

Phentolamine Eye Drops Reverse Pharmacologically Induced Mydriasis in a Randomized Phase 2b Trial

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SIGNIFICANCE: After a dilated eye examination, many patients experience symptoms of prolonged light sensitivity, blurred vision, and cycloplegia associated with pharmacological mydriasis. Phentolamine mesylate ophthalmic solution (PMOS) may expedite the reversal of mydriasis in patients, potentially facilitating return to functional vision and reducing barriers to obtaining dilated eye examinations.

PURPOSE: The protracted reversal time after pharmacologically induced pupil dilation impairs vision. We tested the hypothesis that PMOS rapidly reduces pupil diameter in this acute indication.

METHODS: In this double-masked placebo-controlled, randomized, two-arm crossover phase 2b trial, we evaluated the effects of one drop of 1% PMOS applied bilaterally in subjects who had their pupils dilated by one of two common mydriatic agents: 2.5% phenylephrine or 1% tropicamide. End points included change in pupil diameter, percent of subjects returning to baseline pupil diameter, and accommodative function at multiple time points.

RESULTS: Thirty-one subjects completed the study (15 dilated with phenylephrine and 16 with tropicamide). Change in pupil diameter from baseline at 2 hours after maximal dilation with 1% PMOS was -1.69 mm and was significantly greater in magnitude compared with placebo for every time point beyond 30 minutes ($P < .05$). At 2 hours, a greater percentage of study eyes given 1% PMOS returned to baseline pupil diameter compared with placebo (29 vs. 13%, $P = .03$), which was this also seen at 4 hours ($P < .001$). More subjects treated with PMOS in the tropicamide subgroup had at least one eye returning to baseline accommodative amplitude at 2 hours (63 vs. 38%, $P = .01$). There were no severe adverse events, with only mild to moderate conjunctival hyperemia that resolved in most patients by 6 hours.

CONCLUSIONS: Phentolamine mesylate ophthalmic solution at 1% reversed medically induced pupil dilation more rapidly than placebo treatment regardless of which mydriatic was used (adrenergic agonists and cholinergic blockers) with a tolerable safety profile.



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Optometrists and ophthalmologists conduct more than 100 million eye examinations annually.¹ To achieve an optimal posterior segment (i.e., vitreous, retina, and optic nerve) examination, dilation of the pupil (pharmacologically induced mydriasis) is recommended. Regardless of the initial pupil diameter, mydriasis typically dilates the pupil to 6 to 8 mm, a size suitable for ophthalmic examination of the peripheral retina and other structures of the interior of the eye.² Such pharmacologically induced mydriasis can last from a few hours (typically 6 hours) up to 24 hours, depending on the pigmentation of the iris, the age of the subject, and other still-unknown factors.³

One known adverse effect of such dilation is light sensitivity, and many mydriasis-inducing eye drops cause cycloplegia.⁴ In a

study that evaluated the effects of pupil dilation on driving performance, subjects with dilated eyes had a significant increase in glare and obstacles struck when compared with subjects with undilated eyes.⁵ Therefore, accelerating the reversal of mydriasis after an eye examination may be beneficial for many subjects.

Pupil size is under the control of two opposing sets of muscles: the iris sphincter muscles controlled by the cholinergic nervous system and the iris dilator muscles controlled by the adrenergic nervous system. Pharmacologically induced mydriasis can be achieved either by stimulating the iris dilator muscle with the use of α_1 -adrenergic agonists (e.g., phenylephrine) or by blocking the iris sphincter muscle with the use of muscarinic antagonists (e.g., tropicamide, cyclopentolate).⁴ Therefore, it is possible to inhibit

mydriasis with an α_1 -adrenergic antagonist that can either directly antagonize the α_1 receptor or indirectly reduce the effects of muscarinic antagonists. Pupil constriction can also improve near and intermediate vision in dilated, cyclopleged subjects by increasing the depth of focus of the eye by blocking aberrant, unfocused rays of light.⁶

α_1 -Adrenergic antagonists have been shown to be safe and effective for the pharmacological reversal of mydriasis. Dapiprazole hydrochloride ophthalmic solution 0.5%, an α_1 -adrenergic receptor antagonist, was approved by the U.S. Food and Drug Administration in 1990 for the treatment of iatrogenically induced mydriasis produced by adrenergic or parasympatholytic agents.^{7–9} However, the product was withdrawn and discontinued by the manufacturer for reasons not related to safety or efficacy.⁹ Thymoxamine eye drops, another α_1 antagonist, have also shown efficacy in reducing pupil diameter from iatrogenic mydriasis but were never approved by the U.S. Food and Drug Administration for ocular indications.¹⁰

Phentolamine mesylate ophthalmic solution is a nonselective α_1 - and α_2 -adrenergic antagonist. It is known to inhibit contraction of the iris dilator muscle, resulting in a miotic pupil. To counteract mydriatic agents (α_1 agonists and muscarinic antagonists), the following trial assessed the efficacy and safety of 1% phentolamine mesylate ophthalmic solution in inducing a rapid reversal of mydriasis and thereby minimizing the adverse effects and discomfort after a dilated eye examination. We hypothesize that, at the 1% concentration,

- (1) phentolamine mesylate ophthalmic solution will accelerate the reversal of pupil diameter back to its baseline when dilated with either phenylephrine or tropicamide;
- (2) phentolamine mesylate ophthalmic solution will reduce the time taken for subjects to return to their baseline accommodative function when dilated with tropicamide;
- (3) phentolamine mesylate ophthalmic solution will reduce subject symptoms associated with pharmacologically induced mydriasis; and
- (4) phentolamine mesylate ophthalmic solution will exhibit a tolerable safety profile.

