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MyopiaX-1 Safety and Efficacy of a Novel Approach to Slow Juvenile Myopia Progression: A Multicenter, Randomized, Controlled Trial

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Purpose: To investigate the safety, tolerability, and signals of effect of MyopiaX, a smartphone app that selectively delivers blue light to the optic nerve head to control myopia progression in children and adolescents.

Design: Multicenter, randomized, active-controlled, examiner-masked proof-of-concept clinical trial (ClinicalTrials.gov identifier NCT04967287).

Participants: Eligible children aged 6 to 12 years, with myopia of cycloplegic spherical equivalent refraction (SER) between −0.75 and −5.00 diopters (D) at baseline. Children were screened and enrolled between November 2021 and September 2023.

Methods: Children were randomly assigned in a 2:1 ratio to MyopiaX or active control. Participants were instructed to use MyopiaX for 10 minutes twice daily for the first 6 months and, during the second 6 months of the trial, also wear defocus incorporated multiple segments (DIMS) myopia control spectacles. The active control group wore DIMS spectacles for the entire 12-month trial.

Main Outcome Measures: The primary outcome was change in axial length (AL) and change in SER at month 6. Clinical safety examinations and the frequency and severity of device-related adverse events (AEs) were analyzed for all participants who began treatment.

Results: Of the 124 randomized participants, 101 were enrolled under the 12-month active-control study design (MyopiaX: n = 66, DIMS: n = 35). After 6 months, the mean AL change from baseline in the MyopiaX (n = 50) and DIMS (n = 34) groups, respectively, was 0.14 ± 0.11 mm and 0.08 ± 0.09 mm. The 6-month change in SER was −0.18 ± 0.39 D in the MyopiaX group and −0.16 ± 0.41 D in DIMS participants. Among the 73 participants who used MyopiaX, including those randomized under the original study design (prior to introduction of an active control), there were 23 related AEs among the 16 participants (22%), including transient ocular discomfort and headache, all of which resolved without any need for treatment.

Conclusions: MyopiaX was safe and well tolerated over 12 months in treatment-naive children with myopia. This exploratory study provides the first clinical data on the impact of MyopiaX's selective blue light stimulation on myopia progression and ocular growth. This novel approach may offer a complementary therapeutic solution for the clinical management of progressive myopia.

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Supplemental material available at www.ophthalmologyscience.org.

The continuous rise in myopia prevalence represents a complex global public health challenge. Widely attributed to changes in modern lifestyles, the prevalence of myopia is projected to increase to close to 50% by 2050, affecting approximately 5 billion people worldwide.[1] While there are various myopia control interventions available—including specialized contact and spectacle lenses, pharmaceutical treatments, behavioral interventions, and, more recently, repeated low-level red-light therapy—no single intervention is considered the definitive standard of care.[2]

Within the numerous proposed mechanisms of myopia development, there is strong evidence for the light-mediated dopamine release hypothesis of ocular growth regulation.[3,4] The influence of light on many physiological processes is mediated by the melanopsin system. Melanopsin is a blue light-sensitive photopigment found in the soma and axons

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of intrinsically photosensitive retinal ganglion cells, a unique subset of retinal ganglion cells that are directly photosensitive.[5] These cells play a central role in nonimage-forming visual functions such as circadian photoentrainment, pupillary light reflex, and regulation of retinal physiology. Intrinsically photosensitive retinal ganglion cells have axonal connections with the central nervous system and synaptic connections within the retina, including to dopaminergic amacrine cells, thereby linking ambient light levels to key neurochemical and physiological processes.[6,7] Targeted blue light stimulation of the optic nerve head ("blind spot stimulation"), where the melanopsin-expressing intrinsically photosensitive retinal ganglion cell axons bundle, has been shown to activate this pathway,[8] and holds the potential to slow eye growth by promoting dopamine release. Blue light stimulation of the blind spot triggers the melanopsin-driven pupil light response,[9] enhances retinal electrical activity (increasing the b-wave amplitude of the light adapted full field electroretinogram and the P50-N95 amplitude of the pattern electroretinogram),[10,11] and improves higher spatial frequency contrast sensitivity (an indirect marker of retinal dopamine release),[12] in human adults.[13] It also has been shown to influence ocular dopamine levels in rabbits.[14] Additionally, an increase in subfoveal choroidal thickness—a potential short-term marker of anti-myopia effect—has been reported in young adults after blue light stimulation of the blind spot for 1 minute.[15] A reduction in axial length (AL) has also been measured after 6 days of daily blue light stimulation for 1 minute.[16] In children, a single 60-second exposure induced measurable choroidal thickening (6.2 μm) and AL shortening (−6.8 μm), independent of refractive error, that was not observed after red light stimulation of the optic nerve head.[17] Collectively, these findings suggest that selectively stimulating the blind spot with blue light could serve as a novel, dopamine-mediated approach to slow myopia progression (Supplemental Figure 1, available at www.ophthalmologyscience.org).[8] MyopiaX is a smartphone application which implements this approach by providing blind spot stimulation with blue light.

The MyopiaX-1 proof-of-concept trial is the first clinical investigation of the effects of MyopiaX's selective blue light stimulation of the blind spot on measures of myopia progression. The purpose of this study was to evaluate the safety, tolerability, and signals of effect of MyopiaX on myopia progression and eye growth in European children. This study also evaluates the pattern of use and acceptability of MyopiaX to children and their caregivers.

Methods

Study Design and Setting

MyopiaX-1 was a prospective, randomized, active-controlled, examiner-masked, multicenter international clinical trial. The study was conducted at 11 centers in Germany, Ireland, the Netherlands, Portugal, Spain, and the United Kingdom and prospectively registered at ClinicalTrials.gov (identifier: NCT04967287). The MyopiaX-1 trial was reviewed and approved by the respective ethics committees and competent authorities in all participating countries. Legal guardians provided written informed consent and participants provided assent prior to enrollment in the study. The study was conducted in full conformity with the current revision of the Declaration of Helsinki and according to the International Standard ISO 14155:2020-07 (Clinical investigation of medical devices for human subjects—Good clinical practice). An independent Data Safety Monitoring Board held quarterly reviews of masked safety data.

