.40 (9.44, 248.05)
2 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	26 (57.8)	3 (6.7)	37.06 (8.13, 168.88)
3 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	34 (75.6)	1 (2.2)	101.35 (16.55, 620.64)
4 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	39 (86.7)	9 (20.0)	21.09 (6.99, 63.64)
6 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	43 (95.6)	21 (46.7)	17.71 (4.52, 69.36)
24 Hours			
n	45	45	
Returning to <=0.2 mm of Baseline (-1 hour)	42 (93.3)	31 (68.9)	5.51 (1.59, 19.09)

Source: Table 14.2.1.6

Table 27: Percent of Subjects with Dark Iride with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Iride Type *Eye* *Time Point*	POS(N=49) n/m (%)	Placebo(N=46) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Dark Iride *Study eye*			
30 Minutes			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	1 (2.0)	3 (6.5)	0.53 (0.08, 3.33)
60 Minutes			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	12 (24.5)	2 (4.3)	8.46 (1.85, 38.78)
90 Minutes			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	73 (55.7)	6 (9.1)	27.48 (9.87, 76.46)
2 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	21 (42.9)	5 (10.9)	11.99 (3.26, 44.12)
3 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	35 (71.4)	10 (21.7)	14.81 (4.65, 47.22)
4 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	34 (69.4)	16 (34.8)	6.91 (2.46, 19.44)
6 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	43 (87.8)	19 (41.3)	12.86 (4.16, 39.77)
24 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	44 (89.8)	29 (63.0)	5.45 (1.78, 16.66)

Source: Table 14.2.1.6

Table 28: Percent of Subjects with Dark Iride with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-2

Iride Type *Eye* *Time Point*	POS(N=49) n/m (%)	Placebo(N=46) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Dark Iride *Fellow eye*			
30 Minutes			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	0	1 (2.2)	0.27 (0.02, 3.53)
60 Minutes			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	11 (22.4)	4 (8.7)	4.08 (1.11, 15.00)
90 Minutes			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	22 (44.9)	3 (6.5)	24.47 (5.46, 109.69)
2 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	22 (44.9)	6 (13.0)	12.13 (3.27, 44.95)
3 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	30 (61.2)	12 (26.1)	12.35 (3.30, 46.22)
4 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	32 (65.3)	13 (28.3)	11.59 (3.22, 41.67)
6 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	38 (77.6)	20 (43.5)	8.49 (2.79, 25.82)
24 Hours			
n	49	46	
Returning to <=0.2 mm of Baseline (-1 hour)	41 (83.7)	31 (67.4)	2.77 (0.99, 7.76)

Source: Table 14.2.1.6

Table 29: Percent of Subjects with Light Iride with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Iride Type *Eye* *Time Point*	POS(N=113) n/m (%)	Placebo(N=58) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Light Iride *Study Eye*			
30 Minutes			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	3 (2.7)	1 (1.7)	1.26 (0.22, 7.40)
60 Minutes			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	52 (46.0)	1 (1.7)	50.26 (9.08, 278.21)
90 Minutes			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	69 (61.1)	1 (1.7)	174.25 (28.41, >999.99)
2 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	77 (68.1)	1 (1.7)	270.43 (41.09, >999.99)
3 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	93 (82.3)	4 (6.9)	102.93 (28.02, 378.14)
4 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	104 (92.0)	7 (12.1)	107.96 (32.16, 362.50)
6 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	106 (93.8)	16 (27.6)	46.31 (15.69, 136.70)
24 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	102 (90.3)	42 (72.4)	3.28 (1.42, 7.57)