METHODS

MIRA-1 was a randomized, crossover, multicenter, double-masked, placebo-controlled phase 2b trial to demonstrate the safety and efficacy of 1% phentolamine mesylate ophthalmic solution compared with vehicle (placebo; ClinicalTrials.gov identifier: NCT04024891). Before initiation of the trial, informed consent was submitted to the institutional review board for approval. This trial was approved by Alpha Independent Review Board and was conducted under Good Clinical Practice. The research conformed with the tenets of the Declaration of Helsinki. There were four trial sites—all optometry practices—for data collection (Pikeville, KY; Athens, OH; Warwick, RI; and Pittsburg, KS).

Subject Selection

Healthy subjects were included in the trial if they were 18 years or older and 45 years or younger with brown irides only. Subjects were excluded if they had any clinically significant ocular or systemic disease, had any previous ocular trauma or surgery, had any pupil abnormalities, previously took any ocular medications, or had a resting heart rate or blood pressure outside the normal ranges.

At the screening visit, sites obtained signed informed consent; collected inclusion/exclusion criteria, medical/ophthalmic/concomitant medication histories, demographics, and heart rate/blood pressure measurements; conducted screening ophthalmic examinations (biomicroscopy, intraocular pressure [IOP], and ophthalmoscopy [without dilation]); and performed a urine pregnancy test (for women of childbearing potential only). Subjects who met the eligibility criteria requirements at the screening visit were randomized in a 1:1 ratio to one of two crossover treatment sequences (placebo at visit 1 followed by phentolamine mesylate ophthalmic solution at visit 2 or phentolamine mesylate ophthalmic solution at visit 1 followed by placebo at visit 2). A randomization code for allocating subjects to treatment sequence in a 1:1 ratio was prepared by a masked biostatistician not connected with the trial. Once a subject was qualified for the trial, the subject was assigned a randomization number (1001 to 1044) in the order provided by the biostatistician. Randomization was stratified on mydriatic agent by odds (phenylephrine) and evens (tropicamide) at the sites, with randomization into each stratum capped at approximately 16 subjects (one-half of the randomized subjects were to receive phenylephrine, and one-half were to receive tropicamide).

One hour before treatment with study medication, subjects underwent heart rate/blood pressure measurements and several ophthalmic assessments (pupil diameter, best-corrected distance visual acuity and distance-corrected near visual acuity, accommodation, and conjunctival redness), as well as adverse event assessment. Subjects then received dosing with their mydriatic agent in both eyes (–1 hour).

For this trial, the study eye was defined as the eye at visit 1 with the larger pupil diameter at 0 minutes (maximal dilation), which is 1 hour after instillation of the mydriatic agent. The other eye was the nonstudy eye. If both eyes dilated to the same pupil diameter, the right eye was deemed the study eye. Assessments were conducted followed by the administration of study medication in both eyes. At 30 minutes and at 1, 2, 4, and 6 hours, ophthalmic assessments (pupil diameter, best-corrected distance visual acuity, distance-corrected near visual acuity, accommodation, and conjunctival redness), as well as adverse event assessments, were performed on subjects. Heart rate/blood pressure measurements were assessed at 2 and 6 hours. IOP was assessed at 6 hours.

Because the most common adverse event for phentolamine mesylate ophthalmic solution from previous trials was transient mild conjunctival hyperemia (McDonald MB, et al. AAO 2010:E-Abstract PO433; Holladay JT, et al. AAO 2018:E-Abstract PA025; Pepose JS, et al. IOVS 2020;61:ARVO Abstract 5100), subjects were able to request the administration of brimonidine tartrate ophthalmic solution 0.025% (Lumify; Bausch & Lomb Inc., Rochester, NY) 2 hours after treatment in the nonstudy eye for conjunctival hyperemia (redness).

One week later, subjects returned for visit 2. Subjects at visit 2 were questioned about prior and concomitant medication, and women of childbearing potential received a urine pregnancy test. The same assessments were performed 1 hour before treatment with study medication, as were conducted in visit 1, and the subjects were dilated with the same mydriatic agent they received at visit 1. Subjects at visit 2 crossed over to receive the other study medication. Assessments performed at 0 and 30 minutes and at 1, 2, 4, and 6 hours were the same as in visit 1.

Efficacy and Safety Measurements

Efficacy was measured by assessment of pupil diameter and accommodation. Pupil diameter was measured in millimeters under

photopic conditions (room lights on, light-off mode of the pupillometer) in each eye separately using the NeurOptics Pupilometer VIP-300 (NeurOptics, Laguna Hills, CA).¹¹ Accommodation (in diopters) was measured binocularly and in each eye separately using the near point rule.¹² Return of accommodative function was defined as return to within 1 D of the subject's baseline accommodative amplitude. Visual acuity was evaluated as both an efficacy and safety measurement. Best-corrected distance visual acuity was measured in each eye (right eye first) with high contrast using a standard Early Treatment Diabetic Retinopathy Study light-box chart 4 m away. Monocular and binocular measurements were recorded. Distance-corrected near visual acuity was measured using the Original Series Sloan Letter ETDRS 2000 Series Chart No. 3 Card, right eye first, in photopic conditions. All visual acuity measurements were made using the logMAR scoring system. Ocular tolerability was assessed at study medication administration by asking subjects to rate ocular tolerability in each eye separately using a 4-point scale from 0 (no discomfort) to 3 (severe discomfort). Conjunctival hyperemia was measured with a Cornea and Contact Lens Research Unit reference card 4-point scale. IOP was measured using a Tono-Pen tonometer (Reichert Technologies, Depew, NY).

