# DIFFUSION OPTICS TECHNOLOGY™

## WHITE PAPER

SIGHTGLASS VISION

Powered by Diffusion Optics Technology™

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# 1. MYOPIA – A GLOBAL PROBLEM OF EPIDEMIC PROPORTIONS

## 1.1 Myopia and its Increasing Prevalence

Myopia, or shortsightedness, is a condition in which light rays that should be focused on the retina are focused in front of the retina, making distant objects look blurry.

The prevalence of myopia has dramatically increased over the past several decades. It is estimated that almost half of the world's population, about five billion people, will have myopia by 2050 – and one billion people will have high myopia with increased risk of eye complications.[1] In the early 1970s, only 25 percent of Americans were nearsighted.[2] By the early 2000s, that proportion had jumped to more than 40 percent.[2] Today, the number of nearsighted people is at epidemic proportions globally.[3] In urban China, about 80 to 90 percent of teens and young adults are myopic, up from 10 to 20 percent just 65 years ago.[4]

## 1.2 Myopia Risk Factors

Both genetic and environmental factors influence the onset and progression of myopia, however the fast-rising prevalence of myopia indicates environmental risk factors play a more dominant role.[5]

Established environmental risk factors include more urban societies, greater amounts of near work, higher levels of education and insufficient outdoor time.[6] Increased time outdoors is protective against the onset of myopia[7] and may help control myopia progression.[8]

## 1.3 Health Risks

It has been well established that myopia often progresses rapidly during childhood.[9, 10] This progression continues into the teenage years and early adulthood. This results in the need for stronger prescription glasses and increases the risk of potentially blinding conditions such as glaucoma, retinal detachment, and myopic maculopathy in adulthood (Figure 1).[11]

Although corrective glasses and contact lenses provide clear vision, they do not treat the underlying causes of myopia. Developing technologies that can effectively slow down the progression of myopia would reduce the risk of complications for myopic patients in later life, for example slowing myopia progression by 1.00 D could reduce the likelihood of a child developing myopic maculopathy in adulthood by 40%.[12]

| | Odds ratio (increase in risk) compared to emmetrope | | |
|---|---|---|---|
| Adult level of myopia (D) | Glaucoma[13] | Retinal detachment[14] | Myopic maculopathy[15] |
| -2.00 | 1.7 X | 3.1 X | 2.2 X |
| -4.00 | 2.5 X | 9.0 X | 9.7 X |
| -6.00 | 2.5 X | 21.5 X | 40.6 X |

*Figure 1. Odds ratios for developing ophthalmic complications according to the degree of myopia in adults.*[16]

## 1.4 Impact on Learning, Quality of Life, and the Economy

In addition to ocular health implications, myopia can impact individuals and society by hindering education, reducing quality of life, and burdening the economy. Uncorrected myopia can affect children's learning ability in the classroom, especially when learning is more dependent on distant blackboards/whiteboards than on nearby textbooks.[17, 18] Children who fail visual screening and are subsequently prescribed spectacles can significantly improve their end-of-year test scores for mathematics – by the equivalent of half a semester of extra learning, on average.[17] In addition, high myopia, even when it can be adequately corrected, is associated with decreased quality of life,[19] impaired activities of daily living, and poorer outcomes for refractive surgery.[12]

Financially, an estimated US$ 244 billion (95%CI: $49 billion – $697 billion) was lost globally in 2015 due to uncorrected myopia.[20] The economic burden as a percentage of GDP was greatest in Southeast Asia (1.35%), South Asia (1.30%), and East Asia (1.27%), each having a burden well over twice that of any other region.[20] Moreover, severe vision impairment and blindness due to myopia may have caused global productivity losses in 2019 of approximately US$ 94.5 billion, and the forecast is that the cost can increase to US$ 229 billion by 2050.[21] Myopia also presents a direct cost to individual patients and their families because of expenditure on diagnosis, correction, management, transport, and so on. Faster myopia progression could result in greater costs to individuals because of the need to update their prescriptions more frequently.

## 1.5 Importance of Early Intervention

In addition to increasing myopia prevalence, children are also becoming myopic at a younger age.[22] The younger the age of myopia onset, the higher the risk of high myopia in adulthood.[23]

Myopia management strategies are designed to slow the trajectory of myopia progression, for example a child may progress to -6.00 D by age 16 without myopia management, however if treatment is initiated as early as age 6, it could nearly half the magnitude of myopia at age 16 (Figure 2).[3] Thus, earlier intervention is key to reduce the extent of myopia progression in children.