Source: Table 14.2.1.6

Table 30: Percent of Subjects with Light Iride with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Iride Type *Eye* *Time Point*	POS(N=113) n/m (%)	Placebo(N=58) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Light Iride *Fellow eye*			
30 Minutes			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	3 (2.7)	1 (1.7)	0.87 (0.14, 5.49)
60 Minutes			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	36 (31.9)	1 (1.7)	22.46 (4.13, 122.22)
90 Minutes			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	64 (56.6)	2 (3.4)	60.49 (14.54, 251.74)
2 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	77 (68.1)	2 (3.4)	122.90 (26.95, 560.49)
3 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	90 (79.6)	6 (10.3)	73.85 (21.38, 255.14)
4 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	100 (88.5)	3 (5.2)	128.21 (35.30, 465.71)
6 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	107 (94.7)	16 (27.6)	39.12 (14.64, 104.52)
24 Hours			
n	113	58	
Returning to <=0.2 mm of Baseline (-1 hour)	106 (93.8)	36 (62.1)	8.25 (3.31, 20.56)

Source: Table 14.2.1.6

Table 31: Percent of Subjects with Dark Iride with Study Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Iride Type *Eye* *Time Point*	POS(N=131) n/m (%)	Placebo(N=66) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Dark Iride *Study eye*			
30 Minutes			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	7 (5.3)	4 (6.1)	0.82 (0.25, 2.65)
60 Minutes			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	51 (38.9)	2 (3.0)	24.95 (6.43, 96.76)
90 Minutes			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	73 (55.7)	6 (9.1)	27.48 (9.87, 76.46)
2 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	85 (64.9)	8 (12.1)	24.36 (9.46, 62.73)
3 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	100 (76.3)	13 (19.7)	18.29 (8.02, 41.68)
4 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	106 (80.9)	14 (21.2)	21.76 (9.45, 50.10)
6 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	115 (87.8)	28 (42.4)	9.59 (4.64, 19.83)
24 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	116 (88.5)	47 (71.2)	3.30 (1.53, 7.12)

Source: Table 14.2.1.6

Table 32: Percent of Subjects with Dark Iride with Fellow Eye Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point (mITT Population)-MIRA-3

Iride Type *Eye* *Time Point*	POS(N=131) n/m (%)	Placebo(N=66) n/m (%)	POS vs Placebo Odds Ratio (95%CI)
Dark Iride *Fellow eye*			
30 Minutes			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	6 (4.6)	4 (6.1)	0.68 (0.20, 2.26)
60 Minutes			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	31 (23.7)	5 (7.6)	3.86 (1.42, 10.52)
90 Minutes			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	63 (48.1)	4 (6.1)	21.78 (7.31, 64.90)
2 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	81 (61.8)	7 (10.6)	24.54 (9.29, 64.83)
3 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	92 (70.2)	12 (18.2)	16.75 (7.01, 40.01)
4 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	106 (80.9)	10 (15.2)	26.32 (11.18, 61.98)
6 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	113 (86.3)	22 (33.3)	9.59 (4.64, 19.83)
24 Hours			
n	131	66	
Returning to <=0.2 mm of Baseline (-1 hour)	115 (87.8)	44 (66.7)	3.72 (1.77, 7.83)

Source: Table 14.2.1.6

Table 33: Percent of Female Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point and gender for MIRA-2 and MIRA-3 Studies (mITT Population)

Eye	Study	Treatments		POS vs Placebo ODDS Ratio (95% CI)
		POS	Placebo	
Study Eye	MIRA-2	29/58 (50.0%)	4/55 (7.2%)	24.54 (4.9, 276.4)
	MIRA-3	87/152 (57.2%)	4/65 (6.1%)	61.07 (14.3, 124.3)
Fellow Eye	MIRA-2	26/58 (44.8%)	3/55 (5.4%)	17.23 (2.2, 389.4)
	MIRA-3	85/152 (55.9%)	3/65 (4.6%)	51.45 (9.3, 191.0)

Source: Reviewer's analysis results

Table 34: Percent of Male Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point and gender for MIRA-2 and MIRA-3 Studies (mITT Population)

Eye	Study	Treatments		POS vs Placebo ODDS Ratio (95% CI)
		POS	Placebo	
Study Eye	MIRA-2	17/36 (47.2)	2/36(5.5)	31.75 (21.90, 362.03)
	MIRA-3	55/92 (59.7)	3/59(5.1)	55.64 (6.04, 274.11)
Fellow Eye	MIRA-2	20/36 (55.5)	2/36(5.5)	9.93 (11.90, 546.71)
	MIRA-3	45/92 (48.9)	3/59(5.1)	35.34 (13.04, 359.09)

