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Control of myopia using diffusion optics spectacle lenses: 4-year results of a multicentre randomised controlled, efficacy and safety study (CYPRESS)

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ABSTRACT

Aims To evaluate the myopia control efficacy of Diffusion Optics Technology (DOT) spectacle lenses in children over a 4-year treatment period.

Methods CYPRESS Part 1 (NCT03623074) was a 3-year multicentre, randomised, controlled, double-masked trial comparing two investigational spectacle lens DOT designs (Test 1, Test 2) and standard single vision Control lenses in 256 North American children aged 6–10 years. Children completing Part 1 (n=200) were invited to enrol in CYPRESS Part 2 (NCT04947735) for an additional 1-year period. In Part 2, Test 1 (n=35) and Control groups (n=42) continued with their original lens assignment and the Test 2 group (n=21) were crossed over to Test 1 (DOT 0.2) lenses. The co-primary endpoints were change from baseline in axial length (AL) and cycloplegic spherical equivalent refraction (cSER).

Results Test 1 spectacle lenses demonstrated superiority to the Control in both co-primary endpoints: with a difference between means (Test 1−Control) of −0.13 mm for AL (p=0.018) and 0.33 D for cSER (p=0.008) in Part 1 and −0.05 mm for AL (p=0.038) and 0.13 D for cSER (p=0.043) in Part 2. Comparing treatment effects in Part 1 and 2 suggests that COVID-19 public health restrictions negatively impacted treatment efficacy in study years 2 and 3.

Conclusion DOT 0.2 spectacle lenses are safe and effective at reducing myopia progression, with additional benefit evident in year 4 of wear. These results support the hypothesis that a mild reduction in retinal contrast can slow myopia progression in young children. The unprecedented disruption in participant schooling and lifestyle during the COVID-19 pandemic may have depressed treatment efficacy in Part 1.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myopia is a global public health issue and is known to increase the risk of permanent vision loss. Optical myopia control interventions are designed to manipulate key visual signals to slow myopia progression in children. Mild reductions in retinal contrast via novel spectacle lenses (Diffusion Optics Technology; DOT) have shown promise in slowing eye growth and myopic progression after 12 months of wear.

WHAT THIS STUDY ADDS

⇒ This study expands the evidence base on the long-term safety and efficacy of DOT spectacle lenses, demonstrating a significant slowing of eye growth and myopic progression over 4 years of DOT 0.2 spectacle lens wear. The study is the first multicentre spectacle lens clinical trial to demonstrate myopia control efficacy in an ethnically diverse population from age 6.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support the hypothesis that slightly lowering retinal contrast can slow the progression of myopia. DOT 0.2 spectacle lenses are a safe and efficacious myopia management treatment for children from age 6 and are a suitable early treatment option for myopic children.

INTRODUCTION

Myopia is a global public health issue with increasing prevalence[1] and earlier age of onset[2] in recent decades. Age of onset is an important predictor of high myopia (≥6 D myopia)[3] in later life.[4 5] High myopia is associated with an increased risk of sight-threatening ocular pathology.[6 7] Slowing myopia progression is likely to improve long-term ocular health and visual outcomes.[8]

Myopia control optical interventions have been designed to manipulate key visual signals that regulate eye growth and refractive state: defocus and contrast.[9 10] Abnormally high retinal contrast signalling has been reported to be associated with progressive myopia.[11] Mild reductions in retinal contrast via novel spectacle lenses (Diffusion Optics Technology; DOT, SightGlass Vision, Texas, USA) have shown promise in slowing eye growth and myopia progression in a 12-month

interim analysis of a randomised, controlled, multicentre clinical trial (CYPRESS).[12]

The subsequent 2 years of the CYPRESS clinical trial coincided with the COVID-19 pandemic, which resulted in an abrupt change to children's school routine, lifestyle and activities. Consequently, the original 3-year study (CYPRESS Part 1) was extended by 12 months (CYPRESS Part 2) to collect further data, outside of the period of public health restrictions in North America. Data from Part 1 and Part 2 were used to address the following key questions:

1. Are the first-year myopia control benefits of the test lenses retained?
2. Was treatment efficacy impacted by COVID-19 public health restrictions in years 2 and 3?