The original study protocol underwent a significant amendment first approved in October 2022 from a sham-controlled to an active-controlled design. With the wide availability within Europe of spectacle-based solutions when the study was commenced, it proved challenging to recruit participants for 12 months of intervention with a treatment of unproven efficacy. To ensure adequate recruitment, the final protocol therefore added defocus incorporated multiple segments (DIMS) at 6 months. An overview of the changes between the 2 protocol versions is provided in Supplemental Appendix 1 (available at www.ophthalmologyscience.org). This article focuses on the study procedures and outcomes of participants enrolled under the amended protocol which comprise the majority of the study population (101 of 124 randomized participants), except for MyopiaX safety outcomes, which are reported for all participants.

Eligibility Criteria

A total of 101 treatment-naïve aged 6 to 12 years inclusive children, who had not received any prior form of myopia control, were randomized under the active control design. Eligible participants had myopia of cycloplegic spherical equivalent refraction (SER) from -0.75 to ≤ -5.00 diopters (D), a least myopic meridian of ≥ -0.50 D in each eye, visual acuity of ≥ 0.2 on the logarithm of the minimum angle of resolution scale in each eye, anisometropia ≤ 1.5 D, and astigmatism ≤ 3.0 D. Children were excluded if they had ophthalmic comorbidities, optic nerve abnormalities, or were suspected to have syndromic or monogenetic myopia. Other exclusion criteria included systemic illnesses affecting eye health, eye growth, or refraction; illnesses affecting dopamine function (eg, sleep disorder, attention deficit hyperactivity disorder, and autism spectrum disorders); medication affecting dopamine function, accommodation, pupil size, or the ocular surface (eg, allergy medications); a medical or family history of photosensitive epilepsy; and participation in other clinical studies. Additionally, children were required to demonstrate good tolerability and binocular adequacy during a test session with the investigational virtual reality (VR) system.

Randomization and Masking

Eligible participants were randomized 2:1 to the intervention or active control group, respectively, using static block randomization (block size: 6) and stratified according to baseline age (6–9 years, 10–12 years) and SER (-0.75 less than or equal to SER $<$ -3.00 D, -3.00 less than or equal to SER $\leq$ -5.00 D). The randomization list was generated by Assign BMD using code programmed according to the aforementioned specifications and participants were allocated to a treatment group via the randomization module of the electronic data capture system by an unmasked site member. The active control group was assigned to wear spectacles with DIMS lenses, a clinically validated treatment for myopia management.[18,19] Children in the intervention group used MyopiaX twice daily for 12 months, exclusively for the first 6 months and with the addition of DIMS spectacles for the second 6 months. The active control group wore DIMS spectacles alone for 12 months. The trial was single-masked,

with clinical assessors at each clinical site naïve to the allocated intervention. Participants were unmasked to their treatment allocation (MyopiaX or active control).

Interventions

MyopiaX (Dopavision GmbH) is a software application that selectively administers a blue light intervention to the blind spot of each eye. The blue light is emitted from an active-matrix organic light-emitting diode smartphone display at an illuminance of 60 melanopic lux (λ_{peak} = 464 nm) and a temporal frequency of 15 Hz. Based on the calculations performed in accordance with the IEC 62471:2006 standard (photobiological safety of lamps and lamp systems), blue light at this illuminance is safe to view for up to 28 consecutive hours. The calculated retinal irradiance for the MyopiaX device is 61 μW/cm2. In comparison, the retinal irradiance for repeated low-level red light devices has been reported to be >1000x higher at $8.0 \times 10^4 - 7.2 \times 10^6$ μW/cm2.[20] For more information and a review on safety of artificial blue light in the context of digital devices, please see Wong and Bahmani.[21]

MyopiaX's blue light intervention was administered over six 100-second stimulus intervals, separated by stimulus-free breaks of 15-20 s, for a total light exposure of 10 minutes per treatment session (Supplemental Figure 2A, available at www.ophthalmologyscience.org). MyopiaX sessions were conducted at home, 7 days per week, using commercially available hardware provided on loan to intervention group participants, including a smartphone (Samsung Galaxy S7, SM G930F, Samsung Electronics), VR headset (Merge VR Virtual Reality Headset from iPhone and Android, Merge Labs), and wireless controller (Maegoo Bluetooth Android Controller with Retractable Bracket, 2.4 G Wireless PC/PS3/TV Controller Gamepad with Dual Vibration).

The smartphone running the MyopiaX app emitted the blue light intervention which was calibrated to each individual participant's blind spot location using a fundus image and manual adjustment in the VR environment.[15] The blue light stimulus was directed to the optic nerve head of both eyes through the VR headset while children used a wireless controller to engage with gamified foveal fixation content (Supplemental Figure 2B, available at www.ophthalmologyscience.org). MyopiaX featured 9 custom-designed, age-appropriate mini-games, with 6 randomly selected to appear during each session. This content was designed to maintain foveal fixation within a specified central area to ensure selective stimulation of the optic nerve head with blue light. The intervention schedule comprised two 12-minute sessions per day—one in the morning and one in the afternoon—spaced ≥2 hours apart. Families were advised to complete the afternoon session ≥3 hours before bedtime to avoid potential effects on the sleep-wake cycle.[22] Participants were instructed to wear their corrective lenses when using MyopiaX.