Source: Reviewer's analysis results

Table 35: Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point and race in MIRA-2 Studies (mITT Population)

Race	Eye	Treatments		POS vs Placebo ODDS Ratio (95% CI)
		POS(94)	Placebo(91)	
White	Study Eye	39/70(55.7)	4/74(5.4)	67.5(28.7, 158.1)
	Fellow Eye	37/70(51.4)	4/74(5.4)	59.7 (22.4, 114.7)
Black	Study Eye	7/17(41.2)	1/16(6.2)	5.2 (2.4, 79.8)
	Fellow Eye	6/17(35.2)	0/16	12.8 (1.39, 946.9)

Source: Reviewer's analysis results

Table 36 Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point and race in MIRA-3 Studies (mITT Population)

Race	Eye	Treatments		POS vs Placebo ODDS Ratio (95% CI)
		POS(244)	Placebo(124)	
White	Study Eye	106/182(58.2)	4/93(4.3)	78.5(32.7, 188.1)
	Fellow Eye	105/182(57.6)	5/93(4.9)	49.7(21.9, 112.9)
Black	Study Eye	19/38(50.0)	2/21(9.5)	7.5(2.0, 28.2)
	Fellow Eye	18/38(47.3)	2/21(9.5)	8.0 (1.9, 33.0)
Other	Study Eye	17/27(62.9)	1/10(10)	16.2(2.4, 109.8)
	Fellow Eye	18/27(66.6)	0/10	38.55(2.3, 632.7)

Source: Reviewer's analysis results

Table 37: Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point and age group in MIRA-2 Studies (mITT Population)

Age group	Eye	POS (N=94) n/m (%)	Placebo (N=91) n/m (%)	POS vs Placebo ODDS Ratio (95% CI)
<18	Study Eye	6/10(60)	0/4(0)	164.06(2.57, >999.99)
	Fellow Eye	4/10(40)	0/4(0)	102.06(4.37, >999.99)
>=18	Study Eye	40/84 (47.6)	6/87(6.8)	35.96(6.52, 198.67)

	Fellow Eye	42/84(50)	5/87(5.57)	55.54(17.31, 229.63)

Source: Reviewer's analysis results

Table 38: Percent of Subjects Returning to ≤ 0.2 mm From Baseline (-1 Hr) Pupil Diameter by Time Point and age group in MIRA-3 Studies (mITT Population)

Age group	Eye	POS (N=244) n/m (%)	Placebo (N=124) n/m (%)	POS vs Placebo ODDS Ratio (95% CI)
<18	Study Eye	13/22(59.9)	0/9 (0)	142.06(3.67, >999.99)
	Fellow Eye	9/22(40.9)	2/9(22.2)	30.03 (14.2, 156.61)
>=18	Study Eye	129/222 (58.1)	7/115 (6.0)	27.89(4.99, 165.43)
	Fellow Eye	118/222 (53.1)	4/115 (3.5)	47.73(10.22, 109.87)

Source: Reviewer's analysis results

Table 39: 68 Sequential tested in the Hierarchical Analysis in MIRA-3 (mITT POPULATION)

