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CLINICAL TRIAL REPORT

Reversal of Pharmacologic Mydriasis in Pediatric Subjects with Ryzumvi (0.75% Phentolamine Ophthalmic Solution): A Post-Hoc Pooled Analysis from Three Randomized, Placebo-Controlled Phase 3 Trials

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Purpose: To evaluate the safety and efficacy of 0.75% phentolamine ophthalmic solution (POS), a non-selective adrenergic antagonist, in reversing pharmacologically induced mydriasis in a post-hoc exploratory analysis of pediatric subjects aged 3–17 years.

Methods: The 68 pediatric subjects included in this analysis were enrolled in one of three randomized, double-masked, controlled phase 3 clinical trials. Subjects received 1 or 2 drops of POS or placebo in each eye, administered 1 hour after pharmacologically induced mydriasis with 1% tropicamide, 2.5% phenylephrine, or Paremyd™ (0.25% tropicamide/1% hydroxyamphetamine). The fellow eye, which received a uniform single drop of study medication across all trials, was selected for this pooled efficacy analysis. The primary endpoint was the percentage of subjects returning to ≤0.2 mm of baseline photopic pupil diameter (PD) at 90 minutes. Secondary endpoints included return to ≤0.2 mm at additional time points, change in photopic PD from maximum dilation (0 minutes), time to return to baseline PD, and safety outcomes including adverse events (AEs) or serious AEs (SAEs).

Results: At 90 minutes, 19/38 (50%) of POS-treated eyes and 4/30 (13%) of placebo-treated eyes returned to ≤0.2 mm of baseline PD. The greatest separation occurred at 3 hours, when 82% of POS-treated eyes and 20% of placebo-treated eyes achieved reversal. Mean time to recovery to ≤0.2 mm of baseline PD was more than 5 hours faster with POS. POS was well tolerated, with no SAEs or discontinuations. Treatment-related AEs in ≥5% of POS subjects consisted of mild, transient conjunctival hyperemia and instillation-site discomfort. No clinically meaningful changes in intraocular pressure, blood pressure, heart rate, or distance visual acuity were observed.

Conclusion: In this exploratory pooled analysis, POS appeared to accelerate the reversal of pharmacologically induced mydriasis in pediatric subjects and demonstrated an acceptable safety profile. Larger, prospectively powered pediatric studies are warranted.

Trial Registration: All three trials were registered with ClinicalTrials.gov (MIRA-2, NCT04620213; MIRA-3, NCT05134974; MIRA-4, NCT05223478).

Keywords: adrenergic alpha-antagonists, cycloplegia, phenylephrine, tropicamide, photophobia, glare

Introduction

A comprehensive dilated eye exam, conducted by an optometrist or ophthalmologist, plays an important role in diagnosing eye disease at early stages when treatment is most effective.[1] Over 100 million eye exams are performed in the US annually.[2,3]

Eye and vision disorders constitute a major and distinct public health concern in children, whose visual systems are still in a critical stage of development. If left undetected or untreated, conditions such as uncorrected refractive error, strabismus, or amblyopia can result in lasting visual impairment and disrupt normal visual maturation.[4] Approximately

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one in five preschool-aged children have a vision problem,[5–7] and in the United States, nearly one in four school-aged children wear corrective lenses.[8] Despite this, fewer than 15% of preschoolers receive a comprehensive eye examination by a healthcare professional.[9] These data highlight the critical importance of early detection and timely intervention to support optimal visual development, reduce the risk of amblyopia, and prevent avoidable vision loss.[4]

Dilated ophthalmic examinations including cycloplegia are the standard of care for several scenarios common in pediatric and adolescent patients, such as constant or intermittent esotropia, fluctuating accommodation, accommodative insufficiency, fatigue, or spasm, asthenopia or suspected latent hyperopia.[5,10] Cycloplegia is particularly recommended in examining children with amblyopia or strabismus.[11] The American Optometric Association recommends the use of cycloplegic retinoscopy as the preferred technique for the first ophthalmic evaluation of preschool children, where early detection is crucial for timely diagnosis and treatment.[4,5] The American Academy of Ophthalmology recommends visual acuity screening beginning at 3 years of age.[11] For children, a comprehensive ophthalmic examination including pupillary dilation is indicated if the child fails vision screening, vision screening cannot be performed or is inconclusive, if the patient is referred by another healthcare professional, or if there is a vision complaint, abnormal visual behavior, a family history of eye disease such as amblyopia or glaucoma, or behavioral issue such as a learning disability.

Dilation of the pupil affords adequate viewing of the posterior segment (eg, vitreous, peripheral retina and optic nerve). A study of 90 pediatric patients examined pre-and post-pharmacological dilation showed that 25% had one or more posterior pole anomalies not detected and 51% had peripheral retinal anomalies not detected by a non-dilated fundus examination.[12,13] Regardless of the initial pupil diameter (PD), pharmacologically-induced mydriasis typically dilates the pupil to a diameter of 6 to 8 mm; a size suitable for ophthalmic examination of the peripheral retina and other structures of the interior of the eye.[14]

Topical mydriatic eye drops or sprays[14] are used for pupillary dilation. Two classes of mydriatic agents are sympathomimetic drugs, such as phenylephrine, that activate the iris dilator muscle, and anticholinergics, including tropicamide, cyclopentolate, and atropine, that inhibit the iris sphincter and ciliary muscle.[15] Cycloplegic drops such as tropicamide and longer acting cycloplegic agents, such as cyclopentolate, concurrently dilate the eye by inhibiting the iris sphincter muscle and block accommodative function by paralyzing the ciliary muscle, each of which have parasympathetic innervation mediated by the acetylcholine receptor.[15,16]