Phentolamine mesylate ophthalmic solution and placebo were provided in identical-appearing bottles for single-dose use to mask the identity of study medication. Each bottle was packaged in individual foil pouches (with two bottles per kit, one of each study medication for this crossover design), and the pouches and kit were labeled with the same masked randomization codes. Upon randomization, clinical sites dispensed study medication in accordance with the randomization procedure. The study medication and assignment to treatment sequence were masked to both investigator and study subjects. Only in case of medical emergency or occurrence of serious adverse events was the randomization code to be unmasked by the study pharmacist and made available to the investigator and/or other personnel involved in the monitoring or conduct of this study.

The primary end point of the trial was the change in pharmacologically induced mydriatic (maximum) pupil diameter (measured at 0 minutes) at 2 hours after treatment in the study eye. Other secondary end points included measurements of pupil diameter, accommodation, best-corrected distance visual acuity, distance-corrected near visual acuity, conjunctival hyperemia, and other assessments of the drug's safety profile.

Statistical Analyses

A sample size of 28 completed subjects was needed for the study. Twenty-eight completed subjects provided approximately 90% power to detect a difference of 2 mm between the phentolamine mesylate ophthalmic solution and placebo treatments in the reversal of mydriasis. This calculation was based on a two-sided *t* test at the 5% level of significance ($\alpha = 0.05$) and a within-subject standard deviation (square root of the mean square error) of 2.2. In addition, it was assumed that there would be approximately 10% dropout between visit 1 and visit 2. To account for this dropout, a total of 32 subjects were planned to be randomized into the study in a 1:1 ratio to one of the two treatment sequences.

All statistical analyses and reporting were performed using the SAS System version 9.4 or later (SAS Institute, Cary, NC). χ^2 Tests were used to compare categorical survey responses between the two groups. Fisher exact tests were used when there were small sample sizes among comparison groups. Unpaired, two-sample *t* tests were performed for comparing continuous outcomes such as pupil diameter and visual acuity. The primary efficacy end point

was analyzed using a mixed model, with change from maximum pupil diameter (0 minutes) as the dependent variable; treatment sequence, period, treatment, and mydriatic agent as fixed effects; subject within-treatment sequence as a random effect; and maximum pupil diameter (0 minutes) as the covariate. Each of the continuous secondary efficacy end points was also analyzed using similar mixed models. For subgroup analyses of continuous end points by mydriatic agent, the mydriatic agent fixed effect was removed from the model.

RESULTS

Demographics and Baseline Characteristics

Of the 32 subjects enrolled into the trial, 31 completed the study (1 subject in the placebo-to-phentolamine mesylate ophthalmic solution group was excluded at the second visit because of pregnancy) in August and September of 2019 (Fig. 1). Fifteen subjects were dilated with phenylephrine, and 16 were dilated with tropicamide. The demographics and baseline characteristics of the full analysis set are presented in Table 1. Groups were similar regarding age, sex composition, race, iris color, which eye was used as the study eye, and the initial and maximum pupil diameter.

Pupil Diameter

In the study eye, mean (95% confidence interval) pupil diameters at baseline (–1 hour) was 4.54 (4.25 to 4.82) mm in the phentolamine mesylate ophthalmic solution treatment group and 4.45 (4.18 to 4.71) mm in the placebo treatment group ($P = .64$). At maximum time point (0 minutes), mean pupil diameters were 7.20 (6.78 to 7.61) mm in the phentolamine mesylate ophthalmic solution treatment group and 6.97 (6.49 to 7.45) mm in the placebo treatment group ($P = .46$). At 2 hours (primary efficacy end point), the mean changes from maximum pupil diameter were –1.69 mm with phentolamine mesylate ophthalmic solution treatment and –0.69 mm with placebo treatment, a 1-mm greater decrease favoring phentolamine mesylate ophthalmic solution ($P < .001$). A statistically significant difference in pupil diameter favoring phentolamine mesylate ophthalmic solution treatment over placebo was also observed at 1, 4, and 6 hours (all, $P < .001$; Fig. 2A). The difference in pupil diameter reduction efficacy between phentolamine mesylate ophthalmic solution and placebo treatments held true when stratifying groups by the two mydriatic agents (Figs. 2B, C).

In addition, a greater percentage of subjects in the phentolamine mesylate ophthalmic solution treatment group returned to within ≤ 0.2 mm of baseline pupil diameter after treatment with either phenylephrine or tropicamide. At the 2-hour time point, 29% of subjects given phentolamine mesylate ophthalmic solution returned to baseline at 2 hours compared with 13% in the placebo group ($P = .03$). This difference widened (68% for phentolamine mesylate ophthalmic solution and 23% for placebo) at 4 hours ($P < .001$; Fig. 3).

In an analysis of all subjects dilated with either phenylephrine or tropicamide, phentolamine mesylate ophthalmic solution treatment returned pupil diameter to baseline over a mean (standard deviation) of 4.10 (2.427) hours compared with 6.06 (2.337) hours with placebo treatment ($P < .001$). In addition, 40% of subjects with phenylephrine and 30% of subjects with tropicamide achieved a time savings of ≥ 4 hours with phentolamine mesylate ophthalmic solution. Twenty percent of subjects with phenylephrine achieved a time savings of ≥ 6 hours.

