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Control of myopia using diffusion optics spectacle lenses: 12-month results of a randomised controlled, efficacy and safety study (CYPRESS)

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ABSTRACT

Background Mutations in the L/M cone opsin gene array cause abnormally high perceived retinal contrast and the development of myopia. Environmental factors may also lead to high visual contrast and cause myopia. Diffusion optics technology (DOT) lenses are designed to reduce contrast signalling in the retina and slow myopia progression.

Methods The Control of Myopia Using Peripheral Diffusion Lenses Efficacy and Safety Study (CYPRESS, NCT03623074) is a 36-month, multicentre, randomised, controlled, double-masked trial evaluating two investigational spectacle lenses versus control lenses in myopic children aged 6–10, with a planned interim analysis at 12 months. The primary endpoints are change from baseline in axial length (AL) and spherical equivalent refraction (SER).

Results 256 children (58% female; mean age at screening, 8.1 years) were dispensed spectacles. Across all groups, baseline averages were AL 24.02 mm ($SD\pm 0.77$ mm), SER -2.01 D ($SD\pm 0.9$ D) using manifest refraction, and SER -1.94 D ($SD\pm 1.0$ D) using cycloplegic autorefractometry. At 12 months, mean difference in SER progression for test 1 versus control was -0.40 D ($p<0.0001$), representing a 74% reduction and -0.32 D for Test 2 ($p<0.0001$), representing a 59% reduction. The difference in AL progression for test 1 versus control was 0.15 mm ($p<0.0001$) and test 2 versus control was 0.10 mm ($p=0.0018$).

Conclusion 12-month results from this ongoing trial demonstrate the safety and effectiveness of DOT spectacles for reducing myopic progression.

INTRODUCTION

Myopia is a significant public health issue that affects an estimated 2.6 billion people worldwide: 34% of the global population. The prevalence is expected to increase to 50% by 2050, including 938 million individuals projected to have high myopia (worse than -5 D). These projections are of particular concern given the association between high myopia and an increased risk of visual impairment, including blindness.^{1,2} In children, myopia is associated with an increased risk of future ocular diseases, including cataract, glaucoma, retinal detachment and other chorioretinal abnormalities.³ Age of onset is an important predictor of progression to high myopia in later childhood and adulthood.^{4–7}

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myopia, a significant public health issue affecting billions of people worldwide, is known to increase the risk of visual impairment and blindness. Recent research in patients with an inherited form of high myopia has identified defects in cone photoreceptors associated with dramatic reductions in functional opsin in affected cones, which suggests that abnormal contrast signalling between neighbouring cones may stimulate axial elongation.

WHAT THIS STUDY ADDS

⇒ This study tests the hypothesis that environmental factors which produce abnormal contrast between adjacent cones are a signal for axial elongation and development of myopia. The study demonstrates that novel diffusion optics technology (DOT) spectacle lenses—designed to modulate retinal contrast by creating lower signal differences between adjacent cones—are effective in slowing myopia progression in children.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ These findings support the hypothesis that high retinal contrast signals the eye to grow, and that reducing contrast can slow axial growth and prevent myopia progression. DOT spectacle lenses represent a novel, non-invasive technology to help children with myopia.

Much of the research on myopia to date has focused on environmental factors such as increased screen time and decreased time spent outside.^{8–11} Although several interventions have shown efficacy in slowing the progression of myopia in children—including atropine,¹² dual-focus contact lenses¹³ and orthokeratology¹⁴—they can be difficult to implement in very young children and may have adverse effects.^{15–17}

Numerous lines of evidence support a genetic contribution to myopia, including clustering of myopia cases within families and a higher correlation of myopia onset in monozygotic twins than in dizygotic twins.¹⁶ Rare variants that can lead to the development of high myopia have been identified