Cycloplegic refraction using cyclopentolate 1% is a recommended component of the American Academy of Ophthalmology's Preferred Practice Pattern for pediatric eye evaluations in full-term patients aged 12 months to 12 years, sometimes supplemented by tropicamide 0.5% or 1% and phenylephrine 2.5% in patients with heavily pigmented irides.[17] However, a recent systematic review and meta-analysis of randomized-clinical trials found that tropicamide 1% and cyclopentolate 1% showed similar efficacy for cycloplegic refraction in non-strabismic children and adults, whereas the former agent had better tolerability and safety profile.[18] Accordingly, in this publication we present data on the safety and efficacy of 0.75% POS in reversing mydriasis induced by 1% tropicamide and 2.5% phenylephrine in pediatric subjects between ages 3 and 17. Cyclopentolate was not evaluated in this study. This limits the generalizability of our findings to clinical scenarios involving longer acting cycloplegic agents. Nonetheless, since POS is a sympatholytic agent acting selectively on the iris dilator muscle rather than the ciliary muscle, its mechanism of action in the reversal of pharmacologically-induced mydriasis is likely independent of the specific cycloplegic agent used.

Cycloplegic drops are often given in conjunction with a topical sympathomimetic drug, such as phenylephrine, to enhance pupillary dilation. Pharmacologically-induced mydriasis using typical agents, such as 2.5% phenylephrine or 1% tropicamide,[19] can last from a few hours to as many as 24 hours depending on the pharmacologic agent, age of the patient, level of iris pigmentation, and other factors. Cycloplegia in pediatric subjects can last up to 14 days, depending on the choice and concentration of the anti-muscarinic parasympatholytic agent.[10] However, the duration of pharmacological mydriasis in pediatric subjects has not been carefully studied using objective pupillometry measurements and is one focus of this report.

The side effects of mydriatic agents can have a negative impact on vision as well as daily functioning.[17,19–26] These adverse effects include stinging, photophobia, discomfort in highly lit areas, glare, blurred vision, and increased IOP. A larger pupil size is correlated with increased glare due to a broader pathway for light scatter,[27] as well as an increase in higher order aberrations.[28] Glare can be uncomfortable, interfering with the ability to perform tasks such as driving and

reading.[29,30] Impaired depth perception resulting from mydriatic agents poses a safety issue that can lead to mishaps.[26] In darkly pigmented eyes, retinal illumination is directly proportionate to entrance pupil area,[3] and so reduction in pupil diameter will exponentially benefit post-mydriatic difficulty with glare. Rapid reversal of pupil diameter may help reduce symptoms such as photophobia and glare in children and adolescents, although effects on accommodation and near vision were not evaluated in this study.

POS is an aqueous, preservative-free eye drop containing 0.75% phentolamine as the active ingredient.[31] Phentolamine, a relatively non-selective alpha-adrenergic antagonist, inhibits contraction of the iris dilator muscle, causing miosis and possibly restoring depth of focus through miosis,[31] although accommodation was not systematically evaluated in this study. The drop is designed to be instilled in the eyes to promote rapid reversal of mydriasis thus minimizing the discomfort, blurred vision, and other side effects of a dilated eye exam. It was approved by the FDA in September of 2023 for the reversal of pharmacologically-induced mydriasis in patients age 3 and older, giving one drop in each dilated eye in subjects between age 3 to 11 and 1 to 2 drops in each dilated eye in patients 12 and older.[24,32]

In the MIRA-2 and MIRA-3 Phase 3 trials, POS demonstrated statistical superiority over placebo in rapidly restoring dilated pupils to ≤0.2 millimeters of their initial size within 60 to 90 minutes.[31] The MIRA-4 Phase 3 trial was a randomized, parallel-arm, double-masked, placebo-controlled Phase 3 study of POS versus placebo, designed to evaluate the safety of POS used to expedite the reversal of pharmacologically-induced mydriasis in pediatric subjects aged 3 to 11 years, but was not powered for efficacy.

In this report, we provide a post-hoc pooled analysis of all 68 pediatric subjects aged 3 to 17 years enrolled in the three Phase 3 MIRA trials, combining the 23 subjects aged 3–11 from MIRA-4, with the 45 subjects aged 12 to 17 from the MIRA-2 and MIRA-3. This analysis characterizes the time course of pupillary recovery using objective pupillometry and evaluates exploratory efficacy and safety of POS in reversing pharmacologically induced mydriasis in pediatric subjects.

Methods

Design

This post-hoc analysis was conducted on the pooled data (n=68; 38 receiving POS and 30 receiving placebo treatment) of all pediatric subjects aged 3 to 17 years old, enrolled in 3 prospective, randomized, parallel-armed, double-masked, placebo-controlled Phase 3 trials (MIRA-2, MIRA-3, MIRA-4).[32] Following successful screening, each subject was randomized to an unmasked mydriatic agent and masked treatment. The objective of this post-hoc analysis was to assess the safety and efficacy of 0.75% POS for expediting the reversal of pharmacologically-induced mydriasis in pediatric subjects. All three trials were registered with ClinicalTrials.gov (MIRA-2, NCT04620213; MIRA-3, NCT05134974; MIRA-4, NCT05223478) and complied with the principles of the Declaration of Helsinki. The Alpha Independent Review Board provided approval for the studies and their protocols. Parental consent was obtained for all pediatric subjects aged 3–17, and written assent was also obtained from participants aged 7–17 years, consistent with federal regulations and ethical guidelines for pediatric research.