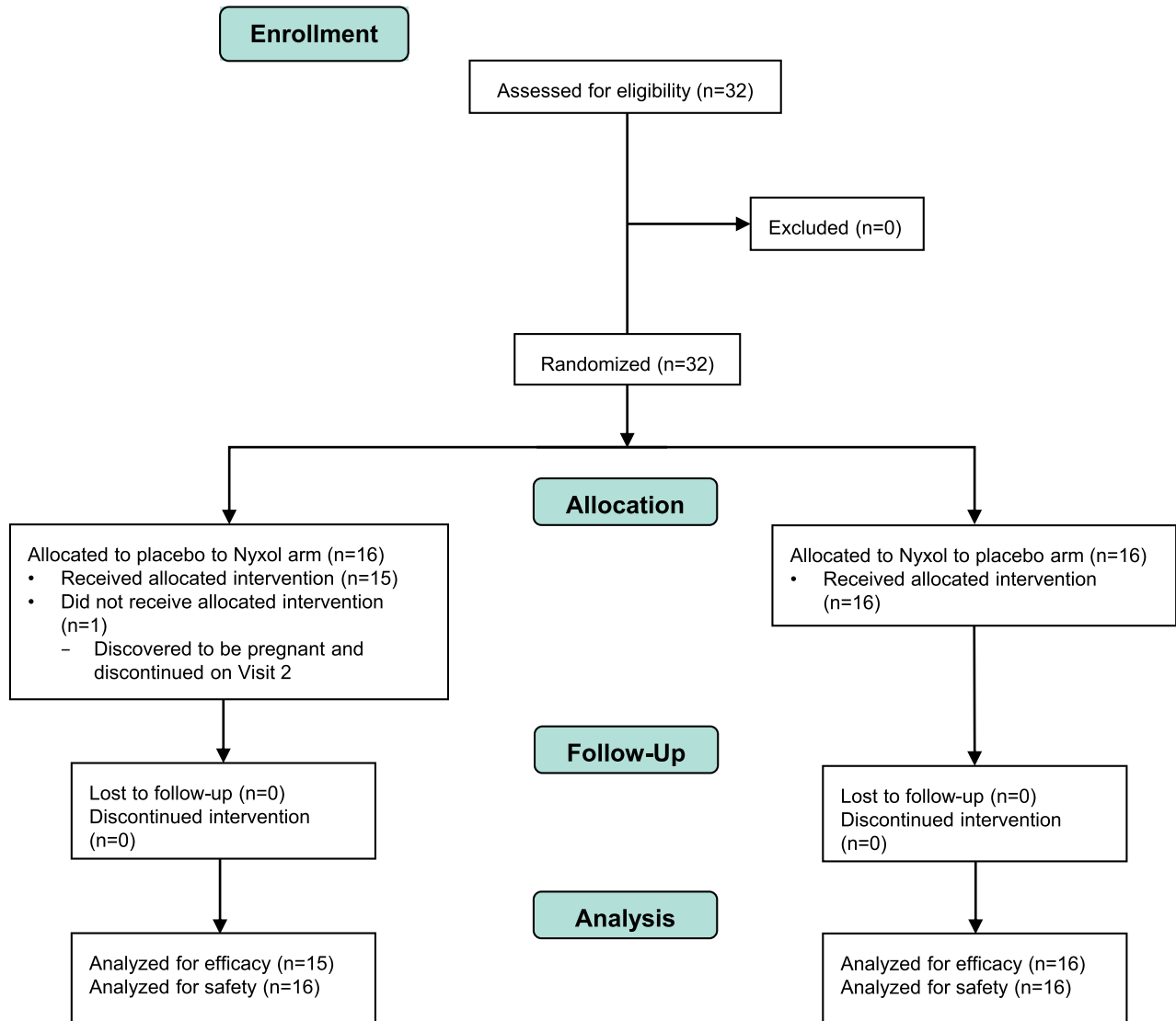


FIGURE 1. Study flow diagram.

Accommodation

Accommodative function was studied across both mydriatic agents, but a decrease in the amplitude of accommodation with mydriasis was only seen with tropicamide, consistent with its mechanism of action as an anticholinergic agent. A statistically significant worsening in study eye accommodation within groups from time -1 hour to time 0 was observed only in subjects treated with tropicamide. At time 0, 81% of phentolamine mesylate ophthalmic solution-treated subjects and 75% of placebo subjects had worsening of accommodation. When subjects treated with tropicamide were analyzed, a significant percentage of subjects receiving phentolamine mesylate ophthalmic solution treatment showed a return to accommodative amplitude back to baseline in one or both eyes compared with placebo treatment at 2 hours (63 vs. 38%, respectively; $P = .01$).

Visual Acuity

Among subjects receiving phenylephrine, a significant, albeit small, improvement in distance-corrected near visual acuity of -0.02 logMAR

was observed after treatment with phentolamine mesylate ophthalmic solution compared with placebo at 30 minutes and 1 hour ($P < .04$ and $.05$, respectively). Among subjects receiving tropicamide, a significant improvement in distance-corrected near visual acuity of -0.08 logMAR was observed at 2 and 6 hours compared with placebo ($P = .03$ and $.03$, respectively). Regarding best-corrected distance visual acuity, there were a few time points where the mean difference in best-corrected distance visual acuity between treatments was statistically significant. At each of those time points, the mean difference favored phentolamine mesylate ophthalmic solution and ranged from -0.05 to -0.02 logMAR, which reflects an improvement of one to three Early Treatment Diabetic Retinopathy Study letters.