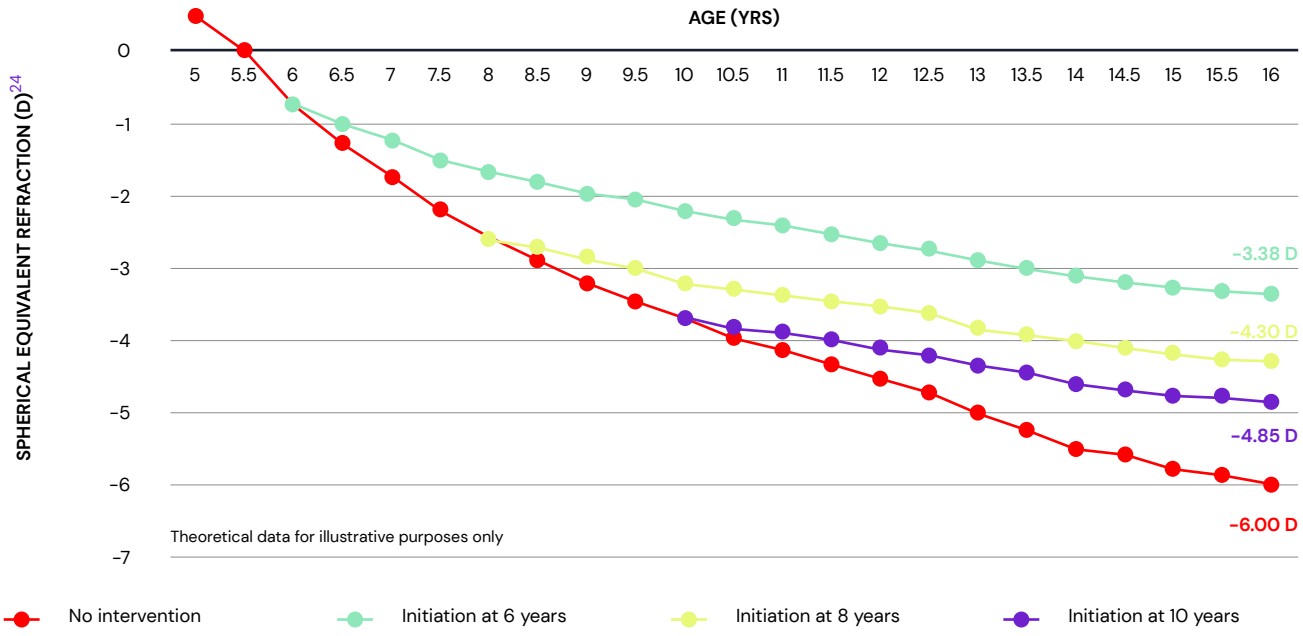
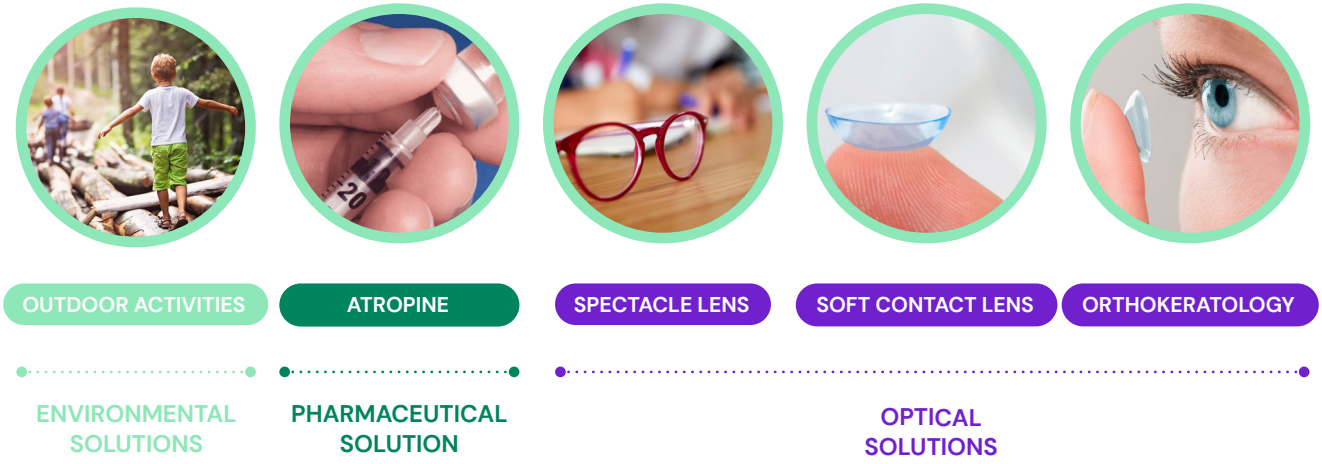