Treatment randomization was 1:1 in MIRA-2 and MIRA-4 and 2:1 in MIRA-3 (POS or placebo [vehicle]). Randomization was stratified 1:1 by light/dark color irides and further randomized 3:1:1 to mydriatic agent (2.5% phenylephrine, 1% tropicamide, or Paremyd, respectively). Subjects received 1 drop of the mydriatic agent OU 1 hour before instillation of POS OU. The right eye served as the study eye while the left eye served as the fellow eye. Subjects in the original MIRA-2 and MIRA-3 trials received 2 drops of POS (administered 5 min apart) in the study eye and one drop in the fellow eye. Those in the MIRA-4 trial received only one drop of POS in either eye. In the current analysis we included only the fellow eyes to ensure a consistent comparison across subjects and trials, as these were the eyes receiving 1 drop of POS. To further maintain consistency, the analysis incorporated only those datasets shared across all three clinical trials, with harmonized timepoints and endpoints. The study medications were masked to the investigator, site study staff, study subjects, and the sponsors. No additional mydriatic or miotic ophthalmic medications were permitted during the study period. All instillations were performed by study personnel at the investigative sites to ensure adherence.

Participants

This pooled analysis included healthy subjects 3 to 17 years of age with the ability to comply with all protocol-mandated procedures independently and to attend all scheduled office visits. Inclusion and exclusion criteria were similar among the three studies and key exclusion criteria included: clinically significant ocular disease as deemed by the investigator to potentially interfere with the study (eg, amblyopia, congenital cataract, congenital glaucoma); history of ocular trauma or ocular surgery; use of any topical prescription or over-the-counter ophthalmic medications of any kind within 7 days of screening; recent or current evidence of ocular infection or inflammation in either eye (such as current evidence of clinically significant blepharitis, conjunctivitis, or keratitis); closed or narrow angle deemed to be potentially occludable with dilation; history of ocular trauma or surgery; pupil abnormalities; or clinically significant systemic disease (eg, cardiovascular disorders, resting heart rate or blood pressure outside the normal ranges) that might have interfered with the study.

Outcome Measures

Efficacy

Pupil diameter (PD) was measured in mm under photopic and scotopic conditions using the NeurOptics automated infrared Pupillometer VIP-300, using the Light Off mode. The device was calibrated according to manufacturer guidance and has demonstrated high reproducibility in clinical use. A threshold of ≤0.2 mm from baseline PD was predefined to indicate return to near-baseline pupil size within the precision limits of the measurement system.

Safety

Resting heart rate (HR) and resting systolic and diastolic blood pressure (BP) were recorded. Adverse events (AEs) including severity (mild, moderate, severe) as well as a relationship to study medication were assessed. Best-corrected distance visual acuity (BCDVA) was measured under photopic conditions by a standard Early Treatment Diabetic Retinopathy Study (ETDRS) illuminated chart at 4 m. For subjects who are unable to read the letters on an ETDRS chart, the Patti Pics Series ETDRS chart was used.

Statistical Methods

Study Populations

The modified intent-to-treat (mITT) analysis included all randomized subjects < 18 years of age who received 1 drop of study medication in the fellow eye and then underwent at least one scheduled post-treatment PD measurement during Visit 1 in the fellow eye. The fellow eye was selected for analysis because fellow eyes received a single drop of study medication in all the trials, whereas 2-drops were administered to the study eye in the MIRA-2 and MIRA-3 studies. The mITT population was used to analyze selected efficacy endpoints, with subjects included in their randomized treatment regardless of the treatment they received. The Safety population included all randomized subjects who received at least one drop of study medication. The Safety population was used to summarize the safety variables.

Efficacy Endpoints

This is a post-hoc exploratory analysis combining pediatric participants from three Phase 3 trials, none of which were powered for pediatric efficacy outcomes. The primary efficacy endpoint was the percentage of eyes returning to ≤ 0.2 mm from baseline (−1 h) photopic PD at 90 min post-treatment (POS vs placebo). The percentage of eyes returning to ≤ 0.2 mm from baseline (−1 h) photopic PD was also assessed at each remaining time point (3 h, and 24 h). Change (in mm) in photopic PD from max pupil dilation (0 min) was calculated at each time point, and the mean time (hours) to return to ≤ 0.2 mm from baseline (−1 h) photopic PD was assessed.

Safety Endpoints

Change from baseline (−1 h) in vital signs (HR and BP) at 3 hours and 24 hours were measured. Change from baseline (−1 h) in BCDVA was measured at 24 hours. Frequency of adverse events was compared between treatment groups.

Statistics

Statistical analyses were descriptive and exploratory, consistent with the post-hoc nature of the pooled pediatric population studied. All statistical analyses were performed using SAS® System Version 9.4 (Cary, NC) or higher. Descriptive summaries of variables were provided where appropriate. For continuous variables, the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum were tabulated by treatment group. For categorical variables, the counts and proportions of each value were tabulated by treatment group and timepoint.