Safety

Nineteen treatment-emergent adverse events, all of which were conjunctival hyperemia, were reported in 11 of the 31 subjects when treated with phentolamine mesylate ophthalmic solution and to treatment-emergent adverse events in 1 subject when

TABLE 1. Demographic and other baseline characteristics of the full analysis set in the MIRA-1 trial

	Placebo to PMOS	PMOS to placebo	Total
n (Full analysis set)	15	16	31
Median age (y)	30.0	26.0	27.0
Sex: female, n (%)	10 (67)	9 (56)	19 (61)
Race: White, n (%)	14 (93)	15 (94)	29 (94)
Brown iris color, n (%)	15 (100)	16 (100)	31 (100)
Study eye, n (%)			
OD	7 (47)	6 (37.5)	13 (42)
OS	8 (53)	10 (62.5)	18 (58)
Mydriatic agent, n (%)			
Phenylephrine	7 (47)	8 (50)	15 (48)
Tropicamide	8 (53)	8 (50)	16 (52)
Starting pupil diameter: study eye (mm), mean (SD)	4.5 (0.79)	4.5 (0.80)	4.5 (0.78)
Maximum pupil diameter: study eye (mm), mean (SD)	7.2 (1.04)	7.3 (1.04)	7.3 (1.02)

OD = right eye; OS = left eye; PMOS = phentolamine mesylate ophthalmic solution; SD = standard deviation.

treated with placebo. No subjects had serious treatment-emergent adverse events leading to withdrawal or study medication discontinuation, and no subjects experienced a serious adverse event. All 11 subjects were found to have mild conjunctival hyperemia, which was found to be mild-moderate in the first 2 hours.

To assess conjunctival hyperemia, mean Cornea and Contact Lens Research Unit scores of the phentolamine mesylate ophthalmic solution and placebo treatments in the study eye were compared. At study medication administration (0 minutes), the mean difference between treatments was not statistically significant ($0.11, P = .18$). At all other time points from 30 minutes to 6 hours, mean conjunctival hyperemia change from baseline was statistically significantly greater with phentolamine mesylate ophthalmic solution treatment compared with placebo treatment ($P < .01$ for each time point). The highest mean conjunctival hyperemia scores occurred at 1 hour, with a phentolamine mesylate ophthalmic solution mean score of 1.55 and a placebo mean score of 0.45. In addition, the hyperemia largely subsided after 6 hours. The percentages of subjects with conjunctival hyperemia at various severities as determined by Cornea and Contact Lens Research Unit scale are displayed in Fig. 4.

At study medication administration, all 31 (100%) phentolamine mesylate ophthalmic solution–treated study eyes had either no discomfort or mild discomfort compared with all 32 (100%) of placebo-treated study eyes.

There were no clinically meaningful changes from baseline in mean IOP 6 hours after treatment with either phentolamine mesylate ophthalmic solution or placebo (7 hours after exposure to the mydriatic agent).

There were no changes in heart rate or blood pressure (systolic or diastolic) between treatment arms, and these values stayed in the normal ranges throughout the duration of the study. No other signs of systemic toxicity were observed.

DISCUSSION

The adverse effects of mydriatic agents limit an individual's quality of life for a period of time after dilation, including issues with light sensitivity, cycloplegia, driving, and reading. Here we present the randomized, crossover, multicenter, double-masked, placebo-controlled phase 2b MIRA-1 trial in 31 normal healthy subjects evaluating the safety and efficacy of 1% phentolamine mesylate ophthalmic solution to reverse pharmacologically induced mydriasis by a parasympatholytic (tropicamide) or sympathetic (phenylephrine) mydriatic agent.

Pupil Diameter

Regarding the primary efficacy end point, phentolamine mesylate ophthalmic solution successfully demonstrated a significant improvement over placebo in reducing pupil diameter at 2 hours from the time of maximum pupil diameter. This effect was also observed at 1, 4, and 6 hours. When separately analyzing subjects dilated with parasympatholytic (tropicamide) and adrenergic (phenylephrine) agents, these continuous data of change in mean pupil diameter held true. In addition, a categorical end point of percent of subjects returning to pupil diameter baseline demonstrated significance at 2 and 4 hours. Furthermore, the onset of action of phentolamine mesylate ophthalmic solution in this trial was consistent with prior clinical trials of phentolamine mesylate ophthalmic solution.

The placebo outcomes demonstrate that natural reversal of mydriasis takes longer with tropicamide than with phenylephrine. Despite this difference, phentolamine mesylate ophthalmic solution was able to reverse mydriasis before natural reversal in the vast majority of eyes regardless of the mydriatic agent used. As expected, for subjects treated with phentolamine mesylate ophthalmic solution, those dilated with phenylephrine experienced a quicker return to baseline compared with those dilated with tropicamide.

Two other pharmacological α_1 -adrenergic antagonist agents have been discussed in the literature regarding reversal of mydriasis: dapiprazole and thymoxamine. Both drugs have been efficacious in reducing pupil diameter after pharmacological dilation with either phenylephrine or tropicamide.^{7,8,10} The Food and Drug Administration approved the use of dapiprazole in 1990, but it was later removed from the market. Albeit not the reason for its removal from the market, the drug was noted to cause severe conjunctival hyperemia, ptosis, and a high rate of burning on instillation.^{7,9} This trial has shown phentolamine mesylate ophthalmic solution is also effective in reversing pupil dilation but with a tolerable safety profile.