*Figure 2. Theoretical progression of myopia in children at different ages depending on starting age of intervention, assuming a 50% treatment effect. Based on data from Polling et al. (2022).*[24]

# 2. MYOPIA MANAGEMENT STRATEGIES

The World Council of Optometry has passed a resolution that supports myopia management as standard of care for myopic children.[25] Several different myopia management strategies exist today, and these fall into three broad categories: prevention through managing environmental factors, a pharmaceutical approach, and optical solutions. The decision as to which strategy to offer will depend on individual patient needs and lifestyles and on practitioner discussion with parents. The safety and effectiveness of myopia management strategies is paramount when making these decisions.




## 2.1 Environmental Solutions

The main preventative measure promoted to protect against the onset and possible progression of myopia is spending sufficient time outdoors.[26, 27] Reducing the amount of near work also reduces the risk of myopia, but this behavioral change can be difficult to achieve because of education demands and the increasing use of smartphones and similar devices.[27, 28] Furthermore, the protective effect of increased outdoor time largely outweighs the effects of near work.[26, 27]

## 2.2 Pharmaceutical Solution

The pharmaceutical approach to myopia management uses anti muscarinic eye drops, such as atropine.[29] The exact mechanism of action of pharmaceutical interventions is not fully understood. The effect of atropine on myopia progression is dose-dependent, with high concentrations (1.0% and 0.5%) demonstrating greatest efficacy; however, high concentrations also have a higher rate of significant adverse effects[30] and can cause cycloplegia and photophobia.[31] Also longer term effects of atropine use still needs to be determined.[32]

However, low concentrations of atropine (0.01%) are increasingly used as they do not cause the side effects associated with high concentrations and still efficacious as demonstrated by a recent 3-year randomized clinical study (CHAMP NCT03350620) evaluating 0.01% and 0.02% atropine for treatment option for childhood myopia progression.[33]

Rebound typically observed with higher concentration of atropine is not evident with the lower concentrations.
There are several studies examining the use of atropine in combination with other approaches.[34]

For now, atropine remains the only widely accessible pharmacologic treatment for practitioners for slowing down myopia progression.

## 2.3 Optical Solutions

Unlike other categories of myopia management, optical solutions have the benefit of simultaneously correcting refractive errors as well as managing the progression of myopia. Optical strategies are designed to manipulate visual signals to slow myopia progression.

It has been well established that eye growth and refractive development is a visually-guided process.[35] The primary visual signals that influence eye growth are contrast and defocus, both of which are processed locally within the eye.[36]

An interruption to normal visual experience can alter the course of refractive development, as evidenced by short-term manipulation of retinal image quality with optical defocus[37, 38, 39, 40] and mild,[41] moderate,[42] and severe[43, 44] contrast reduction.

At present, most optical solutions for myopia management are designed to induce peripheral relative myopic defocus in the lens periphery. The myopic-defocus-based contact lens designs include dual focus, extended depth-of-focus, center distance, and orthokeratology. Contact lenses and orthokeratology can provide children with good vision, enable them to participate in a wide range of activities, and increase their confidence; however, the children must be mature enough to carefully comply with the lens wear instructions in order to reduce the risk of infection.

With spectacle lenses, the patient only needs to use one device; thus, they are simpler to use and potentially more cost effective than contact lenses. However, none of the optical spectacle lenses are commercially available in the USA or have not received FDA clearance, although they are commercially available in many other parts of the world. The spectacle lens designs based on myopic defocus include Highly Aspherical Lenslets (HAL), Defocus Incorporated Multiple Segments (DIMS), Peripheral Hyperopia Reduction Lens, executive bifocals, and Progressive Addition Lenses (PALs).