For all efficacy endpoints, baseline was defined as 1 hour prior to treatment on Visit 1 (−1 h), immediately prior to the instillation of the mydriatic agent. The returning to ≤ 0.2 mm from baseline (−1 h) photopic PD endpoint was analyzed for the fellow eye at each time point using a logistic regression model with treatment as a factor and the baseline PD as a covariate. The percentage of subjects in each treatment group meeting the criteria and the odds ratio with 95% confidence interval and *P*-value was calculated.

The continuous secondary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) with the change from baseline as the dependent variable, mydriatic agent, and light/dark irides as factors, with the respective baseline value included as the covariate. The output from the ANCOVA included the least-squares (LS) mean and standard error (SE) for both treatment groups, along with the placebo-corrected LS mean, its 95% CI and associated *P*-value. The analysis of the time (hours) to return to ≤ 0.2 mm from baseline PD (time-savings analysis) endpoint was performed using a Cox proportional hazards regression model with treatment as a factor and the baseline PD as a covariate. Time to return to baseline (−1 h) PD was measured beginning at the maximum pupil dilation (0 min) time point, and subjects whose PD did not return to ≤ 0.2 mm of baseline by the 6-hour time point, their time to return was censored at 12 hours.

Safety

Treatments were compared using the same ANCOVA model proposed for the change in photopic PD from max pupil dilation efficacy endpoint. Visual acuity assessment for BCDVA was summarized at −1 h, 0 minutes, and 24 h using letters and logMAR units. A descriptive summary of BCDVA was presented by treatment and age group. Additionally, a categorical summary of BCDVA was presented, with counts and percentages of subjects with improvement or loss from baseline by treatment and time point. Descriptive statistics of observed values were presented for vital sign data at each time point (Screening, 3 h, and 24 h), including systolic BP (mmHg), diastolic BP (mmHg), and HR (bpm) by treatment group and overall. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 25.0.[32] The number and percentage of subjects with any treatment emergent adverse events (TEAEs) were summarized by System Organ Class, Preferred Term, and relationship to study medication by treatment group and overall.

Results

Disposition

Thirty-eight (38) pediatric subjects were included in the POS group and thirty (30) in the vehicle group. All subjects completed the study with no major protocol deviations and were included in the safety and exploratory efficacy analyses.

Demographics and Baseline Characteristics

The average ages of the subjects in the POS and placebo groups overall were 12.34 and 11.17 years, respectively. Most (56/68, 82.4%) of the subjects were white (not Hispanic or Latino) (Table 1). Phenylephrine was the most common mydriatic in both treatment groups (65.8% for POS and 50.0% for placebo). The mean baseline PD in the fellow eye was 5.90 mm in the POS group and 5.73 mm in the placebo group. Baseline BCDVA in the fellow eye averaged 56.7 and 56.0 letters in the POS and placebo groups, respectively. There were no statistically significant differences between the POS and placebo groups with respect to baseline demographics.

Table 1 Demographics and Baseline Characteristics

Demographic and Baseline Characteristic Statistic	0.75% Phentolamine (n = 38)	Placebo (n = 30)
Age, years (p=0.28)		
N	38	30
Mean (SD)	12.34 (3.96)	11.17 (4.84)
Median	14.00	13.00
Min, max	3, 17	3, 17
Sex, n (%)	38	30
Male	20 (52.6)	12 (40.0)
Female	18 (47.4)	18 (60.0)
Race, n (%) [a]	38	30
White	31 (81.6)	25 (83.3)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	1 (2.6)	0
Black or African American	6 (15.8)	5 (16.7)
Asian	0	0
Ethnicity, n (%)	38	30
Hispanic or Latino	6 (15.8)	2 (6.7)
Not Hispanic or Latino	32 (84.2)	28 (93.3)
Irides type, n (%)	38	30
Light	16 (42.1)	11 (36.7)
Dark	22 (57.9)	19 (63.3)
Mydriatic agent, n (%)	38	30
Phenylephrine	25 (65.8)	15 (50.0)
Tropicamide	5 (13.2)	9 (30.0)
Paremyd	8 (21.0)	6 (20.0)
PD (−1 h) in the fellow eye, mm (p=0.36)		
n	38	30
Mean (SD)	5.90 (0.82)	5.73 (0.68)
Median	5.90	5.62
Minimum, maximum	3.92, 7.84	4.65, 7.31
BCDVA (−1 h) in the fellow eye, letters [b] (p=0.54)		
n	38	30
Mean (SD)	56.7 (3.63)	56.0 (5.60)
Median	57.0	55.5
Minimum, maximum	49, 64	45, 70

Notes: [a] Subjects can be included in more than one category, so the sum of the percentages may be greater than 100%. [b] For BCDVA, the number of letters read was from the 4-m distance only, so that 55 letters read is equivalent to a Snellen acuity of 20/20.
Abbreviations: BCDVA, best-corrected distance visual acuity; PD, pupil diameter; SD, standard deviation.