METHODS

Study design

CYPRESS Part 1 (NCT03623074) was a 3-year randomised, controlled, multicentre, double-masked, three-arm parallel group clinical trial evaluating two investigational spectacle lenses. The test lenses were designed to slow myopia progression by slightly lowering retinal contrast, mimicking a more natural contrast (experienced in the outdoor natural world) compared with the modern visual environment, which frequently exposes children's eyes to high artificial contrast sources, including books, digital devices and urban environments.[11] Test 1 lenses (DOT 0.2) and Test 2 lenses (DOT 0.4) incorporated translucent microscopic diffusers with 0.365 mm and 0.240 mm spacing, respectively. Test 2 lenses were designed with a denser pattern of microscopic diffusers to scatter light and modulate retinal contrast to a greater extent than Test 1 lenses. To help enable masking of the Control group, spectacles with a different appearance compared with habitual spectacles were desired, so a light green tint that reduced light transmission by approximately 5% was applied to the standard single vision lenses (light transmission of the Test lenses was 91%). A detailed description of the study lenses has been published previously.[12] All lenses were replaced every 6 months, even if a prescription update was not warranted.

Participants were recruited across 14 clinical sites in North America. Part 1 took place between July 2018 and March 2022. The study protocol for Part 1 has been described previously[12] and was retained for Part 2. Treatment compliance and adverse events were assessed through questionnaires and ocular examination at each 6-monthly study visit.

Participants completing Part 1 were invited to enrol in CYPRESS Part 2 (NCT04947735). No refractive limits were set for inclusion into Part 2. Part 2 was a 1-year open-label, multicentre clinical trial in which Test 1 and Control groups continued with their original lens assignment while the Test 2 group crossed over to Test 1 lenses. Part 2 took place between July 2021 and March 2023.

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Efficacy and safety endpoints

The co-primary efficacy endpoints were change from baseline in axial length (AL) and cycloplegic spherical equivalent refraction (cSER) compared with Control. AL was measured every 6 months using the Lenstar 900 biometer[13] (Haag-Streit Diagnostics, Koeniz, Switzerland). Six measurements were acquired per eye. cSER was measured at baseline and annually from 12 to 48 months using the Grand Seiko Binocular Autorefractor WR-5100K[14] (Grand Seiko, Hiroshima, Japan). 10 measurements were acquired per eye.

Safety endpoints included binocular best-corrected visual acuity (BCVA) and adverse events.

Statistical analysis

As described previously,[12] the modified intention-to-treat population was analysed to evaluate primary efficacy endpoints. Single values for AL and cSER were calculated for each participant at each visit by taking the average of the right and left eye measurements. A mixed effect model was used to assess intergroup differences with respect to treatment, age group, sex and the baseline value of the endpoint as a covariate. A multiple imputation approach using a regression model with factors for baseline value, visit, baseline age and gender using SAS code PROC MI was employed to impute missing data. The proportion of data that was imputed was 3.6% for both cSER and AL. The least squares mean±SE for change from baseline was determined at 12, 24 and 36 months for Part 1, and also with matched participants in Part 2 at 12, 24, 36 and 48 months (to address question 1).

The impact of COVID-19 public health restrictions on treatment efficacy (question 2) was explored by comparing change in AL and cSER during the period of COVID-19 public health restrictions and school closures (study years 2 and 3) with outcomes before restrictions were mandated (study year 1) and once restrictions were relaxed and schools had re-opened (study year 4).

RESULTS

In Part 1, 200 participants completed the 36-month visit (Test 1 n=71, Test 2 n=46, Control n=83). The attrition rate was higher in the Test 2 lens arm (36%) than for Test 1 (19%) and Control (13%) groups (figure 1).

The demographics of children in CYPRESS Part 1 have been reported previously.[12] Table 1 summarises the demographics of the children who enrolled in CYPRESS Part 2.