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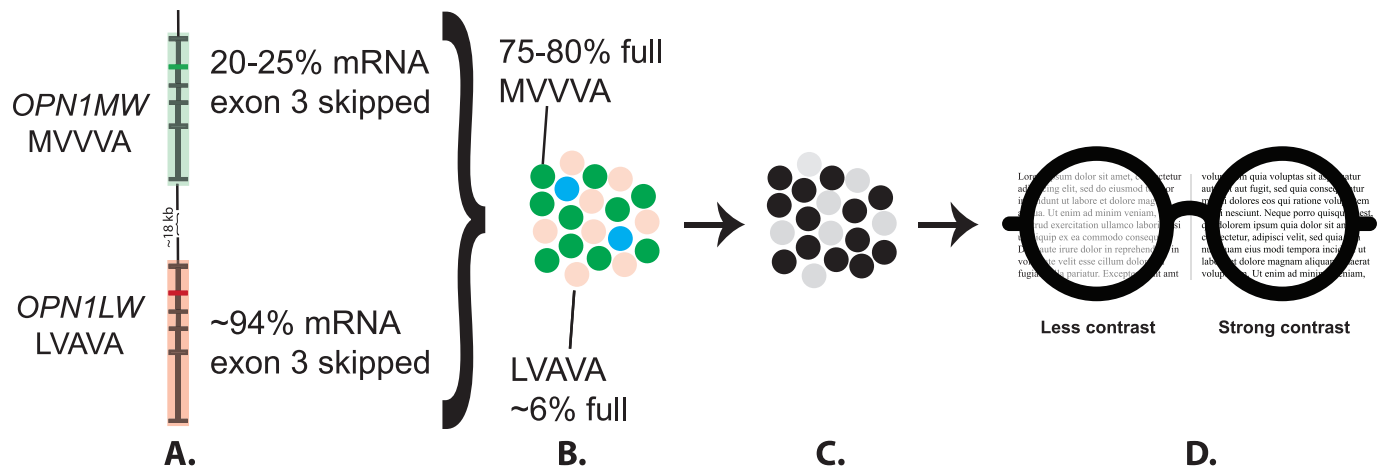


Figure 1 Contrast hypothesis of myopia and development of DOT lens. X-chromosome opsin gene array for a male with high myopia due to the LVAVA haplotype is shown. (A) *OPN1LW* gene (pink) with LVAVA exon 3 haplotype and *OPN1MW* gene (green) with MVVVA exon 3 haplotype. The LVAVA haplotype causes exon three to be skipped in pre-mRNA splicing so only about 6% of the mRNA is full length. (B) L (pink) and M (green) cones have dramatically different photopigment OD because of mis-splicing. S cones are blue. (C) Retina signals high contrast even under uniform white light because of OD differences. Activity of L cones (grey) is low, activity of M and S cones (black) is high. We hypothesised that the constitutive contrast signalling due to photopigment OD differences stimulates axial elongation of the eye and causes myopia. (D) The hypothesis led to the development of a novel spectacle lens (DOT lens) that reduces contrast (left lens) compared with a standard of care lens (right). DOT, diffusion optics technology; OD, optical density.

in numerous genes¹⁸; and genome-wide association studies have identified single-nucleotide polymorphisms at multiple loci associated with refractive error and myopia.^{19 20}

The first myopia locus identified, *MYP1*, was recognised in families with a form of high myopia called Bornholm Eye Disease.^{21–23} *MYP1* is located on the X-chromosome at Xq28, where the long-wavelength (L) and middle-wavelength (M) cone opsin genes (*OPN1LW* and *OPN1MW*, respectively) reside.^{24 25} L and M cones are mediators of high acuity vision and play a key role in emmetropisation, the visually guided process that matches the axial length (AL) of the eye to the power of the optical components.²⁶

Rare *OPN1LW* and *OPN1MW* haplotypes (notably LVAVA) have been directly linked to the cellular defect in cone photoreceptors that causes high myopia.^{26–29} LVAVA causes incorrect splicing of exon 3, which in turn leads to a dramatic reduction in functional opsin in affected cones (figure 1A–C).^{26 27 29 30} High myopia is the characteristic of males expressing the LVAVA haplotype in one cone submosaic and expressing another opsin gene haplotype with unimpaired splicing that produces photopigment-filled cones in a second submosaic. This observation suggests that abnormal contrast signalling between neighbouring full and empty cones may stimulate axial elongation.^{26 31} This, in turn, led us to speculate that environmental factors that produce abnormal contrast between adjacent cones is a signal for axial elongation.³¹

This idea is directly at odds with the orthodox view derived from animal studies that reduced contrast is the signal for myopia development.³² However, our current understanding of the optical signals used in refractive development in humans is incomplete. While the literature is somewhat mixed on the association of near vision activities on myopia progression,^{33 34} the accommodated eye has less vergence-related blur during indoor activities and thus may generate higher contrast signalling.³⁵

To test the contrast hypothesis, SightGlass Vision developed diffusion optics technology (DOT) lenses; novel spectacle lenses that modulate retinal contrast (figure 1D, online supplemental figure 1).^{36 37} SightGlass Vision DOT lenses contain light

scattering centres that disperse light as it passes through the lens, creating lower signal differences between adjacent cones while maintaining excellent visual acuity and functional peripheral vision. Unlike other spectacle lenses for myopia management, DOT lenses allow the wearer to function when looking through the treatment zone: the light scattering features are integrated across the entire lens except for a small clear aperture aligned with the pupillary axis.