Cholinergic agents have also been studied in reversing mydriasis. Although topical pilocarpine acts as a miotic, its off-label use in this setting is limited by drug adverse effects including induced accommodation causing a myopic shift, headache, brow ache, blurred distance vision, and shallowing of the anterior chamber.¹³

It is well established that pupil dilation is a risk factor for patients with narrow angles to precipitate an attack of intermittent or frank angle closure. Quigley et al.¹⁴ have shown that eyes with open-angle glaucoma lose more iris volume per millimeter of pupil dilation than in eyes with closed angles. In the latter group, this narrows the anterior chamber angle space and brings the trabecular meshwork and peripheral iris closer into apposition. An added benefit to a more rapid return to smaller pupillary diameter is a reduction in glare and photophobia (Martin J, et al. IOVS 2011;52:E-Abstract 831). Furthermore, this trial represents an acute indication for phentolamine mesylate ophthalmic solution in the reversal of pharmacologically

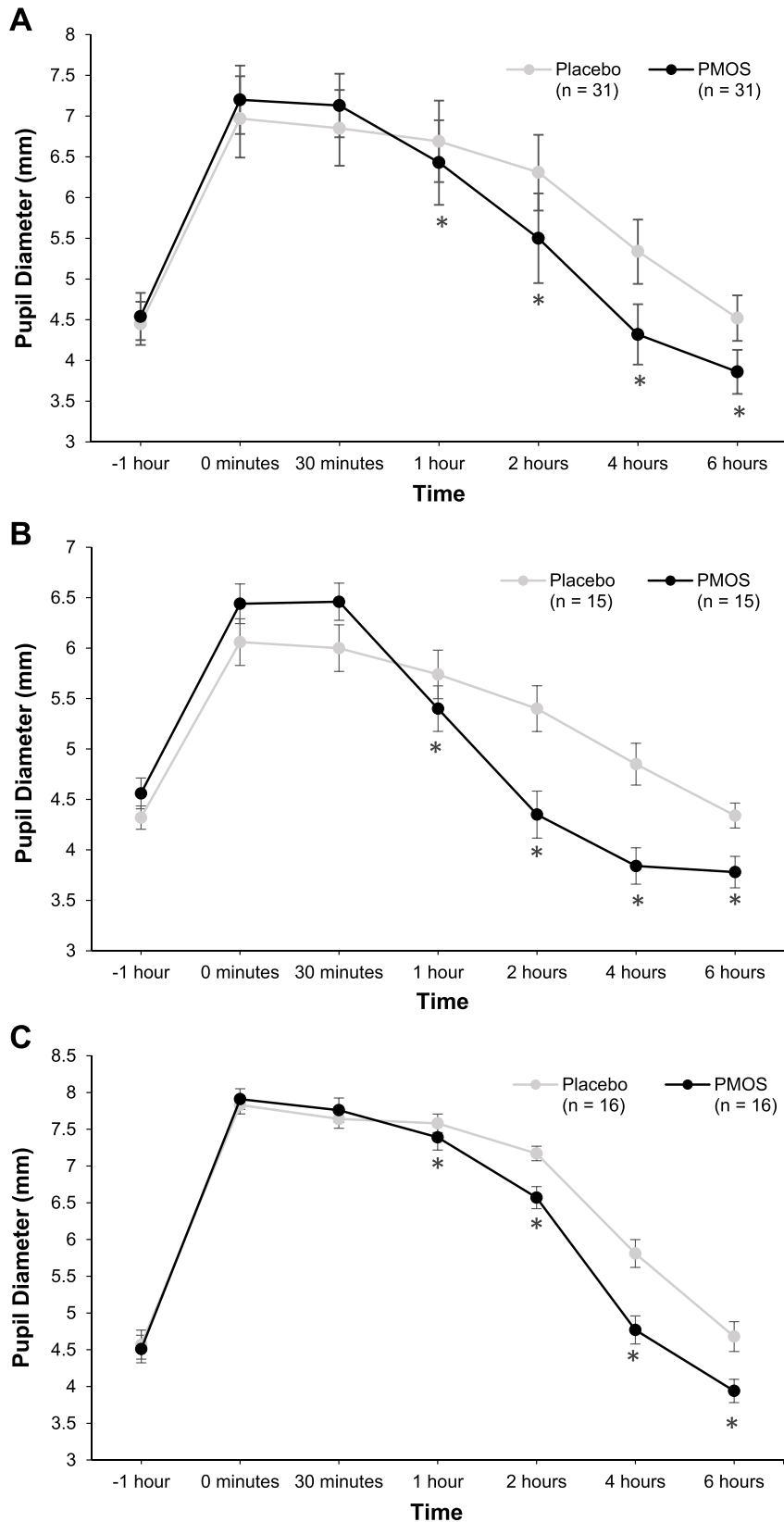


FIGURE 2. Mean reduction in pupil diameter after subjects received either phenylephrine 2.5% or tropicamide 1.0% in the study eye between phenolamine mesylate ophthalmic solution (PMOS)– and placebo-treated subjects. (A) Combined data (n = 31); error bars represent 95% confidence intervals. (B) Subjects who received phenylephrine 2.5% (n = 15 for each treatment arm); error bars represent standard error. (C) Subjects who received tropicamide 1% (n = 16 for each treatment arm); error bars represent standard error. * $P < .05$.