All children were dispensed DIMS spectacles, either at baseline (active control group) or at month 6 (intervention group).[18,19]

MyopiaX Adherence Monitoring

For participants assigned to use MyopiaX, treatment adherence was monitored via the app, with a session marked as complete only if the participant received ≥8 minutes of blue light stimulation during each session out of a possible maximum of 10 minutes and met the minimum score set for each game in at least half of the games. Game performance was logged as a proxy for the participants' fixation and consequently successful treatment delivery to the optic nerve head. The participant needs to fixate on the correct part of the screen to respond correctly and score points in the game. For each child, the game and blue light positions are calibrated to ensure the light stays on the blind spot while the game is played, and these locations remain fixed across all games. The frequency of successfully completed sessions was logged to track adherence to the treatment and adherence data was available to participants and their families in the MyopiaX app (Supplemental Figure 2C, available at www.ophthalmologyscience.org). Pseudonymized adherence data were accessible to clinical trial sites via an investigator report platform, allowing clinical site personnel to follow up with families showing low adherence at their discretion.

Study Outcome Measures

The primary study outcomes were change in AL and SER from baseline to month 6. Safety outcomes, including tolerability, were frequency and severity of device-related adverse event (AE) reports, visual acuity changes from baseline, and color fundus imaging findings over 12 months. Exploratory outcomes included change in AL and SER from month 6 to month 12 and baseline to month 12, in addition to retinal and choroidal imaging parameters and device usability (as measured with a user feedback questionnaire).

Participants completed 5 clinic visits: at baseline, 1, 3, 6, and 12 months. A phone call was also made at week 1 and month 9 to ensure proper treatment use and check on participants' wellbeing. Axial length was measured at baseline, 3, 6, and 12 months using ocular biometry. Autorefraction after administration of 2 drops of 1% tropicamide, instilled 5 minutes apart, was performed every 6 months to assess SER.[23] The WAM-5500 open-field binocular autorefractor (Grand Seiko) was standardized across sites. For all other assessments, sites used available equipment but were not permitted to change devices throughout the study.

All participants who began treatment, regardless of their assigned study group or the protocol version under which they were first randomized, were analyzed for safety. Adverse events and device deficiencies were monitored and reported continuously over the course of the trial. Devices showing any deficiencies, as reported by participants or their caregivers, were replaced. The following clinical safety examinations took place at each visit: visual acuity, slit lamp examination, intraocular pressure (applanation tonometry or similar calibrated contact tonometer), Worth 4 Dot test as implemented in the MyopiaX VR system, fundus ophthalmoscopy, and optic nerve head examination. Pupil size measurements were also taken at baseline, 6, and 12 months using a handheld pupilometer under photopic (85 cd/m^2) and mesopic (3 cd/m^2) conditions, allowing for 3 minutes to adapt to the low light condition. Color fundus photographs were obtained for all participants, and for participants randomized at sites with access to a high-resolution spectral-domain OCT device, additional cross-sectional and *en face* images of the central retinal and central choroidal regions were obtained every 6 months. Caregivers were requested to contact the trial site immediately if their child experienced an AE or issue with the MyopiaX device.

Complementary data on participants' sleep quality (modified Pittsburgh Sleep Quality Index[24]) were collected every 6 months to understand any potential effect of the blue light stimulus on participants' sleep-wake cycle.

Sample Size

The planned enrollment target in the amended protocol was 81 participants, randomized 2:1 to MyopiaX (n = 54) versus the active control (n = 27), in addition to the participants previously randomized into the study (n = 23) under the original protocol. With an estimated dropout rate of 20%, it was anticipated that

there would be a minimum of 43 and 21 evaluable participants in the MyopiaX and active control groups, respectively.

Statistical Analyses

The effect outcomes were analyzed for each treatment group separately and for each defined stratum (age group and refractive error at baseline). Absolute change ± standard deviation from baseline was calculated to month 6 and month 12 and from month 6 to month 12. Descriptive statistics for the frequency of device-related AEs were summarized by treatment group and severity. The Common Terminology Criteria for Adverse Events (version 5) was used to define mild (grade 1), moderate (grade 2), and severe (grade 3) AEs. For the analysis of treatment group differences, linear mixed models were used including data from both eyes, random intercepts for participants, and adjusting for baseline randomization strata (age and refractive error group) and the baseline value of the outcome. Statistical analysis was conducted with R v4.3.2 (R Foundation for Statistical Computing) and pairwise group differences calculated using the estimated marginal means (emmeans) package.

Given the exploratory nature of analyses, a 2-sided significance level of 0.05 was applied.

Results

Baseline Characteristics

An overview of participant enrollment, randomization, and follow-up is provided in Figure 1. Enrollment and baseline measurements were performed between November 2021 and September 2023. The final follow-up visit was completed in October 2024. Baseline characteristics and demographics of all randomized participants who attended both the month 6 and month 12 visits (per-protocol set) are provided in Table 1. Supplemental Table 1 (available at www.ophthalmologyscience.org) provides the baseline characteristics and demographics for all randomized participants who started their assigned intervention (safety analysis set). Baseline characteristics of participants included in the per-protocol set were generally well-matched; however, relative to the DIMS spectacles group, the MyopiaX group had a slightly lower reported median age of onset (7 vs. 8 years) and a lower proportion of participants identified as Asian by their parents (4.3% [2 participants] vs. 24% [8 participants]). These 2 differences would be expected to influence myopia progression in opposite directions, with a younger age leading to faster progression and few Asian participants leading to slower progression, so are likely to balance out.

A lower proportion of participants in the MyopiaX group completed the 12-month visit (n = 47, 71.2%), compared with the active control group (n = 34, 97.1%). Compared with participants included in the per-protocol set, participants who discontinued the study were slightly older (median age 11 vs. 10 years). All other variables were similar between groups.

Effect Outcomes

The mean AL change at month 6 primary endpoint was significantly greater ($P = 0.004$) in the MyopiaX group (0.14 ± 0.11 mm) than in the DIMS spectacles group (0.08 ± 0.09 mm). The changes in SER over the same period were not significantly different between the MyopiaX (−0.18 ± 0.39 D) and DIMS (−0.16 ± 0.41 D) groups ($P = 0.82$). The mean AL change from month 6 to month 12 was 0.04 ± 0.11 mm in the MyopiaX group and not significantly different ($P = 0.20$) from the AL growth in the DIMS group (0.06 ± 0.07 mm) over the second half of the trial (Fig 2). Overall, the 12-month AL growth in the MyopiaX (0.18 ± 0.17 mm) and DIMS (0.14 ± 0.14 mm) groups were not significantly different ($P = 0.24$). The mean SER changes from month 6 to month 12 ($P > 0.99$) and from baseline to month 12 ($P = 0.86$) were not significantly different between study groups (Table 2).