The Control of Myopia Using Peripheral Diffusion Lenses Efficacy and Safety Study (CYPRESS) is a 36-month, randomised controlled trial evaluating the efficacy and safety of SightGlass Vision DOT spectacle lenses for slowing the progression of juvenile myopia. This report summarises results from a planned 12-month interim analysis.

MATERIALS AND METHODS

Study design

CYPRESS is a 36-month, randomised, controlled, multi-centre, subject-masked and observer-masked clinical trial being conducted at 14 sites in North America.

The first screening visit was completed in July 2018 and the last subject was enrolled in March 2019. Preplanned analyses are scheduled at 12, 24 and 36 months. The final 12-month visit used for this analysis was completed in March 2020. The full study is expected to be completed in May 2022.

Subjects were randomised to one of three study spectacle lenses in a 1:1:1 ratio (online supplemental table 1). Because age and degree of myopia are known to impact myopia progression rates, a stratified randomisation scheme was devised so that the study arms were balanced for these variables (online supplemental table 2). The random allocation sequence was generated using Microsoft Excel. Randomisation was concealed and interventions were assigned by Electronic Data Capture.

All spectacles consisted of standard, commercially available frames with impact-resistant, off-the-shelf single vision lenses made from PPG Trivex[®] monomer (PPG Industries Ohio) and matched to the subjects' prescriptions. For the test lenses, DOT

technology, consisting of microscopic diffusers, was applied to the surface of the lens. Wide-angle scatter, rather than narrow-angle scatter, was used to achieve even contrast reduction over a large range of spatial frequencies while minimising any potential effect on visual acuity.

Each microscopic diffuser is translucent and irregularly shaped, having a diameter of approximately 0.14 mm and a height of approximately 0.2 mm, with an irregular radial curvature that is steeper on the sides and flattened across the top. Whereas the base lens has a refractive index of 1.53, diffusers are translucent, having a nominal refractive index of approximately 1.50. They are designed to scatter light, with the intent of reducing contrast and therefore reducing the relative activity difference between L and M cones.

For test 1 (called DOT 0.2 commercially), diffusers were applied with 0.365 mm spacing. Test 2 had a higher density (ie, closer spacing) of diffusers of 0.240 mm. For both designs, microscopic diffusers were integrated across the entire lens, except for an approximately 5 mm aperture centred on the optical centre of the lens; lenses were edged and mounted into spectacle frames to align to the wearer's pupils.

Subjects randomised to the Control arm were fitted with standard single vision spectacles. To make the spectacles appear different from standard spectacles and facilitate subject masking, a light, green tint that reduces light transmission by ~5% was applied to Control lenses. Spectral transmission analysis for control lenses showed equivalent curves to test lenses (online supplemental figure 2) and in a preliminary study, a green tint had no impact on myopia progression. All lenses are replaced every 6 months even if a prescription update is not required.

Subjects in this analysis were evaluated at baseline, month 1, month 6 and month 12. Spherical equivalent refractive error (SER) was measured by cycloplegic autorefractometry using open-field auto refractometers (WR-5100K - Grand Seiko, Hiroshima, Japan) or equivalent at baseline and month 12. To achieve cycloplegia, one drop of 0.5% proparacaine or tetracaine was instilled in both eyes followed by two drops of 1.0% tropicamide, given 5 min apart, in both eyes. Cycloplegic autorefractor measurements were taken 25 min after the final drop of tropicamide was instilled. AL was measured at baseline, month 1, month 6 and month 12 using the Lenstar 900 (Haag-Streit Diagnostics, Koeniz, Switzerland). Likert-style subject questionnaires were administered at each visit to monitor the visual and social impact of study spectacles, including visual artefacts such as glare, halos and hazy vision. Parent questionnaires were administered to monitor compliance and the visual impact of study spectacles. Adverse events were assessed at each study visit.