Contrast modulation is a novel and unique mechanism of action that is utilized in Diffusion Optics Technology (DOT) spectacle lenses. Instead of inducing myopic defocus, the lens is designed to manage myopia by slightly lowering contrast at the retina by softly scattering the incoming light to the eye. DOT lens is comprised of a central clear aperture (~5mm diameter) surrounded by thousands of micro-dot scattering centers that are organized across the entire lens surface.

# 3. MYOPIA, CONTRAST AND THE RETINA: WHAT'S THE RELATIONSHIP?

SightGlass Vision introduced a breakthrough technology based on contrast theory to slow down the progression of myopia. In the context of vision, contrast is the difference of brightness or color between objects that a person is viewing. Low contrast weakly stimulates the visual system. In nature, it helps prey or predator's camouflage. High contrast strongly stimulates the visual system. In nature, it is used to attract attention or signal a danger.

**Low contrast weakly stimulates the visual system.** In nature, it helps prey or predator's camouflage.

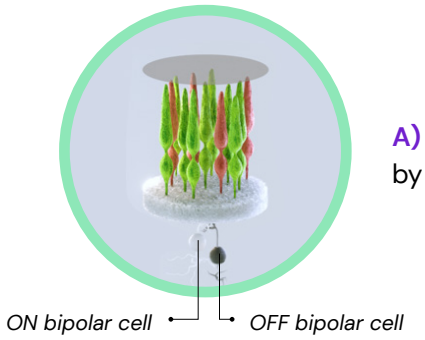
**High contrast strongly stimulates the visual system.** In nature, it is used to attract attention or signal a danger.

## 3.1 Importance of Contrast in Vision

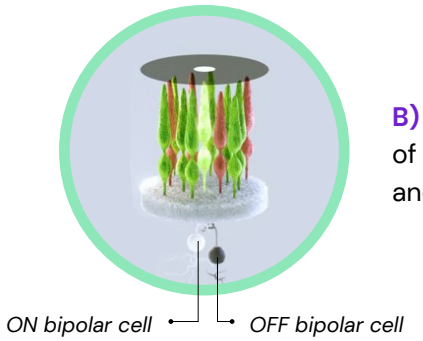
The visual environment exposes our eyes to a wide range of light intensities. The retina's function is to encode the full range of light intensities whilst remaining sensitive to subtle variations in intensity and changes in ambient light levels. The electrical response range of the neurons in the retina is relatively narrow; therefore, to enable transfer of such a vast amount of information, the retina signals relative variations in intensity (i.e., contrast) rather than absolute light intensity values.

Retinal bipolar cells detect contrast by comparing incident light intensity between neighbouring photoreceptors and horizontal cells. Bipolar cells have centre-surround receptive fields that signal when incident light intensity in the centre is above (On-centre) or below (Off-centre) the mean incident light intensity (Figure 3). Bipolar cell contrast signals are transferred to amacrine cells and On and Off ganglion cells and are then transmitted to the visual cortex for processing via distinct parallel neural pathways.

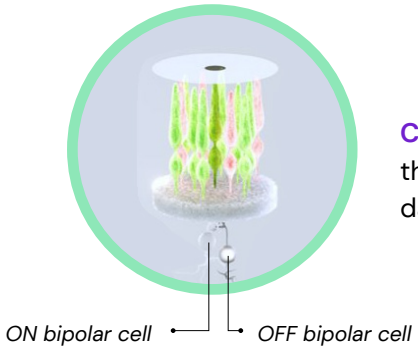
The natural outdoor environment is an example of a low contrast visual experience that elicits a low-level bipolar cell response. Reading black text on a white background provides a higher contrast visual experience that elicits a more intense bipolar cell response.




**A)** When both the center cones and the surround are covered by uniform illumination: **no contrast response.**




**B)** More light on the center cone than the average of the surrounding cones: the **ON bipolar cell** is activated and signals light against a dark background contrast.




**C)** More light on the average of the surrounding cones than the center cone: the **OFF bipolar cell** is activated and signals dark against a light background contrast.