There were no significant interactions between baseline age (6-9 years or 10-12 years at baseline) group and study group for change in AL ($P = 0.08$) or SER ($P = 0.18$), nor between baseline refractive error (−0.75 to < −3.00 D or −3.00 to −5.00 D) group and study group on either effect outcome (AL: $P = 0.63$, SER: $P = 0.49$) (Supplemental Appendix 2, available at www.ophthalmologyscience.org). There were no significant between-group differences in the changes at 6 months ($P = 0.95$), 12 months ($P = 0.90$), or 6 to 12 months ($P = 0.54$) for the exploratory outcome of central choroidal thickness. Similarly, changes in central retinal thickness were not significantly different between groups at 6 months ($P = 0.92$), 12 months ($P = 0.72$), or 6 to 12 months ($P = 0.77$; Supplemental Appendix 3, available at www.ophthalmologyscience.org). The possible impact of seasonal variation in ocular growth was also examined. This potential effect was largely mitigated by the fact that participants were recruited over approximately a year. Hence, start and end dates were evenly spread over the year. When an adjustment seasonality was included, there were no significant changes to the findings.

Adherence to MyopiaX

MyopiaX adherence was measured as the percentage of expected sessions completed and logged as "valid," where "expected sessions" is the number of sessions participants would have completed if they performed 2 valid sessions daily. Figure 3A, B show that adherence declined from a median (interquartile range) adherence of 57.3% (44.6 to 73.4) between baseline and month 6 to 25.7% (9.9 to 62.3) between month 6 and month 12. There was a significant association between better cumulative adherence over the 12 months of the study and less cumulative AL growth over 12 months (slope = −0.002, $P = 0.01$) after adjusting for baseline AL and randomization strata (Fig 3C).

Safety Outcomes and Tolerability

Safety outcomes were evaluated through clinical examinations conducted on site and by participant- or caregiver-reported AEs. Among the 118 participants exposed to the MyopiaX or control intervention, 12 AEs in 11 (9.3%) participants were reported as possibly related, 2 AEs in 2 (1.7%) participants were assessed as probably related to an

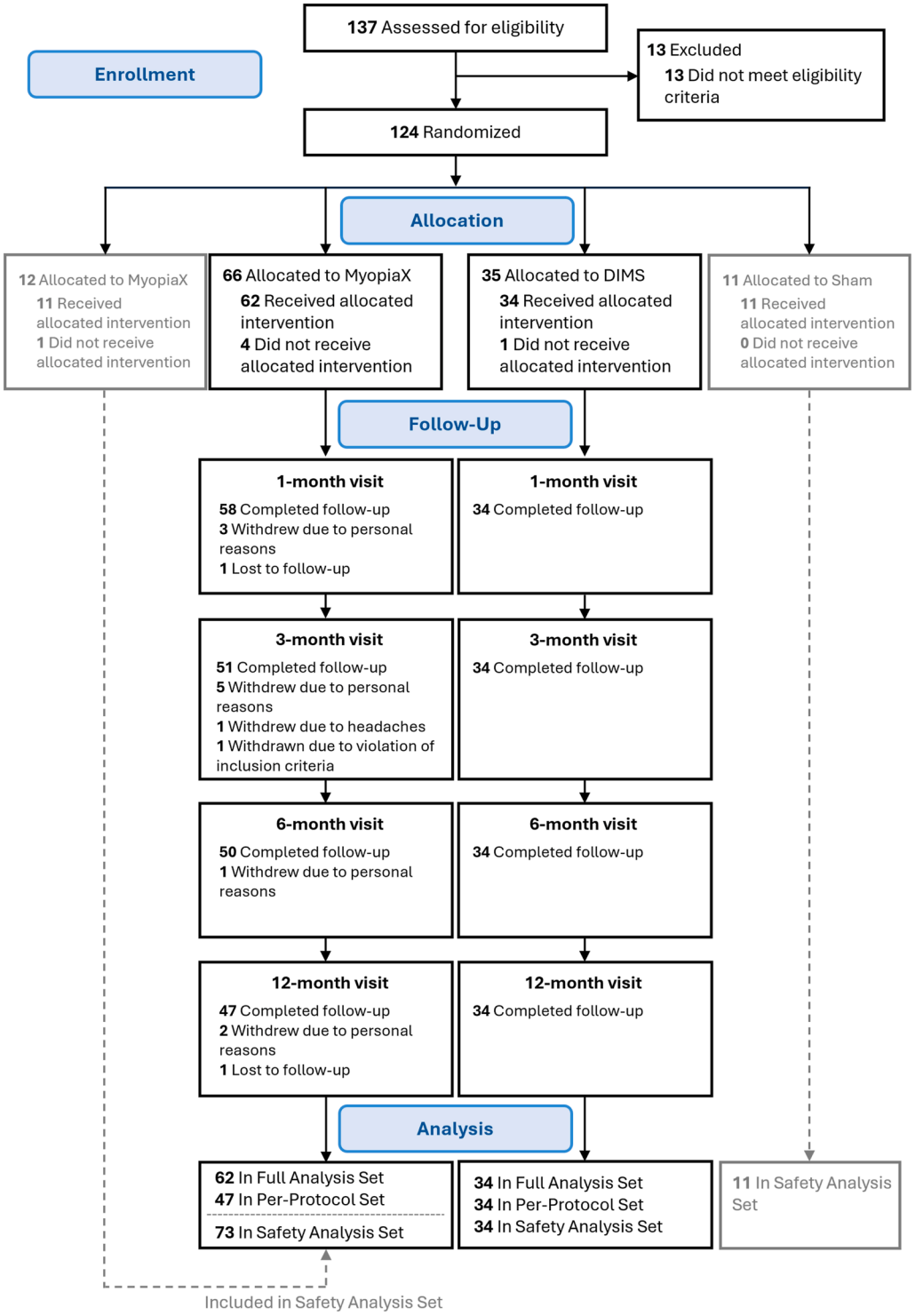

Figure 1. Flow chart of participant recruitment, enrollment, and follow-up. DIMS = defocus incorporated multiple segments.