A total of 111 children enrolled in Part 2. 10 were subsequently excluded from analysis due to the closure of a study site before any children completed their 48-month visit. From the remaining 101 children, 56 were in the Test group and 45 were in the Control group. The Test group included 21 children (38%) who wore Test 2

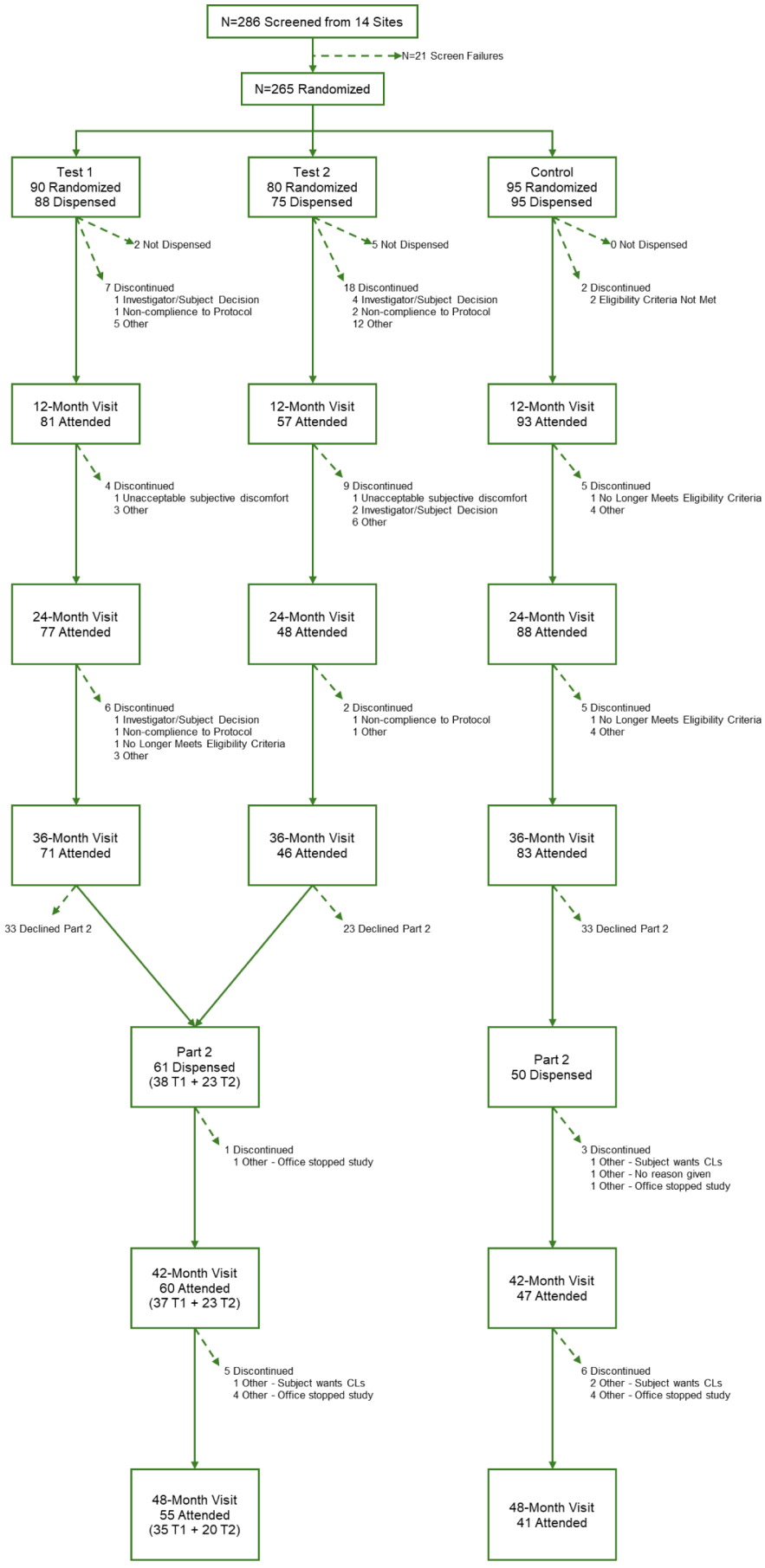

Figure 1 Flowchart of participant disposition. T1, Test 1; T2, Test 2.