Efficacy

A significantly higher proportion of subjects on POS achieved a pupil diameter within ≤ 0.2 mm of baseline compared to those that received placebo at all timepoints beginning at 90 minutes, which was the primary endpoint (Figure 1). At 90 minutes, 19/38 (50%) of POS-treated subjects achieved reversal of mydriasis compared to 4/30 (13%) of placebo subjects (p=0.003; odds ratio [OR]=32.53; 95% CI 3.26-325.14). The greatest separation occurred at 3 hours, at which point 31/38 (82%) of POS-treated subjects achieved reversal compared to 6/30 (20%) of placebo-treated subjects

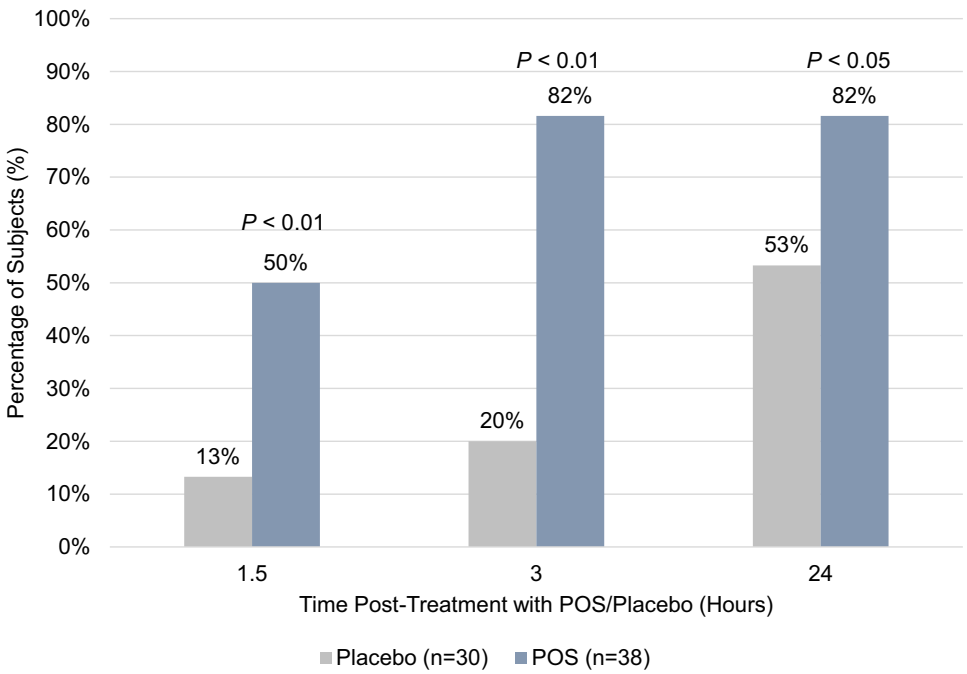

Figure 1 Percent of pediatric participants 3 to 17 years of age with eyes returning to ≤0.2 mm from baseline (−1 hour) pupil diameter by time point.

(p=0.0002; OR = 19.99; 95% CI 4.20-95.22). At 24 hours, 14/30 (47%) of placebo-treated eyes had not yet returned to baseline PD.

A significantly greater proportion of subjects treated with POS who were dilated with phenylephrine achieved reversal of mydriasis compared with placebo at 90 minutes (72% vs 27%; p= 0.0069; OR = 31.98; 95% CI 2.59-395.36) and at all timepoints tested (Figure 2). Following dilation with tropicamide or Paremyd, a higher proportion of

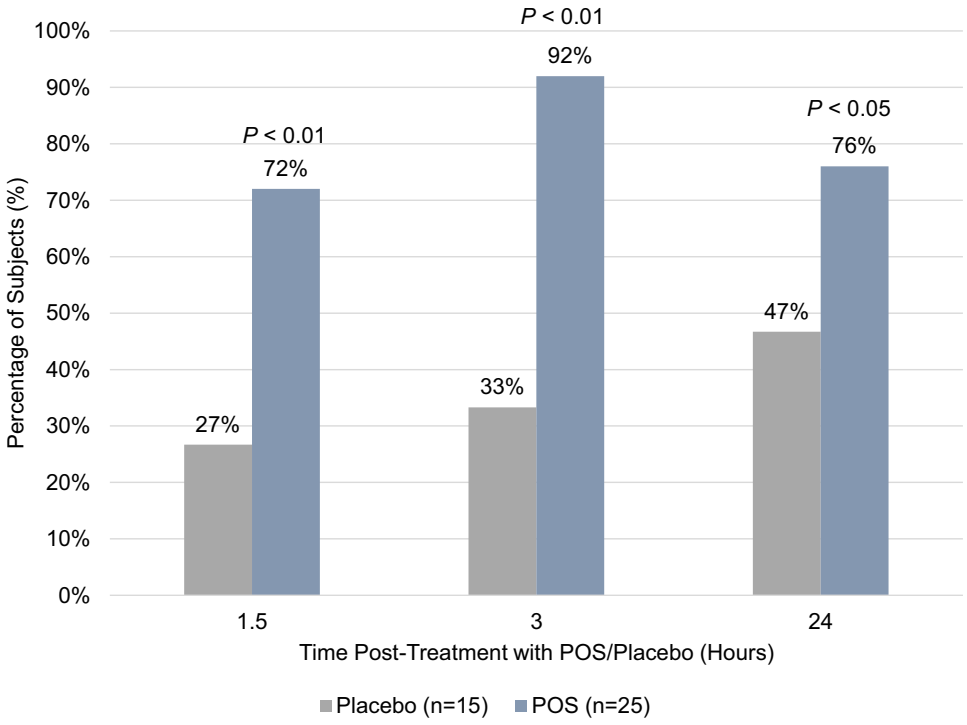

Figure 2 Percent of pediatric participants aged 3 to 17 years receiving phenylephrine with pupils returning to ≤0.2 mm from baseline (−1 hour) pupil diameter by time point.