Study population

Children ages 6–10 years (inclusive) with SER between -0.75 and -4.50 D were eligible to participate. Subjects were required to have a best corrected visual acuity of $+0.10$ logarithm of the minimum angle of resolution (logMAR,) or better in each eye, with no more than 1.50 D anisometropia (ie, between-eye difference) in spherical equivalent power. Subjects agreed to participate in the trial for 3 years without contact lens use and to wear the assigned spectacles constantly (≥ 10 hours per day) except for when sleeping, swimming or engaging in activities such as contact sports in which spectacle wear would be dangerous.

Subjects reporting current or prior use of contact lenses (> 1 month), bifocals, progressive lenses or myopia control treatment (including atropine) were excluded. Other key exclusion criteria included amblyopia or astigmatism greater than 1.25 D

in either eye, ocular or systemic conditions that could influence refractive development or status, and strabismus by cover test at far (4 m) or near (40 cm) when wearing distance correction.

Twelve-month efficacy and safety endpoints

The primary efficacy endpoints for this preplanned interim analysis were changes from baseline at 12 months in AL and cycloplegic SER. The secondary endpoint was the proportion of subjects with less than 1.00 D myopic progression at 12 months based on SER change from baseline.

Twelve-month safety endpoints included best-corrected visual acuity (high-contrast and low-contrast logMAR, near and distance), device deficiencies and adverse events. Device deficiencies were defined as any inadequacy of the study spectacles (lenses or frames) with respect to their quality, durability, reliability, safety or performance.

Statistical analysis

The sample size was calculated to ensure adequate power at an overall alpha level of 0.05 for comparisons of AL and SER change from baseline to 36 months. Assuming a drop-out rate of ~20%, a target of 85 subjects per arm (ie, 68 evaluable subjects per arm) was calculated to have $> 90\%$ power to detect a difference between two groups based on a two-sided t-test at an alpha level of 0.048 when the treatment effect is 35%. Of note, the assumed treatment effect of 35% may be higher than the minimum clinically important difference for this population.

The main analysis of change from baseline in AL and SER is based on the modified intention-to-treat (mITT) population. For each subject, single AL and SER values were generated for each visit by taking the average over the two eyes' AL and SER values. An analysis of covariance model was used to analyse measurements of AL and SER including the following terms: treatment, age group, gender and the baseline value of the endpoint as a covariate. The multiple imputation approach using the regression method was employed to impute missing data. All analyses were conducted using SAS V.9.4. Physiological AL growth was estimated by applying AL growth rates for persistent emmetropes from Jones et al 2005,³⁸ weighted by age at enrolment for each study arm.

RESULTS

Subjects

A total of 265 subjects were enrolled, 258 of whom were dispensed study product and comprise the ITT population. Two subjects were dispensed control spectacles but were subsequently found to be ineligible (both were hyperopic via cycloplegic autorefractometry); all efficacy analyses are therefore based on the mITT population of 256 subjects: test 1, $n=88$; test 2, $n=75$; control, $n=93$.

The demographic and clinical characteristics for mITT population are summarised in table 1. The three groups were well balanced for all characteristics; overall mean integer age at baseline was 8.1 years, more than half (58.2%) of subjects were female, and approximately three-quarters (74.2%) were white. Most subjects (87.5%) had at least one parent with myopia.

In addition to the control subjects who were found to be ineligible, 22 subjects who were dispensed spectacles discontinued from the study during the first 12 months, 5 in test 1 and 17 in test 2 (online supplemental figure 3). The most common reason for discontinuation across all groups was voluntary withdrawal: one in test 1 and 7 in test 2. None of the test 1 subjects discontinued for reasons related to the appearance of study spectacles,

Table 1 Demographic and clinical characteristics (mITT population)