Table 1 Demographics and clinical characteristics for children enrolled in Part 2 (n=101)

Variable	Test (previously wore Test 1 or 2)	Test (previously wore Test 1)	Test (previously wore Test 2)	Control
Subjects (n)	56	35	21	45
Integer age* (n (%))				
9 years old	9 (16.1)	6 (17.1)	3 (14.3)	6 (13.3)
10 years old	5 (8.9)	3 (8.6)	2 (9.5)	8 (17.8)
11 years old	15 (26.8)	10 (28.6)	5 (23.8)	8 (17.8)
12 years old	19 (33.9)	12 (34.3)	7 (33.3)	15 (33.3)
13 years old	6 (10.7)	3 (8.6)	3 (14.3)	7 (15.6)
14 years old	2 (3.6)	1 (2.9)	1 (4.8)	1 (2.2)
Mean (SD)	11.3 (1.34)	11.2 (1.32)	11.4 (1.40)	11.3 (1.36)
Axial length (mm)				
Mean	24.62	24.73	24.45	24.75
SD	0.898	0.856	0.959	0.743
Min	22.98	23.22	22.98	22.98
Max	26.72	26.72	25.83	26.24
Cycloplegic spherical equivalent refraction (D)				
Mean	−2.85	−2.93	−2.73	−3.22
SD	1.598	1.620	1.592	1.346
Min	−7.20	−7.20	−6.07	−7.13
Max	−0.23	−0.37	−0.23	−0.58

*Integer age is the participant's age rounded down to the nearest whole year.

spectacle lenses in Part 1. All children in the Test group wore Test 1 spectacle lenses between 36 and 48 months. 96 participants (95%) completed the 48-month visit: 55 (98%) in the Test group and 41 (91%) in the Control group.

The mean wearing times were reported as greater than 13 hours per day for each group at each time point.

Part 1

Changes in AL over 36 months

At 36 months, the least squares mean change±SE in AL for Test 1, Test 2 and Control lenses was 0.59±0.04 mm, 0.67±0.05 mm and 0.72±0.04 mm, respectively (figure 2A). The difference between means (Test lens−Control) was significant for Test 1 (−0.13 mm; 95% CI −0.23 to −0.02; p=0.018) but not Test 2 (−0.04 mm; 95% CI −0.17 to 0.09; p=0.52).

Changes in cSER over 36 months

At 36 months, the least squares mean change±SE in cSER was −0.83±0.09 D for Test 1, −1.19±0.11 D for Test 2 and −1.16±0.09 D for Control (figure 2B). Similar to AL results, the difference between means was significant for Test 1 (0.33 D; 95% CI 0.09 to 0.58; p=0.008) but not Test 2 (−0.03 D; 95% CI −0.32 to 0.26; p=0.85).

Significant between-group differences emerged in the number of participants who were refractively stable after 36 months (defined as <0.50 D myopic change from baseline): 43% of Test 1 spectacle lens wearers and 19% of Control participants (p<0.001).

Impact of COVID-19 pandemic

Test 1 lens treatment effect from year 1 was retained into year 3; incremental treatment effect was not observed during years 2 and 3 (mean difference in AL and SER progression between Test 1 and Control was 0.03 mm and −0.08 D from 12 to 36 months).

Following completion of all year 1 study visits (13 March 2020), a global public health emergency was declared due to the unprecedented COVID-19 pandemic. Stay-at-home orders were put in place across most of the USA and Canada (where the study sites were located) from late March or early April 2020, lasting until at least July 2020 in most cases. Social restrictions were in place for approximately another year, which affected the school routines, lifestyles and activities of participants during study years 2 and 3. Study participants reported being unable to physically attend school for between 3 and 11 months in study year 2, and between 2 and 10 months in study year 3. No significant changes in spectacle lens wear were reported during study years 2 and 3, however 76% of children reported an increase in digital device usage while not in full-time, in-person school. No clear trend emerged for a reduction in time spent outdoors