*Figure 3. Bipolar cell signaling for A) a plain uniform visual stimulus, B) light-on-dark, and C) dark-on-light stimuli, respectively.*

## 3.2 Animal Models

Form-deprivation myopia (FDM) develops when large reductions in image contrast – to the extent that form is unidentifiable – produce axial elongation, and FDM has been demonstrated in a large array of animal models.[35] Therefore, the concept of using reductions in image contrast to slow myopia progression may, at first, seem counterintuitive. However, in monkeys, refractive outcomes with form deprivation depend on the intensity of ambient lighting; under low-light conditions, severe form deprivation continues to produce axial myopia, but with some exposure to moderate lighting conditions, the same level of contrast reduction produces axial hyperopia.[43, 44] The levels of contrast reduction used in the animal studies to induce myopia were severe and, thus, significantly different from the approach used by DOT lenses.

## 3.3 Environment Influences Contrast Signaling

The natural outdoor environment provides a low contrast visual experience. This natural contrast elicits low-level, more natural bipolar cell activity that does not appear to disrupt normal eye growth.

Elevated contrast signaling in the retina, whether from genetic predisposition or the modern visual environment, can drive myopia progression. Frequent exposure to more urban environments, near activities, studying and insufficient outdoor time contributes to a higher contrast visual experience. In particular, books, smartphones, laptops and televisions are sources of high artificial contrast. This artificial contrast could overstimulate bipolar cells leading to overstimulation of axial elongation (Figure 4).

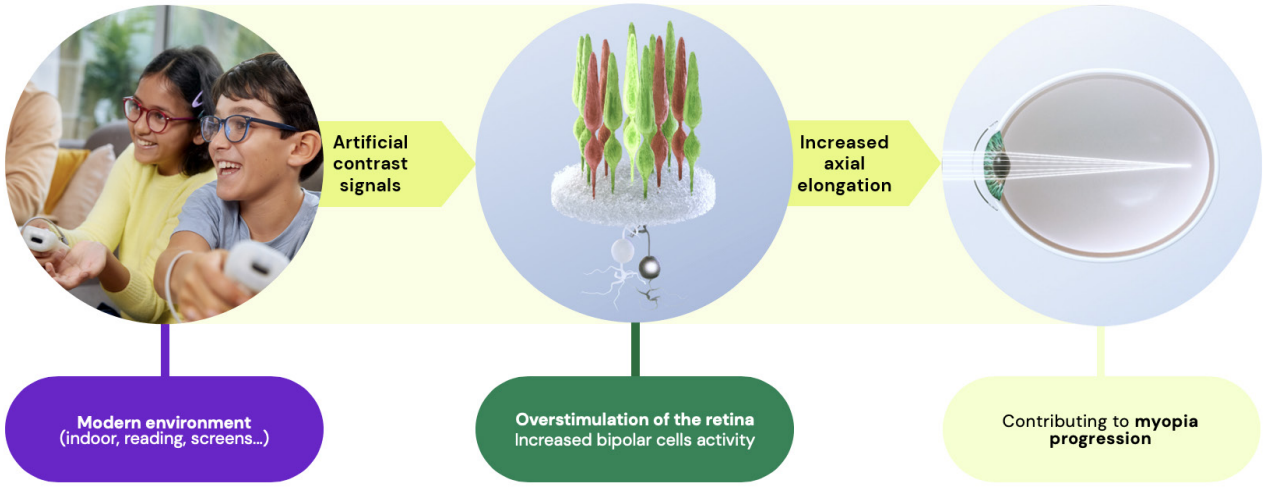
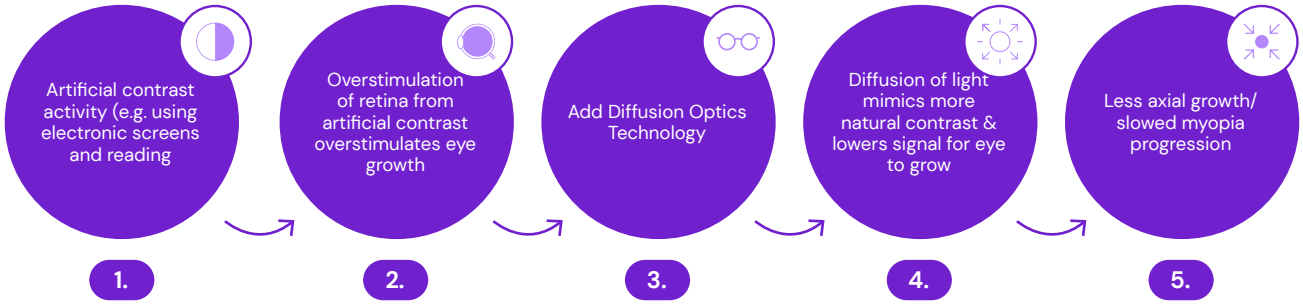