intervention, and 14 AEs in 9 (7.6%) participants were assigned a causal relationship. Of the 28 related AEs, 23 were in the MyopiaX group, 3 in the DIMS group, and 2 in the sham group. Adverse events reported to be related to MyopiaX included transient ocular discomfort (eg, eye strain and irritation) and headache, as well as dizziness and nausea associated with gameplay (VR use). One AE in the MyopiaX group (headache) was reported to be related to both DIMS and MyopiaX, and one to DIMS spectacles wear (vision blurred). Of the AEs related to MyopiaX, most were mild (76%), with 4 (19%) rated moderate and 1 (5%) possibly related to both MyopiaX and DIMS rated severe.

Table 1. Baseline Characteristics of the Per-Protocol Analysis Set of MyopiaX-1 Participants by Study Arm

Characteristic	Per-Protocol Analysis Set	
	MyopiaX N = 47	*DIMS Spectacles* N = 34
Age (years)	10.00 (8.00, 11.00)	10.00 (9.00, 12.00)
Age of myopia onset (years)	7.00 (7.00, 9.00)	8.00 (6.50, 9.00)
Unknown	0	2
Sex		
Male	22 (47%)	18 (53%)
Female	25 (53%)	16 (47%)
Race		
White	41 (87%)	22 (65%)
Asian	2 (4.3%)	8 (24%)
Black	1 (2.1%)	1 (2.9%)
Other	3 (6.4%)	3 (8.8%)
Spend <2 h outdoors per day		
Yes	11 (23%)	9 (26%)
No	36 (77%)	25 (74%)
Number of parents with myopia		
Zero	5 (11%)	7 (21%)
One	23 (49%)	12 (35%)
Two	19 (40%)	15 (44%)
Axial length (mm)*	24.34 (23.68, 24.92)	24.40 (23.87, 25.02)
Spherical equivalent refraction (D)*	−2.38 (−3.13, −1.50)	−2.46 (−3.47, −1.84)

Data shown are n (%) [N = number of nonmissing data points] for categorical and median (Q1, Q3) [N nonmissing] for continuous variables. The per-protocol set includes only participants who attended both month 6 and month 12 visits.
D = diopters; DIMS = defocus incorporated multiple segments.
*Mean of both eyes.

All resolved without intervention. Among the 5 serious AEs recorded, 1 was graded moderate in the MyopiaX group (dizziness requiring out-patient evaluation), 3 were graded severe (1 in each group: MyopiaX [radius fracture], DIMS [enteritis], and sham [ankle fracture]), and 1 was graded life-threatening in the DIMS group (intussusception). None of the serious AEs were related to MyopiaX, control, or study procedures. A complete summary of related AEs is provided in Table 3.

No functional or structural changes in ocular health were observed over the 12-month trial period, as assessed by visual acuity, intraocular pressure, and retinal imaging. The mean change in global Pittsburgh Sleep Quality Index score across all participants who started their assigned intervention was −0.16 ± 1.61 (on a scale of 21) from baseline to month 12, suggesting changes in sleep quality were minimal over the course of the trial.

A total of 202 device deficiencies (DDs) were reported during the study. The majority were related to software malfunctions, such as app errors (160 DDs) or user errors (30 DDs), which were anticipated for an early-stage device, such as MyopiaX. None of the reported DDs were considered a health threat, and no serious AEs were associated with them. One DD was linked to an AE involving eye pain when the game continued for >10 minutes, but without the blue light stimulation.

MyopiaX Device Usability

The results of the end of study parent-reported questionnaire on device usability are presented in Supplemental Table 2 (available at www.ophthalmologyscience.org). Forty-two percent of parents were likely or very likely to recommend MyopiaX, while 42% were neutral and 16% unlikely or very unlikely. Most parents reported that the MyopiaX app was easy for their child to interact with (67% easy or very easy), as were the VR headset and controller (87% easy or very easy). While some parents reported difficulty integrating MyopiaX into their child's daily routine (31%), more found it easy or very easy (42%). The majority of parents were neutral about the treatment session length (53%), but 38% felt the length was either somewhat or very long. Parents also reported that their child became bored by the games; 62% reported their child was somewhat or very bored and only 15% reported that their child was somewhat or very entertained.

Discussion

MyopiaX-1 is the first multicenter, randomized, controlled proof-of-concept clinical trial investigating MyopiaX, a novel light-based intervention designed to control myopia. This study generated initial clinical data supporting a potential slowing effect of MyopiaX on the rate of myopia progression in European children. There were no significant differences in SER change between the MyopiaX and DIMS groups over any trial period. This signal of effect is supported by the significant relationship observed between better 12-month AL outcomes and higher cumulative adherence to MyopiaX, despite the significantly greater AL growth in the MyopiaX group over the first half of the trial. Overall, the 12-month proof-of-concept trial demonstrated a favorable safety profile for MyopiaX and yielded learnings to guide future clinical and device development, with the results supporting MyopiaX's future potential as a myopia intervention with a positive benefit-risk profile.

The primary clinical effect outcome was change in AL and SER from baseline to month 6. Over the first 6 months of the trial, mean SER change in the MyopiaX group (−0.18 D) was comparable to that in the DIMS group (−0.16 D). Axial length growth showed a similar response pattern, although the mean change in the MyopiaX group (0.18 mm) was significantly greater than that in the DIMS group (0.14 mm). The 6-month AL growth in DIMS participants was comparable to that in a recent observational study conducted in Italian children and adolescents aged 6 to 18 years (baseline myopia between −0.50 and −4.00 D). That the myopia progression of the DIMS group in this study was less than that observed by Nucci et al[25] may be attributed, in part, to differences in the samples or the variability of SER outcomes.