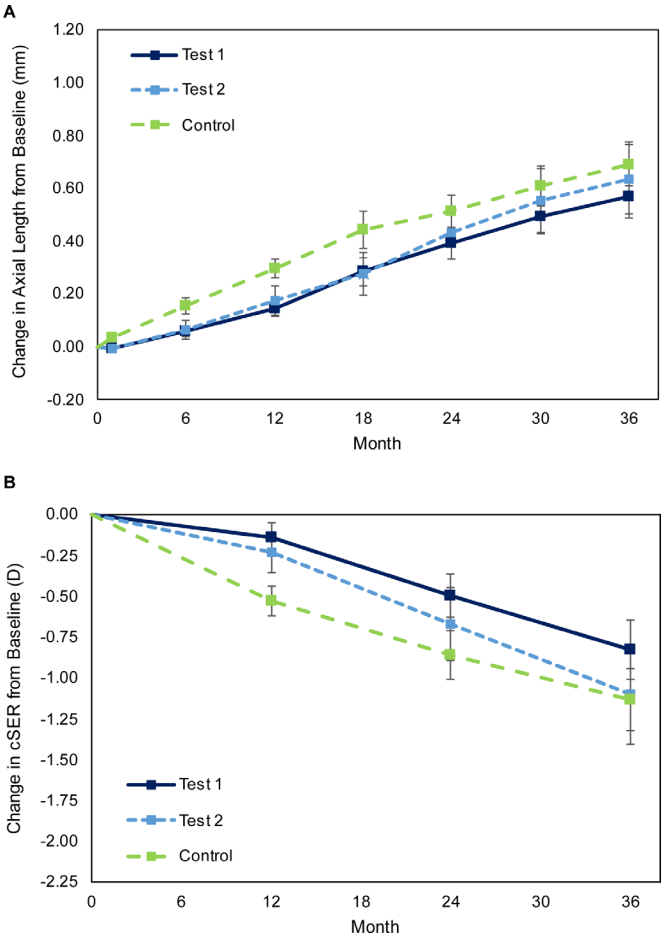

Figure 2 Least squares mean change from baseline with 95% CI for (A) axial length and (B) cycloplegic spherical equivalent refraction (cSER).

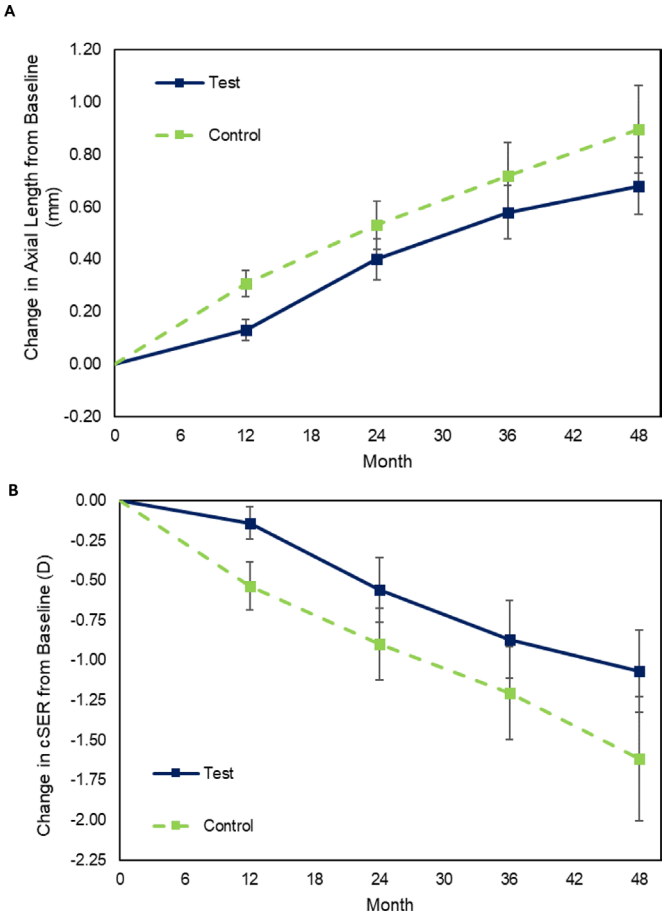

Figure 3 Least squares mean change from baseline with 95% CI for (A) axial length and (B) cycloplegic spherical equivalent refraction (cSER), only including data from the participants who enrolled into Part 2. The Test group includes participants who wore Test 1 or Test 2 lenses for the first 3 years of the study. All participants in the Test group wore Test 1 lenses between study years 3 and 4.

when not in full-time, in-person school (30% less time, 37% about the same, 33% more time).