Variable	Test 1 (n=88)	Test 2 (n=75)	Control (n=93)
Integer age*			
Mean, years (SD)	8.0 (1.2)	8.2 (1.2)	8.2 (1.2)
Age group, n (%)			
6 years	10 (11.4)	8 (10.7)	9 (9.7)
7 years	20 (22.7)	13 (17.3)	18 (19.4)
8 years	23 (26.1)	17 (22.7)	24 (25.8)
9 years	27 (30.7)	28 (37.3)	32 (34.4)
10 years	8 (9.1)	9 (12.0)	10 (10.8)
Sex, (n (%))			
Male	39 (44.3)	29 (38.7)	39 (41.9)
Female	49 (55.7)	46 (61.3)	54 (58.1)
Ethnicity, (n (%))			
Hispanic or Latino	18 (20.5)	10 (13.3)	17 (18.3)
Not Hispanic or Latino	70 (79.5)	65 (86.7)	76 (81.7)
Race†			
White	64 (72.7)	55 (73.3)	71 (76.3)
Black or African American	19 (21.6)	13 (17.3)	17 (18.3)
American Indian or Alaska Native	2 (2.3)	1 (1.3)	2 (2.2)
Asian Indian	1 (1.1)	5 (6.7)	2 (2.2)
Chinese	2 (2.3)	2 (2.7)	3 (3.2)
Filipino	0 (0)	1 (1.3)	0 (0)
Japanese	0 (0)	1 (1.3)	1 (1.1)
Other Asian	2 (2.3)	2 (2.7)	3 (3.2)
Native Hawaiian or Other Pacific Islander	1 (1.1)	0 (0)	0 (0)
Myopic parents‡, n (%)			
Two	29 (33.0)	36 (48.0)	34 (36.6)
At least one	7 (8.0)	8 (10.7)	10 (10.8)
One	36 (40.9)	22 (29.3)	42 (45.2)
Zero	9 (10.2)	8 (10.7)	7 (7.5)
Unknown	7 (8.0)	1 (1.3)	0 (0)
Axial Length, mm (mean (SD), range)	24.09 (0.82) 22.03 to 26.25	23.94 (0.70) 22.33 to 25.42	24.03 (0.78) 22.13 to 25.72
Cycloplegic SER, D (mean (SD), range)§	-2.00 (0.93) -4.52 to -0.19	-1.85 (0.91) -4.60 to -0.50	-1.95 (1.02) -4.94 to -0.38

*Integer age is the subject's age rounded down to the nearest whole year.
 †Proportion may not sum to 100% as subjects selecting more than one race will be counted multiple times.
 ‡Subjects/parents were given the options: unknown, zero, one, at least one or two.
 §Subjects were screened based on manifest refraction and were required have at least -0.75 D SER, however, in a small number of cases the cycloplegic SER revealed less myopia.
 mITT, modified intent to treat; SER, spherical equivalent refractive error.

whereas 5 of the 17 test 2 subjects who discontinued reported issues with the appearance of the spectacles. Three subjects discontinued for reasons related to vision, one in test 1 and 2 in test 2. (online supplemental table 3)

Efficacy

Parent questionnaire data indicated high compliance among study participants, with subjects wearing the study spectacles for ≥10 hours per day. Mean wearing times during weekdays and weekends were ≥12 hours per day for all groups at each time point. (online supplemental table 4)

At baseline the mean±SD measurements of AL for the mITT subjects were 24.1±0.8 mm, 23.9±0.7 mm and 24.0±0.8 mm for the test 1, test 2 and control groups, respectively. At 12 months, the least-squared mean change in AL was 0.15 mm for Test 1 and 0.20 mm for test 2 vs 0.30 mm for the control group; (online supplemental table 5) the difference between means represented a 50% reduction for test 1 (0.15 mm; 95% CI=0.10 to