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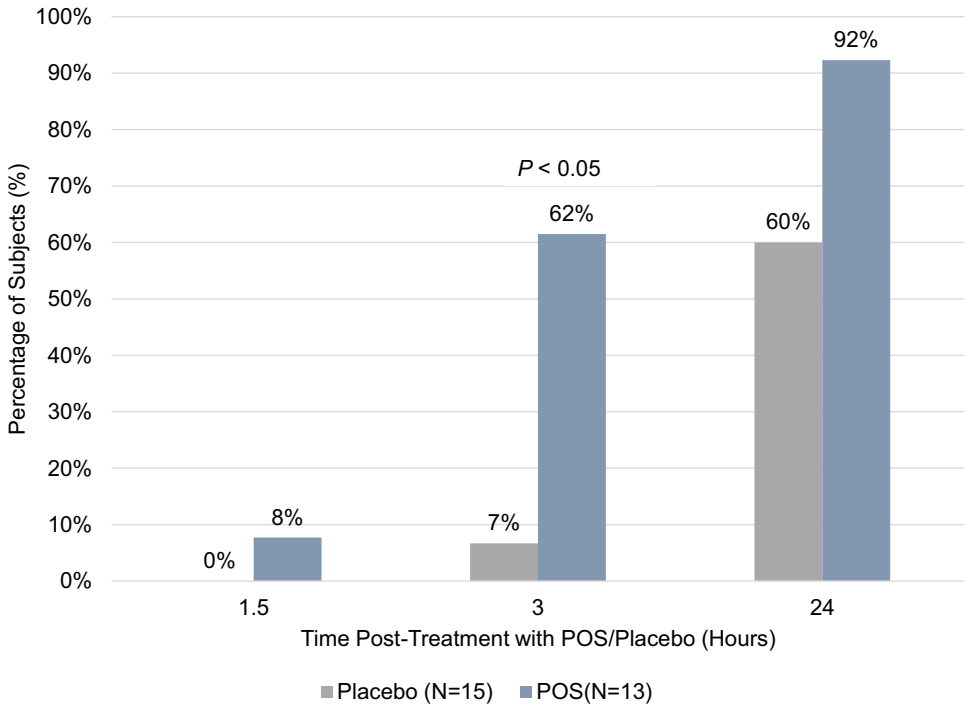

Figure 3 Percent of pediatric participants aged 3 to 17 years receiving tropicamide or Paremyd with pupils returning to ≤0.2 mm from baseline (−1 hour) pupil diameter by time point.

POS-treated subjects than placebo-treated subjects achieved reversal of mydriasis at all time points. This difference reached statistical significance at the 3-hour timepoint in the fellow eye (Figure 3).

Following mydriasis, mean pupil diameter was significantly reduced in POS-treated subjects compared to placebo at all timepoints from 90 minutes to 24 hours post treatment (Figure 4).

Similar trends were observed when stratified by mydriatic agent, with statistically significant differences favoring POS at all time points following phenylephrine dilation (P < 0.01) and at 1.5 and 3 hours following dilation with tropicamide or Paremyd.

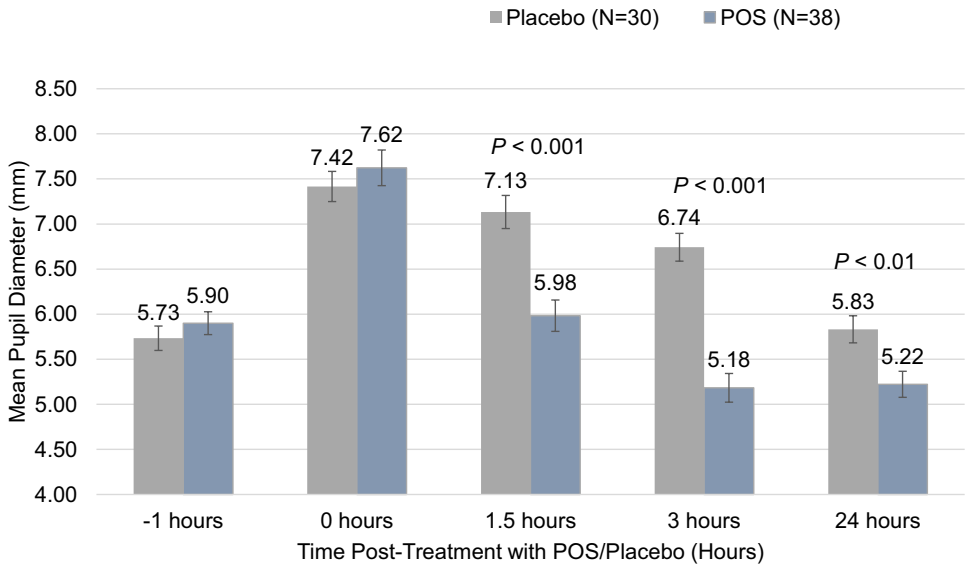

Figure 4 Change from maximum (0 minutes) pupil diameter for pediatric subjects aged 3 to 17 years by time point.