Part 2

Least squares mean change±SE from 36 to 48 months was not statistically different (AL p=0.72, cSER p=0.54) between participants who had worn Test 1 lenses for 48 months (0.12±0.02 mm; −0.23±0.05 D) and participants who crossed over from Test 2 to Test 1 lenses after 36 months (0.11±0.02 mm; −0.27±0.06 D), therefore data were pooled into one 'Test' group for mixed effect modelling with multiple imputation.

Changes in AL over 48 months

The least square mean change±SE in AL from baseline to 48 months was 0.70±0.06 mm in the Test group and 0.89±0.07 mm in the Control group (figure 3A). At 48 months, the difference between means (Test–Control) was −0.20 mm (95% CI −0.38 to −0.02; p=0.033).

Changes in cSER over 48 months

The least square mean change±SE in cSER from baseline to 48 months was −1.11±0.15 D in the Test group and −1.64±0.16 D in the Control group (figure 3B). At 48 months, the difference between means (Test–Control) was 0.52 D (95% CI 0.09 to 0.95; p=0.017). After 48 months of wear, 46% of Test group participants and 29% of Control group participants had <0.75 D myopic change from baseline (p=0.09). Mean spherocylindrical refraction is presented in online supplemental file 1.

Pre-pandemic and post-pandemic efficacy

Considering efficacy results outside of the period of COVID-19 public health restrictions, the Test 1 lens slowed AL progression by 0.15 mm in year 1 (p<0.0001)[12] and 0.05 mm in year 4 (p=0.038) and SER progression by 0.40 D in year 1 (p<0.0001)[12] and 0.13 D in year 4 (p=0.043), compared with Control lenses. Considering the cumulative treatment effect observed after 4 years of wear, approximately 75% of the benefit accrued in year 1 and 25% in year 4.

Safety

During the 4-year study, the only device-related adverse event to occur in either test arm was a single occurrence of

Table 2 Adverse events (AEs) reported or observed in all participants dispensed study spectacles

	Total (N=258)		Test 1 (N=88)		Test 2 (N=75)		Control (N=95)	
Category	Subjects* n (%)	Events (n)	Subjects* n (%)	Events (n)	Subjects* n (%)	Events (n)	Subjects* n (%)	Events (n)
Any event	81 (31.4)	129	29 (33.0)	52	22 (29.3)	30	30 (31.6)	47
Related AEs	5 (1.9)	7	1 (1.1)	1	0 (0)	0	4 (4.2)	6
Not Related AEs	79 (30.6)	122	29 (33.0)	51	22 (29.3)	30	28 (29.5)	41
Ocular AEs	23 (8.9)	36	8 (9.1)	13	5 (6.7)	7	10 (10.5)	16
Blepharitis	3 (1.2)	6	2 (2.3)	4	0 (0)	0	1 (1.1)	2
Hordeolum	3 (1.2)	3	2 (2.3)	2	0 (0)	0	1 (1.1)	1
Viral conjunctivitis	2 (0.8)	2	0 (0)	0	2 (2.7)	2	0 (0)	0
Dry eye	1 (0.4)	2	0 (0)	0	0 (0)	0	1 (1.1)	2
Light sensitivity	1 (0.4)	2	0 (0)	0	0 (0)	0	1 (1.1)	2
Ocular allergies	2 (0.8)	4	0 (0)	0	1 (1.3)	2	1 (1.1)	2
Optic disc drusen	1 (0.4)	2	0 (0)	0	0 (0)	0	1 (1.1)	2
Strabismus	1 (0.4)	2	1 (1.1)	2	0 (0)	0	0 (0)	0
Superficial keratitis	1 (0.4)	2	1 (1.1)	2	0 (0)	0	0 (0)	0
Oedema	1 (0.4)	1	0 (0)	0	1 (1.3)	1	0 (0)	0
Erythema	1 (0.4)	1	0 (0)	0	0 (0)	0	1 (1.1)	1
Lattice	1 (0.4)	1	1 (1.1)	1	0 (0)	0	0 (0)	0
Capped meibomian glands	1 (0.4)	1	0 (0)	0	0 (0)	0	1 (1.1)	1
Operculated hole	1 (0.4)	1	0 (0)	0	1 (1.3)	1	0 (0)	0
Reduction in visual acuity	1 (0.4)	1	0 (0)	0	0 (0)	0	1 (1.1)	1
Retinal haemorrhage	1 (0.4)	1	0 (0)	0	0 (0)	0	1 (1.1)	1
Trauma to eye	1 (0.4)	1	0 (0)	0	1 (1.3)	1	0 (0)	0
Unspecified visual disturbance	1 (0.4)	1	0 (0)	0	0 (0)	0	1 (1.1)	1
Transient shaky vision	1 (0.4)	2	1 (1.1)	2	0 (0)	0	0 (0)	0
Non-ocular AEs	63 (24.4)	93	21 (23.9)	39	19 (25.3)	23	23 (24.2)	31