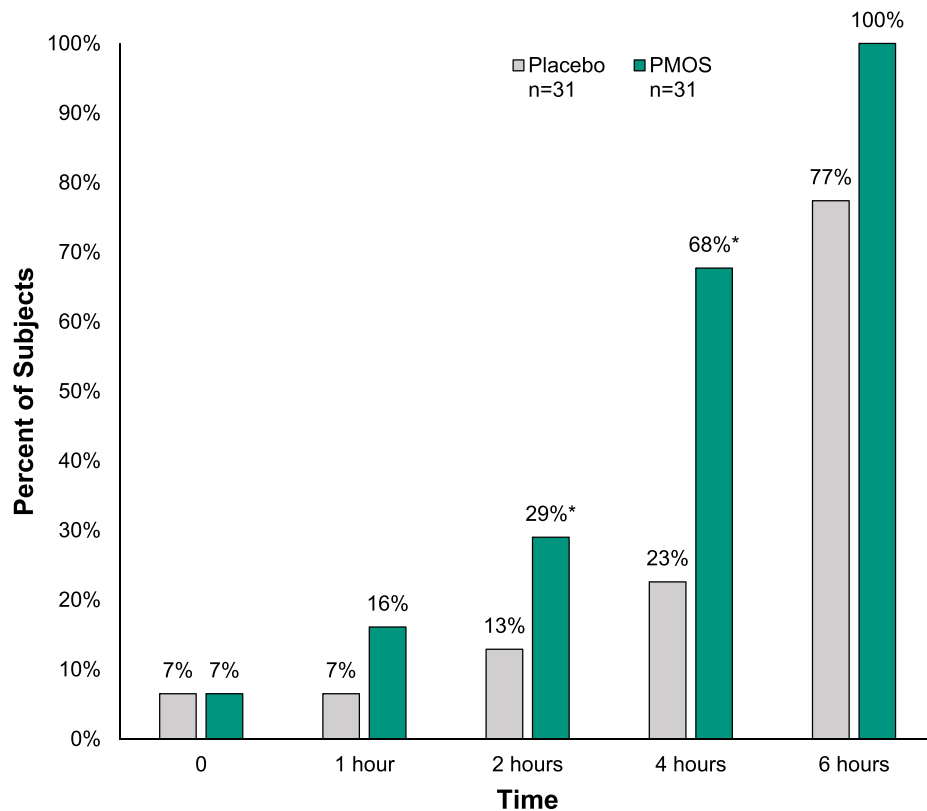


FIGURE 3. Percent of subjects returning to within <0.2 mm of baseline. A significantly greater percentage of subjects in the phentolamine mesylate ophthalmic solution (PMOS) arm versus the placebo arm returned to <0.2 mm of baseline at 2 and 4 hours after maximal dilation. * $P < .05$.

induced mydriasis in healthy subjects, but daily use of this product candidate has also been explored in treatment of dim-light vision disturbances and the elderly population (McDonald MB, et al. OVS 2010:E-Abstract PO433; Holladay JT, et al. OVS 2018:E-Abstract PA025; Pepose JS, et al. IOVS 2020;61:ARVO E-Abstract 5100).

Time Savings

Subjects treated with phentolamine mesylate ophthalmic solution exhibited a return to baseline pupil diameter 2 hours earlier compared with placebo. Considering that many patients return to their normal daily activities after their dilated eye examination, this time savings could translate to 2 additional hours of productivity and avoidance of the subjective “discomfort” of dilation. Moreover, if providers offer an eye drop that reversed mydriasis, there could potentially be fewer barriers to dilated eye examinations.

Accommodation

Although contraction of the ciliary muscle is mainly responsible for accommodation via a dynamic change in shape, curvature, and power of the crystalline lens, pupillary constriction also contributes an additional static component to near vision via pseudoaccommodation. Pupillary miosis increases the depth of focus of the eye by blocking unfocused rays of light and adding onto the improvement of near vision resulting from true lens accommodation.⁶ Both accommodation and pseudoaccommodation work in concert and are integrated in subjective measurements of the amplitude of accommodation using push-up methodology, as used in this trial. However, we postulate that the improvement in near vision and accommodative amplitude shown by phentolamine mesylate ophthalmic solution

likely is working exclusively by facilitating pseudoaccommodation via miosis, as it does not have the cholinergic activity needed to affect true accommodative ability. Because accommodation combined with pseudoaccommodation is important for activities such as reading text on the computer or a car dashboard while driving,¹⁵ the return of smaller pupil diameter and the time savings associated with such imply a quicker return to normal visual function via pseudoaccommodation, even if the return of the true accommodative component may be further delayed.

Safety

Phentolamine mesylate ophthalmic solution at 1% concentration continued to demonstrate a favorable overall safety profile, consistent with prior clinical trials (McDonald MB, et al. AAO 2010:E-Abstract PO433; Holladay JT, et al. AAO 2018:E-Abstract PA025; Pepose JS, et al. IOVS 2020;61:ARVO Abstract 5100). When treated with phentolamine mesylate ophthalmic solution, approximately one-third of subjects experienced mild cases of conjunctival hyperemia, and no other systemic (blood pressure, heart rate) or other ocular treatment-emergent adverse events were observed. There were no serious treatment-emergent adverse events or treatment-emergent adverse events leading to withdrawal or study medication discontinuation. Moreover, whether given phentolamine mesylate ophthalmic solution or placebo, any discomfort occurring after treatment was mild in intensity.

Regarding the conjunctival hyperemia, it peaked at 30 minutes in phentolamine mesylate ophthalmic solution-treated subjects and declined steadily thereafter. Although mild-moderate conjunctival hyperemia was still apparent in some subjects at 6 hours, it