Table Number	Table Title	Eye	Time Point	Population	Subgroup
1	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Study	90 min	mITT	Overall
2	Change from Max (0 Minute) Pupil Diameter by Time Point	Study	90 min	mITT	Overall
3	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter	Study	N/A	PP	Overall
4	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Fellow	90 min	mITT	Overall
5	Change from Max (0 Minute) Pupil Diameter by Time Point	Fellow	90 min	mITT	Overall
6	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Study	2 hours	mITT	Overall
7	Change from Max (0 Minute) Pupil Diameter by Time Point	Study	2 hours	mITT	Overall
8	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Study	3 hours	mITT	Overall
9	Change from Max (0 Minute) Pupil Diameter by Time Point	Study	3 hours	mITT	Overall
10	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Study	4 hours	mITT	Overall
11	Change from Max (0 Minute) Pupil Diameter by Time Point	Study	4 hours	mITT	Overall
12	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter	Fellow	N/A	PP	Overall
13	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Study	6 hours	mITT	Overall
14	Change from Max (0 Minute) Pupil Diameter by Time Point	Study	6 hours	mITT	Overall
15	Change from Max (0 Minute) Pupil Diameter by Time Point	Study	60 min	mITT	Overall
16	Change from Max (0 Minute) Pupil Diameter by Time Point	Fellow	2 hours	mITT	Overall
17	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Fellow	2 hours	mITT	Overall

18	Change from Max (0 Minute) Pupil Diameter by Time Point	Fellow	3 hours	mITT	Overall
19	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Fellow	3 hours	mITT	Overall
20	Change from Max (0 Minute) Pupil Diameter by Time Point	Fellow	4 hours	mITT	Overall
21	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Fellow	4 hours	mITT	Overall
22	Change from Max (0 Minute) Pupil Diameter by Time Point	Fellow	6 hours	mITT	Overall
23	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Fellow	6 hours	mITT	Overall
24	Change from Max (0 Minute) Pupil Diameter by Time Point	Fellow	60 min	mITT	Overall
25	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Study	60 min	mITT	Overall
26	Percent of Subjects returning to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point	Fellow	60 min	mITT	Overall
27	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	90 min	mITT	Phenylephrine
28	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Mydriatic Agent	Study	N/A	PP	Phenylephrine
29	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	2 hours	mITT	Phenylephrine
30	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	3 hours	mITT	Phenylephrine
31	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	4 hours	mITT	Phenylephrine
32	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	3 hours	mITT	Tropicamide or Paremyd
33	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Mydriatic Agent	Study	N/A	PP	Tropicamide or Paremyd

34	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	4 hours	mITT	Tropicamide or Paremyd
35	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	90 min	mITT	Light irides
36	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Irides Type	Study	N/A	PP	Light irides
37	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	2 hours	mITT	Light irides
38	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	3 hours	mITT	Light irides
39	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	4 hours	mITT	Light irides
40	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	90 min	mITT	Dark irides
41	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Irides Type	Study	N/A	PP	Dark irides
42	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	2 hours	mITT	Dark irides
43	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	3 hours	mITT	Dark irides
44	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	4 hours	mITT	Dark irides
45	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	6 hours	mITT	Phenylephrine
46	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	2 hours	mITT	Tropicamide or Paremyd
47	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	6 hours	mITT	Tropicamide or Paremyd
48	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	3 hours	mITT	Tropicamide
49	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Mydriatic Agent	Study	N/A	PP	Tropicamide

50	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	4 hours	mITT	Tropicamide
51	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	6 hours	mITT	Tropicamide
52	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	3 hours	mITT	Paremyd
53	Time to Return to <= 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Mydriatic Agent	Study	N/A	PP	Paremyd
54	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	4 hours	mITT	Paremyd
55	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	6 hours	mITT	Paremyd
56	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	6 hours	mITT	Light irides
57	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	60 min	mITT	Light irides
58	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	6 hours	mITT	Dark irides
59	Change from Max (0 Minute) Pupil Diameter by Time Point and Irides Type	Study	60 min	mITT	Dark irides
60	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	60 min	mITT	Phenylephrine
61	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	90 min	mITT	Tropicamide or Paremyd
62	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	2 hours	mITT	Tropicamide
63	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	2 hours	mITT	Paremyd
64	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	90 min	mITT	Tropicamide
65	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	90 min	mITT	Paremyd
66	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	60 min	mITT	Tropicamide or Paremyd
67	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	60 min	mITT	Tropicamide
68	Change from Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent	Study	60 min	mITT	Paremyd

Source: Table 8 of MIRA-3 Study Report

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/s/

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