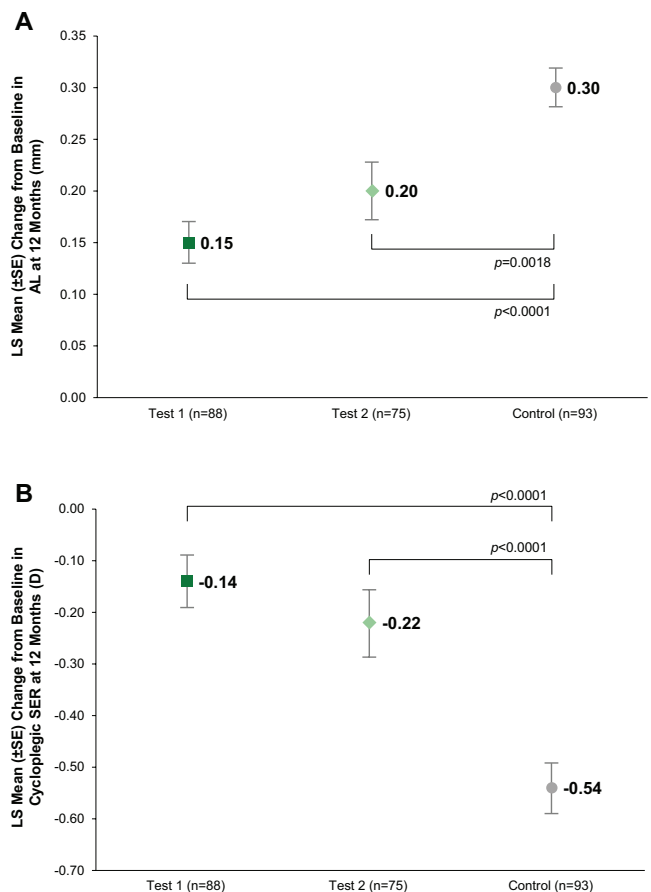


Figure 2 Least squares mean changes (±SE) from baseline for AL (A) and SER (B), mITT population. LS, SR and p values are derived from an ANCOVA model adjusting for age, gender, and baseline AL or SER value. Missing data were handled by the multiple imputation with regression method. The least squares mean changes (±SE) from baseline from the same model with data as observed (ie, no imputation) in AL or SER and was 0.15 (±0.020) mm or -0.14 (±0.052) D for test 1 and 0.19 (±0.023) mm or -0.24 (±0.061) D for test 2 vs 0.30 (±0.018) mm or -0.54 (±0.049) D for the control group. AL, axial length; ANCOVA, analysis of covariance; D, dioptre; LS, least squares; mITT, modified intention-to-treat; SER, spherical equivalent refraction.

0.20 mm; p<0.0001) and 33% reduction for test 2 (0.10 mm; 95% CI 0.04 to 0.17 mm; p=0.0018) (figure 2A). Observed data (mean±SD) were 0.15±0.15 mm for test 1 and 0.18±0.21 mm for test 2 vs 0.30±0.17 mm for control.

Baseline cycloplegic SERs (mean±SD) were -2.00±0.93 D, -1.85±0.91 D and -1.95±1.02 D for the test 1, test 2 and control groups, respectively (online supplemental table 5). At 12 months, the least-squared mean change in SER was -0.14 D for test 1 and -0.22 D for test 2 vs -0.54 D for control; the difference between means was 74% reduction for test 1 (-0.40 D; 95% CI: -0.53 to -0.27 D; p<0.0001) and 59% reduction for test 2 (-0.32 D; 95% CI -0.47 to -0.17 D; p<0.0001) (figure 2B). Observed data (mean±SD) were -0.15±0.39 D and -0.23±0.49 D for the test 1 and test 2 groups, respectively, vs -0.53±0.46 D for the control group. Individual subject data plots for both cycloplegic SER and AL are provided in online supplemental figure 4.

In the younger age group (6–7 years), observed changes in SER (mean±SD) were -0.19±0.47 D and -0.33±0.63 D for the test 1 and test 2 groups, respectively, vs -0.75±0.51 D for

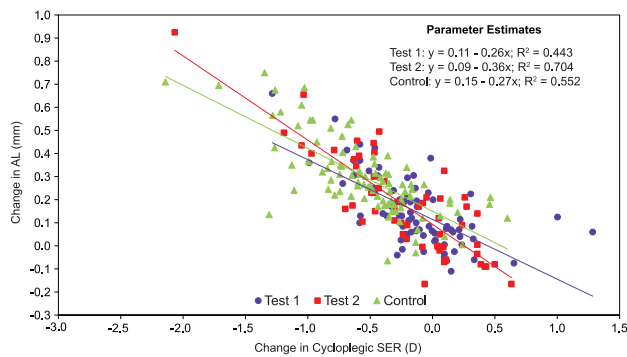


Figure 3 Scatterplot of change from baseline in SER at 12 months versus change from baseline in AL for each treatment group. AL, axial length; D, dioptre; SER, spherical equivalent refraction.

the control group. Corresponding values in the older group (8–10 years) were -0.12 ± 0.34 D and -0.19 ± 0.43 D for the test 1 and test 2 groups vs -0.44 ± 0.41 D for the control group. This was similar for AL where a larger change from baseline was demonstrated in the younger subjects ($p < 0.0001$), but the relative treatment effect was similar ($p = 0.17$).

Correlations between changes in AL and changes in SER were tested using Pearson's correlation coefficients for the test 1, test 2 and control groups and were -0.67 to -0.84 , and -0.74 , respectively. The negative correlation indicates that increases in myopic refractive error are correlated with increasing AL, which is expected in a myopic population (figure 3).