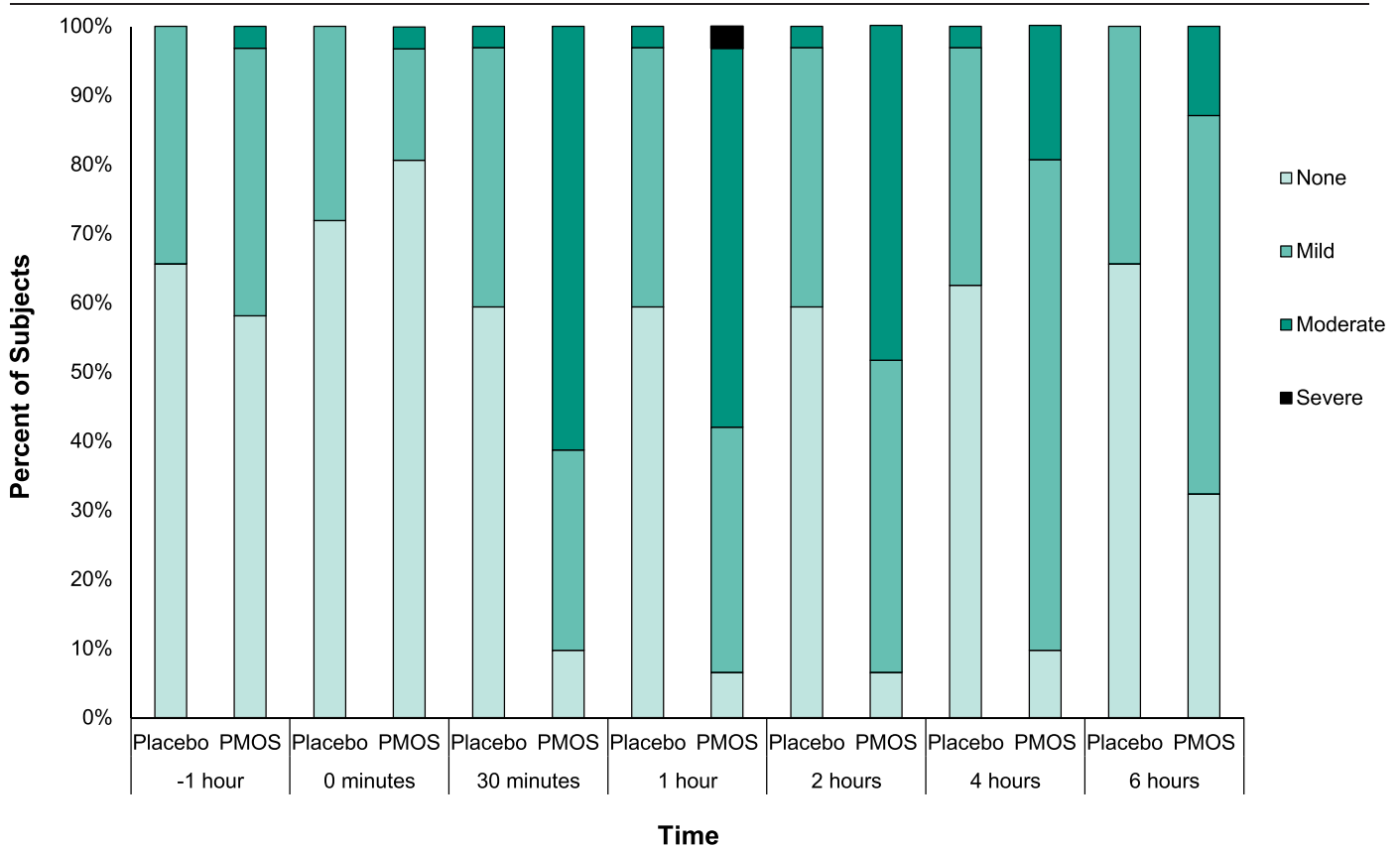


FIGURE 4. Percent of subjects with conjunctival hyperemia compared with placebo at all time points. There was significantly greater conjunctival hyperemia in the phentolamine mesylate ophthalmic solution (PMOS)– versus placebo-treated subjects. Conjunctival hyperemia was graded using Cornea and Contact Lens Research Unit cards, which included levels of none, mild, moderate, and severe.

was approaching baseline levels. Although Lumify was not requested by any subjects in this trial, it might serve to ameliorate hyperemia and could be further investigated.

Examination of near and distance visual acuity after study medication treatment revealed that, although there were some statistically significant improvements in the vision favoring phentolamine mesylate ophthalmic solution, they lacked clinical significance. In contrast, time to return of accommodative function was different among the treatment arms and proved to be a more sensitive measure of visual function than visual acuity for subjects undergoing pharmacologically induced mydriasis. This is supported by findings of Watts et al.,¹⁶ where patients whose eyes were dilated still conveyed subjective complaints and difficulties while driving, although they had passed legal requirements of best-corrected distance visual acuity.

Limitations and Future Plans

Although this was a well-controlled clinical trial that achieved its primary and secondary end points, several limitations were identified in the trial design. First, this trial included only subjects with dark (brown) irides. However, according to Wright and colleagues,¹⁷ light color eyes showed a more pronounced dilation and more rapid reversal of dilation with dapiprazole. Second, only healthy subjects without systemic or ocular disease were enrolled, and further studies may need to include patients with conditions that could affect pupillary dynamics, such as diabetes and other conditions that may affect the autonomic nervous system.¹⁸ In

addition, some subjects treated with phenylephrine had limited dilation likely because of the brown-only irides in this trial. Finally, subgroup analyses were not powered or adjusted for multiplicity, so the tests of significance should be considered exploratory.

Efficacy can also possibly be improved upon with a higher dose of phentolamine mesylate ophthalmic solution. Evaluation of two drops of phentolamine mesylate ophthalmic solution may even further potentiate the time and magnitude of the mydriatic reversal effects.

CONCLUSIONS

In conclusion, pupil diameter reduction with 1% phentolamine mesylate ophthalmic solution was robust and consistent across parameters, with statistically significant and clinically relevant improvements versus placebo in reducing pupil diameter at 1, 2, 4, and 6 hours from the maximum pupil diameter time point. These results were stratified by mydriatic agent and showed that phentolamine mesylate ophthalmic solution's pupil diameter reduction effects were seen with both tropicamide and phenylephrine, consistent with other α_1 antagonists studied. Overall, phentolamine mesylate ophthalmic solution was well tolerated in the eye. The improvement of key efficacy measures suggests that phentolamine mesylate ophthalmic solution should be further investigated as a drug candidate for reversal of pharmacologically induced mydriasis.

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