When contextualized within contemporary reported European studies, the axial elongation observed in the

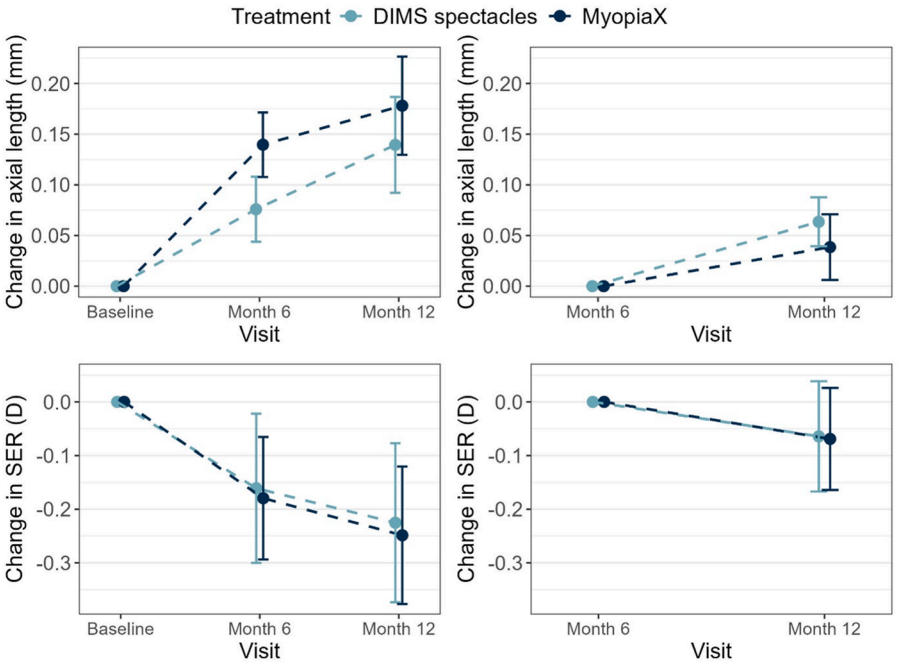

Figure 2. Change in axial length and SER clinical outcomes from baseline to month 6 (primary endpoint), baseline to month 12, and month 6 to month 12. Data points show the mean change, and error bars represent 2 standard errors. D = diopters; DIMS = defocus incorporated multiple segments; SER = spherical equivalent refraction.

MyopiaX group falls between the 6-month changes seen with orthokeratology (0.05−0.12 mm[26,27]) and 0.01% atropine (0.15 mm[28]). While there are fewer relevant studies reporting myopia progression over 6 months, the SER change in the MyopiaX group over the first half of the trial is smaller than reports for 0.01% atropine (−0.21 D to −0.31 D).[25,26] Control group data from these studies, predominantly involving White children aged 6−12 years with baseline myopia of ≥ −0.50 D, suggest that axial elongation in comparable cohorts ranges from 0.12 mm to 0.21 mm, accompanied by myopia progression of −0.37 to −0.58 D.[25,26]

For month 6 to month 12, participants in the MyopiaX group added DIMS spectacles, using both interventions for 6 months, while the active control group continued with DIMS only. During this period, participants in the MyopiaX group had myopia progression and AL growth of −0.07 D and 0.04 mm, respectively, while the DIMS group showed changes of −0.06 D and 0.06 mm, respectively, with no statistically significant differences between groups for either outcome. Limited data are available on combination approaches including DIMS in European children; however, the observational study by Nucci et al[25] reported 6-month myopia progression of −0.23 D and axial elongation of 0.05 mm (simple means calculated based on available online data) in healthy children and adolescents using DIMS with 0.01% atropine. A more recent study conducted in China provides initial evidence that light-based therapies

Table 2. Raw Mean (Standard Deviation) Changes in Myopia Clinical Effect Outcomes by Assigned Intervention Group and Study Period, as Well as between-Group Differences

Visit from	Visit to	MyopiaX	DIMS Spectacles	Adjusted Group Difference (95% Confidence Interval)	*P*
Axial length change (mm)					
Baseline	Month 6	0.14 (0.11)	0.08 (0.09)	0.06 (0.02, 0.10)	0.004
Baseline	Month 12	0.18 (0.17)	0.14 (0.14)	0.03 (−0.02, 0.09)	0.24
Month 6	Month 12	0.04 (0.11)	0.06 (0.07)	−0.03 (−0.07, 0.01)	0.20
Spherical equivalent change (D)					
Baseline	Month 6	−0.18 (0.39)	−0.16 (0.41)	−0.02 (−0.16, 0.13)	0.82
Baseline	Month 12	−0.25 (0.44)	−0.23 (0.43)	−0.01 (−0.18, 0.15)	0.86
Month 6	Month 12	−0.07 (0.33)	−0.06 (0.3)	0.00 (−0.12, 0.13)	>0.99

Adjusted group differences and *P* values are derived from linear mixed models using data from both eyes, random intercepts terms for participants, adjusting for the outcome value at the visit shown in the "Visit from" column, and randomization strata.
DIMS = defocus incorporated multiple segments.