*Subject level counts across subcategories may not add up to the total, subjects could have events in >1 subcategories.

skin irritation from the spectacle frame nose pad, which was non-significant, fully resolved, and was related to the spectacle frame and not the test lens (table 2). No lens related device deficiencies were observed. Mean change in binocular BCVA (±SD) over 4 years was not significantly different between the Test (−0.07±0.10 logMAR) and Control groups (−0.04±0.08 logMAR).

DISCUSSION

The CYPRESS clinical trial is the first multicentre spectacle lens study to demonstrate myopia control efficacy in an ethnically diverse population from age 6. Parts 1 and 2 demonstrated that Test 1 spectacle lenses significantly slowed the progression of myopia compared with standard single vision Control lenses, supporting the hypothesis that slightly reducing retinal contrast can slow myopia progression.

Key study findings include:

1. The Test 1 (DOT 0.2) lens treatment effects on AL and cSER observed in year 1 were retained into year 3.
2. Incremental treatment effect was not observed during years 2 and 3, which coincided with COVID-19 public health restrictions and school closures. Additional benefit was evident post-pandemic in study year 4, once most public health restrictions had ceased and schools fully reopened.

In this relatively slow progressing cohort, the 4-year cumulative treatment effect was lower than expected based on favourable first year performance.[12 15] Extension of the study post-pandemic (year 4) highlighted an anomalous period of depressed performance in study years 2 and 3, which coincided with the period of COVID-19 public health restrictions and school closures in North America, where this study was conducted. Other published studies have also reported the effectiveness of myopia control treatments was negatively impacted during the COVID-19 pandemic restrictions.[16–18] These results indicate the importance of controlling environmental and behavioural myopia risk factors even in children undergoing active myopia control treatment.

Multiple myopia intervention studies have reported enhanced efficacy with greater adherence to treatment.[19–21] In a Chinese single-centre study, full-time wear (at least 12 hours per day) of highly aspherical lenslets (HAL) spectacle lenses, slowed cSER by 0.99 D (67%) and AL by 0.41 mm (60%) after 2 years of wear. Further analysis of CYPRESS at the same 2-year data point indicates enhanced treatment effect for children who did not

remove their DOT 0.2 spectacles for near vision activities (which are typically high contrast, eg, reading and using digital devices): cSER was slowed by 0.52 D (59%) and AL by 0.21 mm (38%).[22] Direct comparison between the DOT 0.2 and HAL spectacle lens study outcomes is complex due to differences in study design and participant age and ethnicity.

Younger children are known to undergo more rapid physiological eye growth (even in persistent emmetropic eyes),[23] which is likely to have dampened percentage efficacy measures in the CYPRESS clinical trial,[12] which recruited children aged 6–10 years (vs 8–13 years in the HAL study).[12 24] Additionally, extrapolation of Asian study outcomes to other regions may not be appropriate due to environmental, behavioural and genetic differences between populations.[18 25 26] Multicentre research is ongoing to evaluate DOT 0.2 efficacy in a Chinese population (NCT05562622).