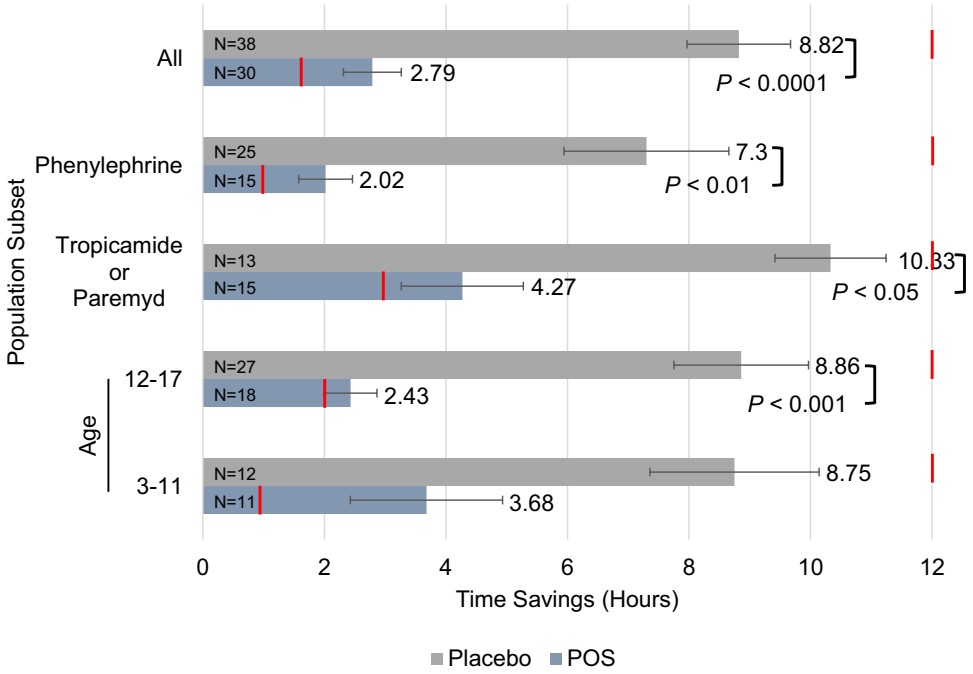

Figure 5 Time-to-event analysis showing average and median (red line) time for pupil diameter to return to ≤0.2 mm of baseline. For participants whose PD did not return to ≤0.2 mm by the 6-hour time point, time to return was censored at 12 hours.

Overall, the mean time for pupils to return to baseline diameter was significantly shorter in the POS treatment group compared to placebo (2.8 h vs 8.8 h for the fellow eye, respectively; P < 0.0001; OR = 6.00; CI 2.73-13.20) with similar findings observed across age subgroups (Figure 5).

When stratified by dilating agent, the mean time savings for POS was 5.28 hours following phenylephrine dilation (P < 0.01; OR = 5.20; 95% CI 1.91-14.19) and 6.06 hours following dilation with tropicamide or Paremyd (P < 0.05; OR = 5.85; 95% CI 1.18-28.93). Similar patterns were observed across age strata.

Safety

BCDVA was evaluated at multiple time points across the three trials. At 24 hours, the LS mean (SE) change from baseline was +2.72 (0.485) letters for the POS group and +2.00 (0.464) letters for the placebo group.

Four of 38 (10.5%) subjects in the POS group reported treatment-emergent adverse events (TEAEs), all of which were mild (grade 1 on a 0–3 scale), transient, and limited to conjunctival hyperemia (5.3%) or instillation site pain (5.3%). All TEAEs occurred in subjects aged 12- to 17-years and were considered related to treatment. No AEs were reported in any of the subjects in the placebo group.

Mean systolic and diastolic blood pressures and heart rate remained stable and within the normal range throughout the study and were similar between treatment groups. BCDVA was evaluated at multiple time points across the three clinical trials, and no subject in either group experienced a loss of ≥5 letters. At 24 hours, the LS mean (SE) change from baseline was +2.72 (0.485) letters for the POS group (improvement) and +2.00 (0.464) letters for the placebo group (improvement).

Discussion

Pharmacologic dilation is essential for high-quality pediatric ophthalmic examinations, but the resulting visual symptoms —photophobia, glare, reduced depth perception, and difficulty with near tasks—can temporarily affect comfort and function in children and adolescents.[17,19–30,33] Although mydriatic combinations such as phenylephrine and tropicamide are widely used in pediatric practice, the expected duration of dilation and the time course of recovery have not been well characterized using objective pupillometry. This post-hoc pooled analysis provides descriptive data on the natural history

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of pharmacologically induced mydriasis in pediatric subjects and explores the potential effect of 0.75% POS on shortening the duration of dilation.

The safety profile observed in the pediatric subjects was favorable, with no serious adverse events and no discontinuations. Reported adverse events were mild and transient and were reported in 4 of 38 subjects (10.5%). The only treatment-related effects were mild transient conjunctival hyperemia, which peaked at 90 minutes post-dose, and mild instillation site pain.

No clinically meaningful changes in intraocular pressure, blood pressure, heart rate or BCDVA were observed during POS treatment, consistent with prior adult and adolescent data. Adverse effects of systemic, rather than topical administration of phentolamine, include tachycardia and bradycardia.[34] Phentolamine mesylate injection is FDA approved for the reversal of soft-tissue anesthesia (numbness) in patients 3 years and older.[35,36] At the 0.8 mg dose (the highest dose tested) 4% of patients experienced tachycardia and/or bradycardia.[35,36] With 0.75% POS eye drop treatment, the systemic concentration of phentolamine is quite low. The MIRA-3 study reported a median peak plasma concentration of 0.45 ng/mL following topical ocular administration of three drops of POS (2 in the study eye and one in the fellow eye).[26,31,37] Even in pediatric subjects with lower body weight than adults, no AEs related to heart rate with POS treatment were observed at the recommended dose confirming the favorable systemic safety of this ophthalmic formulation.