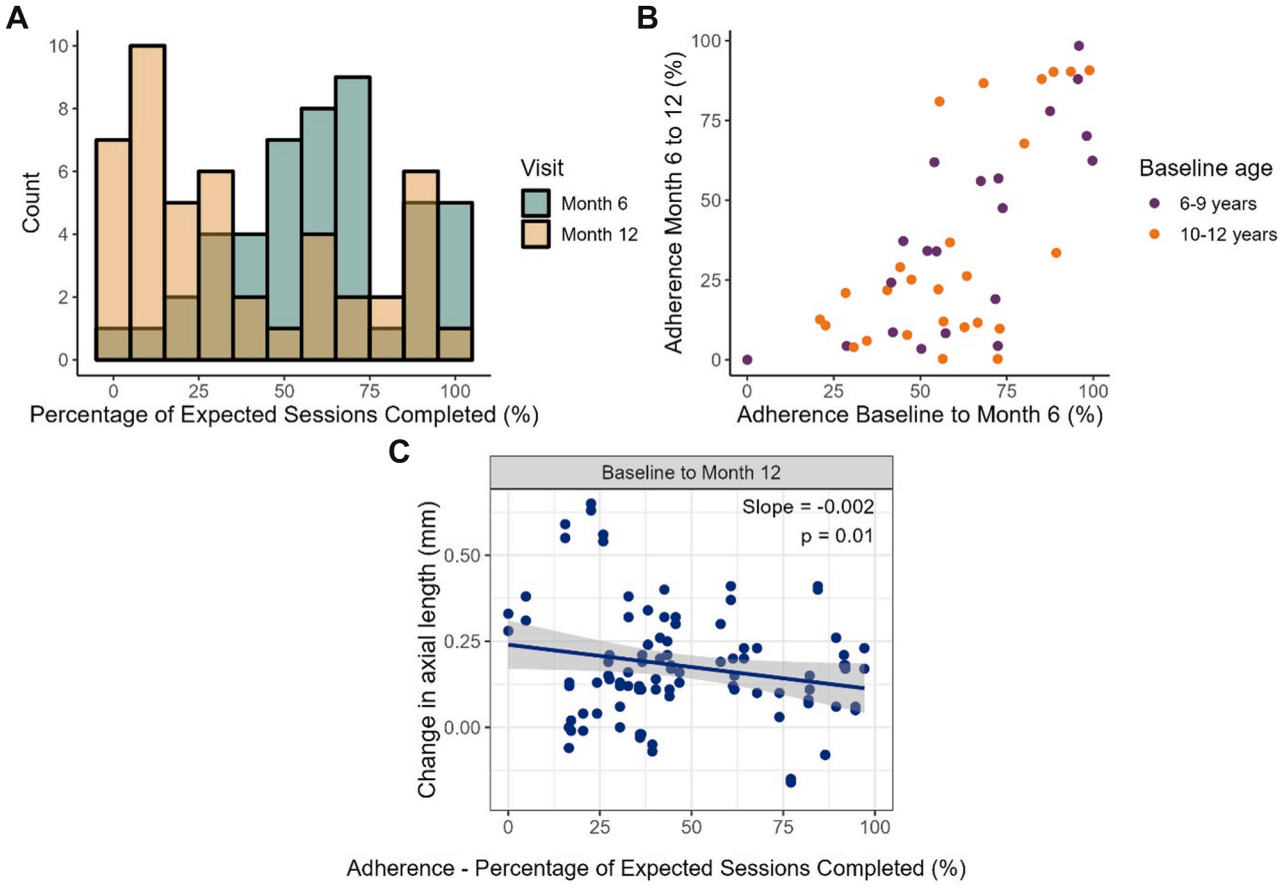

Figure 3. **A,** Distribution of adherence at month 6 (from baseline to month 6) and at month 12 (from month 6 to month 12), with the overlap indicated in darker color, and **(B)** scatterplot of adherence between these two periods. **C,** Relationship between axial length change and adherence over 12 months. The slope and *P* value are from a linear mixed model using data from both eyes, with random intercepts for participant, adjusted for baseline axial length, and age and refractive error randomization strata.

can work synergistically with optical interventions for myopia control. Combining repeated low-level red-light with DIMS resulted in axial shortening (−0.13 mm) and a hyperopic shift (+0.09 D) over 12 months compared with 0.16 mm axial growth and −0.22 D of myopia progression when children used DIMS alone.[29] The results of the study by Yang et al suggest that combining interventions targeting distinct mechanisms of action could offer additional protective effects. Further, longer-term studies are needed to better define the effects of MyopiaX when applied as an adjunct therapy for myopia control.

Over the full 12 months, myopia progression was −0.25 D in the MyopiaX group and −0.23 D in the DIMS group. The corresponding AL changes were 0.18 mm and 0.14 mm in the MyopiaX and DIMS groups, respectively. There were no significant between-group comparisons. European data in children aged 6−18 years (baseline myopia between −0.50 and −8.50 D) indicate that annual AL growth with DIMS ranges from 0.09 mm to 0.19 mm with myopia progression from −0.20 D to −0.39 D.[25,30−32] Control groups in recent studies, predominantly involving White populations aged 6−18 years with baseline myopia ranging from −0.50 D to −7.00 D, report myopia progression of −0.27 to −0.86 D without intervention, accompanied by axial elongation between 0.22 and 0.37 mm.[25,28,30,33−39]

The observed AL outcomes in the MyopiaX group were shown to have a significant relationship with adherence over 12 months, with less cumulative AL growth associated with higher adherence, suggesting some independent myopia control effect from MyopiaX use. MyopiaX's digital approach enables automatic adherence tracking, a feature not available with conventional treatments like low-dose atropine or optical methods. Unfortunately, adherence to MyopiaX was lower than expected and declined throughout the trial, which could be attributed, in part, to device deficiencies that commonly occur with novel software-based devices. In terms of trial retention, there were more dropouts in the MyopiaX group, mostly early on, suggesting an underestimation of the commitment or challenges integrating the intervention into daily routines. Usability feedback from families at the end of the trial showed that while MyopiaX and its hardware are easy to use, integrating it into routines was difficult for almost one-third of households, and boredom and session length were barriers to adherence. These findings emphasize the need for improved onboarding and enhanced gamification to help