At 12 months, 99% of test 1 subjects, 93% of test 2 subjects and 86% of control subjects had < 1.00 D of cycloplegic SER myopia progression. The difference was significant for test 1 vs control ($p = 0.0013$), but not for test 2 ($p = 0.33$). Significant between-group differences were detected among subjects who were refractively stable at 12 months (< 0.25 D change from baseline): 65%, 55% and 23% of test 1, test 2 and control subjects, respectively ($p < 0.0001$ for both test groups vs control).

Safety

During the initial 12 months of the 36-month trial, there were 16 reported ocular adverse events (AEs) in 11 subjects, none of which was serious (table 2). Although one ocular AE due to ocular trauma was classified as significant; none was classified as device related. Forty-four AEs were classified as non-ocular AEs, four of which were classified as device related. These included three cases of headache in one control subject and one case of skin irritation from the spectacle frame nose pad in a test 1 lens user. A total of 55 device deficiencies were reported, 17 of which were related to the lenses (table 2).

DISCUSSION

This 12-month interim analysis of data from the CYPRESS study demonstrated that both test spectacle lenses significantly slowed the progression of myopia versus standard spectacle lenses. The test lenses reduced the progression of refractive error versus control by an average of -0.40 D and -0.32 D for the test 1 and test 2 lenses, respectively, corresponding to a 74% reduction in myopic progression vs control for the test 1 lens and 59% for the test 2 lens. Both lenses demonstrated significant superiority over the control lenses for change from baseline in AL. No serious AEs were reported.

Although there was a strong correlation between change in AL and SER (figure 2), the apparent reduction in percentage

Table 2 Adverse events/device deficiencies (mITT population)

	Test 1 (n=88)	Test 2 (n=75)	Control (n=93)
Ocular AEs, n (%)			
Blepharitis	6 (6.8)	0 (0)	2 (2.1)
Conjunctivitis	0 (0)	2 (2.7)	0 (0)
Headache	0 (0)	0 (0)	3 (3.2)
Hordeolum	1 (1.1)	0 (0)	1 (1.1)
Lattice	1 (1.1)	0 (0)	0 (0)
Operculated retinal hole	0 (0)	1 (1.3)	0 (0)
Reduction in VA	0 (0)	0 (0)	1 (1.1)
Skin irritation	1 (1.1)	0 (0)	0 (0)
Trauma to eye	0 (0)	1 (1.3)	0 (0)
Non-ocular, non-device-related AEs, n (%)	13 (14.8)	13 (17.3)	14 (15.1)
Device deficiencies, n (%)			
Total	12 (13.6)	31 (41.3)	12 (12.9)
Issue with lens	4 (4.5)	11 (14.7)	1 (1.1)
Misaligned optical centre	2 (2.3)	6 (8.0)	0 (0)
Scratched lenses	2 (2.3)	2 (2.7)	0 (0)
Issue with lens edge	0 (0)	2 (2.7)	0 (0)
Wrong prescription	0 (0)	0 (0)	1 (1.1)
Issue with frame	8 (9.1)	19 (25.3)	11 (11.8)
Broken frame and scratched lens	0 (0)	1 (1.3)	0 (0)

AE, adverse event; mITT, modified intention-to-treat; VA, visual acuity.

progression was higher for SER than for AL (50% for test 1 and 33% for test 2). AL is known to increase in younger children, even among emmetropes who remain emmetropic, as part of normal refractive development, and this normal growth is highest in children under age 10.^{38 39} Given the young age of the treated population (age 6–10 years at enrolment), we sought to model how much AL increase might be due to such 'physiological' growth versus 'pathological' myopia progression. Based on AL growth curves for children with persistent emmetropia,³⁸ we estimated the expected physiological growth of an emmetropic age-matched cohort to be 0.15 mm, 0.14 mm, and 0.15 mm for the test 1, test 2 and control arms, respectively. Subtracting this modelled 'physiological' growth, we calculated the percent reduction of pathological AL growth to be 99% for test 1 and 63% for test 2.⁴⁰ Although we acknowledge that mechanisms of AL growth in progressing myopes may differ from those involved with normal AL growth in persistent emmetropes, we speculate that some of the AL growth we observed in younger progressive myopes may be 'normal' physiological growth. This analysis might also provide insight into why, in this younger population vs previous myopia trials, the per cent reduction in progression was higher for SER (74% and 59%, respectively) than for AL (50% and 33%).