Across the pediatric population studied, POS-treated eyes demonstrated a faster return toward baseline pupil diameter compared with placebo, regardless of age group, iris color or dilating agent used. At 90 minutes, the primary time point evaluated across the parent trials, approximately half of POS-treated subjects achieved reversal versus a smaller proportion of placebo-treated subjects. The maximum separation between groups occurred at 3 hours. These findings are directionally consistent with previously reported adult and adolescent data from MIRA-2 and MIRA-3.[31] Importantly, nearly half of placebo-treated eyes had not yet returned to within 0.2 mm of baseline PD at 24 hours, which is a lower percentage than in the adult studies (MIRA-2 and MIRA-3), highlighting a possible longer duration of visual disturbances in pediatric patients due to the effect of mydriasis. The lengthy duration of pharmacological mydriasis in pediatric subjects may be underappreciated, as younger subjects may not be able to readily verbalize their ocular discomfort, photophobia or lack of focus.

Mydriatic agents are commonly used in eye exams to facilitate stereoscopic examination of the peripheral retina and other internal structures of the eye. Pharmacologic mydriasis causes adverse effects including blurred vision, cycloplegia, light sensitivity, glare, impaired driving and reading.[17–24] POS can provide an overall time savings of about 6 hours in returning the PD to pre-dilation levels when subjects from all 3 groups of dilating agents are combined. This was comprised of a > 5 hour time savings in return to baseline PD in subjects dilated with phenylephrine and > 6 hours in subjects dilated with tropicamide containing mydriatics. Studies of POS in a predominantly adult cohort revealed that the subjective benefit in resolving multiple visual symptoms preceded the full return of PD to baseline, reflecting an enhanced functional time savings.[31] A potentially earlier return to school, sports, play, work, and other daily activities with expedited mydriasis reversal may represent a meaningful benefit and warrants further investigation in pediatric subjects.

This post-hoc, pooled analysis of pediatric subjects from three prospective, randomized, multicenter Phase 3 clinical trials, presents several strengths as well as limitations. Notable strengths include the rigorous, double-masked study design and the use of objective, standardized measurements of pupil diameter. Objective pupillometry was used to quantify pupil size changes under standardized light-off conditions, allowing a precise assessment of PD recovery that is not dependent on clinician estimation. This approach strengthens the internal validity of the findings and provides a more granular description of the time course of dilation in the pediatric population.

However, several limitations should be acknowledged. First, this is a post-hoc pooled analysis that was not prospectively powered for efficacy comparisons, and the sample size in some age and agent subgroups was small and may limit the generalizability of these findings to broader pediatric populations. Second, because the subjects aged 3–17 years were not enrolled as a prospectively stratified pediatric cohort with respect to iris pigmentation, mydriatic regimen, or baseline pupil dynamics, the resulting heterogeneity may have contributed to variability in treatment response. Third, the analysis was limited to phenylephrine, tropicamide, and Paremyd™, and therefore does not address cycloplegic

regimens involving cyclopentolate or atropine. Although trends were similar across dilating agents tested, cyclopentolate was not included in these trials, and therefore the results cannot be extrapolated to clinical scenarios involving longer-acting cycloplegic agents. Because POS acts selectively on the iris dilator muscle, its mechanism of action would be expected to be independent of ciliary muscle effects; however, this assumption was not directly tested in the present dataset.

Additionally, the safety and efficacy of topical POS in infants and children younger than 3 years remain unknown. As the current trials enrolled only healthy subjects, further research is needed to evaluate POS in children with ocular or systemic conditions that may influence pupil dynamics. Finally, because these data are derived from multiple parent trials with consistent but not identical designs, the findings should be interpreted as exploratory. Accommodation, near visual function, and patient-reported outcomes were not systematically assessed in all three prospective clinical trials and should be explored in future pediatric studies.

Conclusions

In summary, POS was well tolerated in pediatric subjects aged 3 to 17 years in this post-hoc pooled analysis. The observed effects on the time course of mydriasis reversal were directionally consistent with those reported in adult populations.[26,31,32] While these exploratory findings suggest that POS may help shorten the duration of pharmacologic mydriasis in children, they should be interpreted within the limitations of this analysis. Prospective pediatric studies specifically powered for efficacy, and inclusive of a broader range of cycloplegic regimens, are warranted to further characterize the clinical utility of pharmacologic mydriasis reversal in pediatric ophthalmic care.

Data Sharing Statement

De-identified participant data may be shared by the corresponding author, Konstantinos Charizanis, upon reasonable request, subject to sponsor and IRB approval.

Ethics Approval

Alpha IRB served as the central IRB of record for the multicenter Phase 3 trials.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

JP is Chief Medical Advisor to Opus Genetics, Inc and reports stock options from American Genomics, personal fees from Bausch + Lomb, Brim Biotech, Laurent Pharma and Thea Pharma; personal fees, stock options from OKYO Pharma, Opus Genetics, Mimetogen, Stuart Therapeutics, outside the submitted work. MB and KC are consultants to Opus Genetics, Inc. MB reports personal fees from Adaptive Sensory Technologies, outside the submitted work. The authors report no other conflicts of interest in this work.

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