Table 3. Adverse Events Classified as Related in the Safety Analysis Set

Adverse Event	MyopiaX (Original Protocol*) (N = 11)	MyopiaX (Amended Protocol) (N = 62)	DIMS (N = 34)	Sham (N = 11)	All Treated Participants (N = 118)
Any adverse event reported related to MyopiaX/comparator/procedure	4 (36.4) 7	12 (19.4) 16	2 (5.9) 3	2 (18.2) 2	20 (16.9) 28
Eye disorders	1 (9.1) 1	5 (8.1) 6	2 (5.9) 3	1 (9.1) 1	9 (7.6) 11
Asthenopia	0 (0.0) 0	1 (1.6) 1	1 (2.9) 1	1 (9.1) 1	3 (2.5) 3
Vision blurred	0 (0.0) 0	1 (1.6) 1	2 (5.9) 2	0 (0.0) 0	3 (2.5) 3
Eye pruritus	0 (0.0) 0	2 (3.2) 2	0 (0.0) 0	0 (0.0) 0	2 (1.7) 2
Eye irritation	0 (0.0) 0	1 (1.6) 1	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
Eye pain	1 (9.1) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
Visual acuity reduced	0 (0.0) 0	1 (1.6) 1	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
Nervous system disorders	2 (18.2) 4	7 (11.3) 9	0 (0.0) 0	0 (0.0) 0	9 (7.6) 13
Headache	2 (18.2) 3	5 (8.1) 5	0 (0.0) 0	0 (0.0) 0	7 (5.9) 8
Dizziness	1 (9.1) 1	2 (3.2) 4	0 (0.0) 0	0 (0.0) 0	3 (2.5) 5
Gastrointestinal disorders	0 (0.0) 0	1 (1.6) 1	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
Nausea	0 (0.0) 0	1 (1.6) 1	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
General disorders and administration site conditions	1 (9.1) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
Malaise	1 (9.1) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
Psychiatric disorders	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (9.1) 1	1 (0.8) 1
Enuresis	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (9.1) 1	1 (0.8) 1
Respiratory, thoracic, and mediastinal disorders	1 (9.1) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1
Epistaxis	1 (9.1) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.8) 1

Statistic: n (%) observed.
n = number of participants with event,
DIMS = defocus incorporated multiple segments.
Percentages are based on N.
*MyopiaX participants randomized under the original protocol used MyopiaX alone for 12 months. Participants are counted only once per System Organ Class and per Preferred Term (MedDRA 27.1). Adverse events with reported causality "causal relationship," "probable," or "possible" are counted as related.

participants integrate MyopiaX into daily life and remain engaged in order to support long-term adherence.

Safety

Safety and tolerability are critical outcomes in a proof-of-concept clinical trial. MyopiaX-1 provides the first clinical evidence supporting the safe use of MyopiaX over 12 months in children with myopia, both as a standalone intervention and when combined with DIMS spectacles. Most AEs related to MyopiaX were mild and transient, with eye pruritus, headache, and dizziness being the most common. These side effects are consistent with known discomforts associated with VR headset use.[40] There were no changes in the Pittsburgh Sleep Quality Index scores indicating that MyopiaX's blue light stimulus did not impact sleep quality. No ophthalmic safety events were observed, and quarterly reviews by the Data Safety Monitoring Board raised no concerns.

Limitations and Future Directions

As a proof-of-concept clinical trial, MyopiaX-1 has several limitations that should be considered when interpreting its findings. First, the study was not designed for formal statistical comparisons between groups and was not powered for a specific analysis. As such, the current findings should be viewed as exploratory, rather than definitive. Additionally, the pilot nature of this study means it had a relatively short duration (12 months), which limits conclusions about long-term efficacy. Given that myopia control interventions often show progressively increasing absolute effects over multiple years, future trials should aim for $\geq$2–3 years of follow-up to better capture the full potential of MyopiaX as a long-term intervention.

Moreover, given the availability of clinically validated myopia control therapies (such as DIMS and atropine eye drops), withholding treatment from children at risk of progressive myopia poses an ethical dilemma. As a result, this study used an active control design (DIMS lenses) instead of a placebo group. While this approach ensured that all participants received some level of intervention (2×10 minutes with MyopiaX and all-day wear of DIMS), it also makes it more challenging to isolate the specific effect of MyopiaX alone. Future studies should consider alternative control strategies, such as historical control groups or stratified treatment comparisons, to further refine efficacy assessments in ethically responsible ways. The MyopiaX device was designed specifically to deliver blue

light to the blind spot, based on previous research in animals and adults. A study on the effects of VR headset viewing on the choroid has revealed that 40 minutes of VR viewing of a wide-angle image increased choroidal thickness by approximately 10 microns.[41] This raises the possibility that stimulation of intrinsically photosensitive retinal ganglion cells across the retina may have a similar impact to blind spot stimulation, and also raises the possibility that VR viewing may influence the choroid by other mechanisms. This is an important topic for future research.

Finally, higher rates of withdrawal in the MyopiaX group and declining adherence over 12 months emerged as considerable challenges, limiting the generalizability of the findings and highlighting a need for further investigation of intervention feasibility, acceptance, and attrition effects. While adherence is a common challenge in interventions requiring repeated administration, such as those for myopia control,[42,43] device improvements that support participant engagement and integration into daily routines will be key for long-term adherence in domestic settings.

Conclusions

The MyopiaX-1 proof-of-concept trial supports MyopiaX's favorable safety profile and provides initial clinical data in European children. As the first clinical investigation of MyopiaX's selective blue light stimulation intervention, the study contributes to the emerging evidence on light-based therapies for myopia control and offers insights for future device development and clinical research. These findings warrant further investigation in longer, statistically powered clinical trials.

Footnotes and Disclosures

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The full list of group members in the MyopiaX-1 Study Group is available at *www.ophthalmologyscience.org*.

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Abbreviations and Acronyms:
AE = adverse event; **AL** = axial length; **D** = diopters; **DD** = device deficiency; **DIMS** = defocus incorporated multiple segments; **SER** = spherical equivalent refraction; **VR** = virtual reality.

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