Myopia typically develops in the school age years,² which presents unique challenges for implementing measures to delay myopia onset or progression. Parents are often hesitant to put their young children into contact lenses or use atropine on a chronic basis, and optometrists rarely prescribe contact lenses as the primary form of vision correction in children < 9 years of age.⁴¹ Management of myopia progression using spectacles is, therefore, an attractive option. Previous studies with myopia control spectacle lenses, however, have shown limited success. In a well-designed multicentre trial, progressive-addition lenses reduced progression versus single-vision lenses but had a limited effect of 0.28 D over 3 years.⁴² Peripheral defocus lenses seemed encouraging in an initial, single-centre study in a Chinese population,⁴³ but a subsequent multicentre study failed to show any

effect.⁴⁴ Executive bifocals with or without prism,^{45–46} and more recent designs featuring plus-power spherical^{47–48} or aspherical⁴⁹ lenslets have shown encouraging results in initial, single-centre studies in Asian-only populations; however, these designs have not been tested in a rigorous, multicentre setting, or in racially diverse or Western populations. In addition, these studies on bifocals and lenslet-based designs have enrolled only subjects above age 8,^{45–49} and in at least one study, showed limited effect in children under age 10.⁴⁸

By contrast, in the present multicentre CYPRESS study, DOT spectacle lenses reduced myopia progression (SER) by 74% and 59% on average in a diverse North American population. In 6–7-year-old subjects, test 1 spectacle lenses reduced myopia progression by 0.56 D vs control, on average, during the first 12 months. This level of control has never been demonstrated using spectacle lenses with patients of this age group.

The current report encompasses only the first year of the 3-year CYPRESS study, and results will need to be confirmed with more long-term data. Also, as enrolment was limited to children ≤ 10 years old at screening, the generalisability of these findings to older children with myopia remains to be investigated. In addition, the higher response rate observed with the less densely spaced test 1 spectacles merits further investigation. Although the lack of a dose–response effect may be due to a difference in actual spectacle usage for near vision activities (see online supplemental table 4), the reason is currently unknown and will require additional data to determine. The young age of the subjects also makes it difficult to interpret the percentage reduction in AL, due to the potentially confounding factor of normal physiological growth. Finally, subject masking was challenging due to the unique appearance of the test lenses.

Despite these limitations, the results of this interim analysis of data from the 36-month CYPRESS trial offer further support for the hypothesis that high retinal contrast signals the eye to grow, and that reducing contrast can slow axial growth and prevent myopia progression.

CONCLUSION

This is the first multicentre randomised controlled study of a spectacle lens to show clinically and statistically significant effects on myopia progression. Data from the first year of the CYPRESS trial indicated that DOT spectacle lenses successfully slowed both myopia and AL progression. Compliance was high, and the low rate of adverse events indicate that DOT spectacle lenses are safe for use in children 6 years and older. As such, DOT spectacles lenses represent a non-invasive and commercially promising technology to help children with myopia.

Correction notice This article has been corrected since it was first published. In the last paragraph of the section Efficacy, <0.5 has been changed to <0.25 D change from baseline.

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Competing interests JR is former Chief Medical Officer at SightGlass Vision, and in this role has received meeting and/or travel support, participated in data safety monitoring/advisory boards, and owns stock in the company. CC reports consulting fees from SightGlass Vision and has a pending patent application (17/259,779). GY reports grants from Johnson & Johnson Vision, CooperVision, and Essilor. JN and MN report royalties/licenses, consulting fees and meeting and/or travel support from SightGlass Vision. JN and MN are cofounders and have stock ownership in SightGlass Vision, and are listed as Inventors on patents issued for DOT lens, owned by the University of Washington. TC reports consulting fees, meeting and/or travel support, patents and stock ownership in his role as employee, officer and board member for SightGlass Vision.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study was designed in conformance with the ethical principles in the Declaration of Helsinki; ICH guidelines for Good Clinical Practice; ISO 14155:2011; United States 21 CFR Parts 50, 56, and 812; and all applicable local regulations. The study protocol and informed consent documents were reviewed and approved by the Sterling Institutional Review Board (US) and the Office of Research Ethics of the University of Waterloo (Canada). IRB approval number from Sterling IRB is 6383. Participants gave informed consent to participate in the study before taking part.

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