Initial results from a European observational study evaluating Defocus Incorporated Segments (DIMS) spectacle lenses reported progression in cSER of −0.56 D and AL of 0.32 mm after 1 year of DIMS spectacle lens wear in children younger than 10 years of age.[27] In CYPRESS, progression in the DOT 0.2 spectacle lens group was slower: cSER of −0.14 D and AL of 0.15 mm after 1 year of wear. The apparent differences in performance may have emerged due to differences in study design or lens mechanism of action. The myopia control effect of DIMS lenses has been reported to be greater in children over 10 years of age,[27 28] possibly due to differences in retinal profile or peripheral refraction.[29] Further research is required to evaluate why younger children may respond better to contrast modulation technology.

Contrast theory predicts a positive dose–effect relationship between myopia control efficacy and level of contrast reduction. It was not possible to evaluate this relationship in the present study due to the higher participant drop-out rate (36%; figure 1) and lower compliance in the Test 2 group compared with the Test 1 group. To accurately investigate a dose–effect relationship, sample size and compliance between groups should be adequate and matched. The higher discontinuation in the Test 2 lens arm was partially driven by lens-related reasons (likely due to the denser optical pattern), including dislike of lens appearance and difficulty adapting. This was not evident in the Test 1 arm, where a majority of discontinuations were unrelated to the study lenses (figure 1) and occurred at a similar rate to previous myopia control randomised controlled trials.[30] Overall, the CYPRESS findings suggest Test 1 lenses were better tolerated than Test 2 lenses and therefore are more likely to result in higher compliance and myopia control efficacy.

A study limitation was that wearer compliance was a self-reported outcome and may not accurately reflect actual wearing patterns, particularly during the period of school closures where uncorrected vision may have been adequate to navigate the near-orientated indoor environment. Unencumbering objective compliance monitors are indicated for future studies. An additional study limitation was that many of the 18-month study visits fell within the initial COVID-19 lockdown periods; visits as late as 4 months outside of the visit window were permitted but were not included in the presented analysis. It is possible that 4-year efficacy metrics underestimate the true efficacy of DOT lenses due to unprecedented disruption in participant schooling and lifestyle during study years 2 and 3.

CONCLUSION

Contrast modulation is a novel mechanism of action to slow the progression of myopia. The results of CYPRESS Part 1 and 2 support the theory that modulating retinal contrast can slow the progression of myopia. DOT 0.2 spectacle lenses are a safe and efficacious myopia management treatment for children from age 6 and are a suitable early treatment option for myopic children.

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Competing interests DL, JSH, MMP and VT are SightGlass Vision employees. VT has a patent application for methods and devices for reducing myopia in children. JW reports research grants from SightGlass Vision, Alcon, CooperVision and Johnson and Johnson Vision and consultancy fees from SightGlass Vision and meeting and/or travel support from Alcon and CopperVision. XZ reports grants from SightGlass Vision and Reality Labs Research at Meta Platforms Technologies, LLC and consultancy fees/honoraria from SightGlass Vision and CooperVision. GY, RC and CH report contracts with SightGlass Vision, 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. TWC reports consulting fees, meeting and/or travel support, patents and stock ownership in his role as employee, officer and board member for SightGlass Vision. DJ reports consulting/honoraria from CooperVision, Hoya, SightGlass Vision, Alcon and Essilor. JSW reports consulting fees from CooperVision, DopaVision, Essilor, International Myopia Institute, SightGlass Vision and Thea. JSW reports grants from SightGlass Vision and Espansione and shares in Wolffsohn Research Limited.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. CYPRESS Part 1 and 2 were designed and conducted in accordance with the ethical principles in the Declaration of Helsinki, with the International Council for Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and all applicable local regulations. The study protocol and informed consent documents were reviewed and approved by

the Sterling Institutional Review Board, USA (approval number 6383 for Part 1, 9051 for Part 2) and the Office of Research Ethics of the University of Waterloo, Canada (approval number 23306 for Part 1, 43626 for Part 2) and the trial was registered with ClinicalTrials.gov (NCT03623074, NCT04947735). Written informed assent and consent were obtained before enrolment from the participant and guardian, respectively.

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Data availability statement Data are available upon reasonable request.

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