*Figure 4. Artificial contrast signals can overstimulate the retina leading to excessive axial length growth.*[45]

# 4. SIGHTGLASS VISION'S DIFFUSION OPTICS TECHNOLOGY™ – A NEW GENERATION OF MYOPIA MANAGEMENT SOLUTIONS

**SightGlass Vision** (Los Altos, California) was established to further develop myopia management technology based on contrast management. SightGlass Vision designed novel DOT spectacle lenses to mimic more natural levels of contrast. With this technology, contrast is modulated by softly scattering the incoming light to the retina. Also, the amount of contrast reduction is not vergence dependent (i.e., not affected by the fixation distance). The device has an excellent safety profile, is visually well-tolerated, and cosmetically acceptable.[41]




## 4.1 The DOT Lens and the Mechanism of Action

The DOT lens comprises a base single vision lens with minus power to correct the refractive error combined with a proprietary pattern of thousands of microscopic scattering dots, from edge to edge, that make up the treatment zone of the lens (Figure 5). Each dot softly scatters light as it passes through the lens. (Figure 6).

The DOT lens also has a central aperture (~5mm in diameter) that is aligned with the optical center of the lens. Children can see well throughout the treatment zone and the central aperture of the lens provides an untreated zone if additional extra fine detail is required. The central zone also allows practitioners to verify lens power with a focimeter. The location of the aperture relative to the spectacle frame is unique for each wearer: pupillary distance and pupil center height needs to be assessed for each eye, so the apertures are aligned with the patient's pupils at intermediate fixation at 60–65 mm.

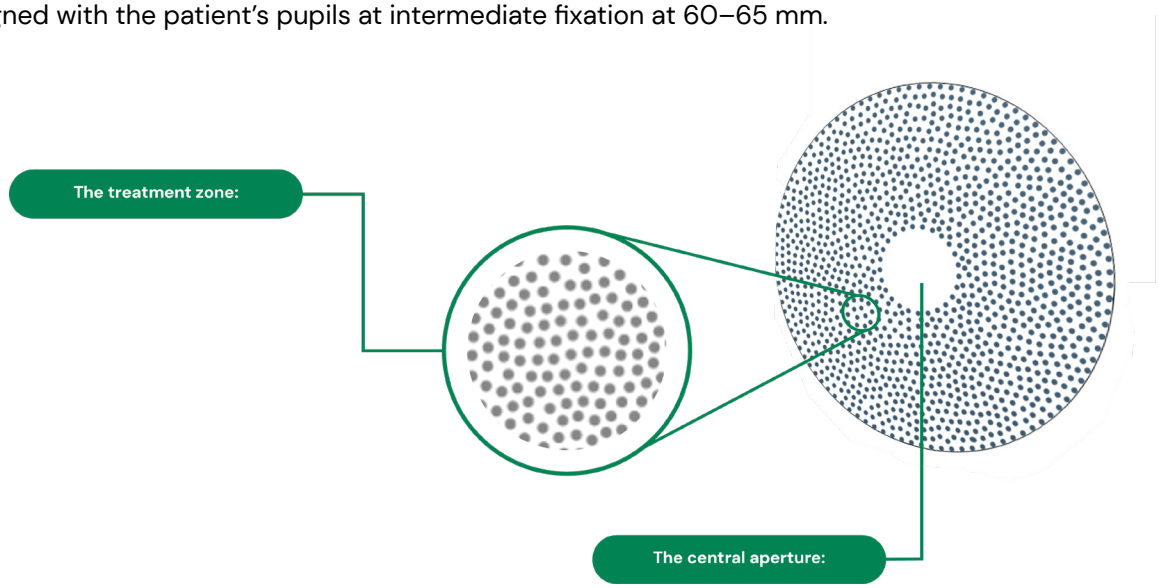



*Figure 5. Diagram of the Diffusion Optics Technology lens design.*

Design of Diffusion Optics Technology:

- The DOT lens is designed to softly scatter light into the eye.
- Microscopic scattering centers are organized throughout the treatment zone of the lens surface in a controlled manner (Figure 5).
- DOT lenses have a central aperture (~5 mm in diameter) devoid of scattering centers to help measure lens power (Figure 5).

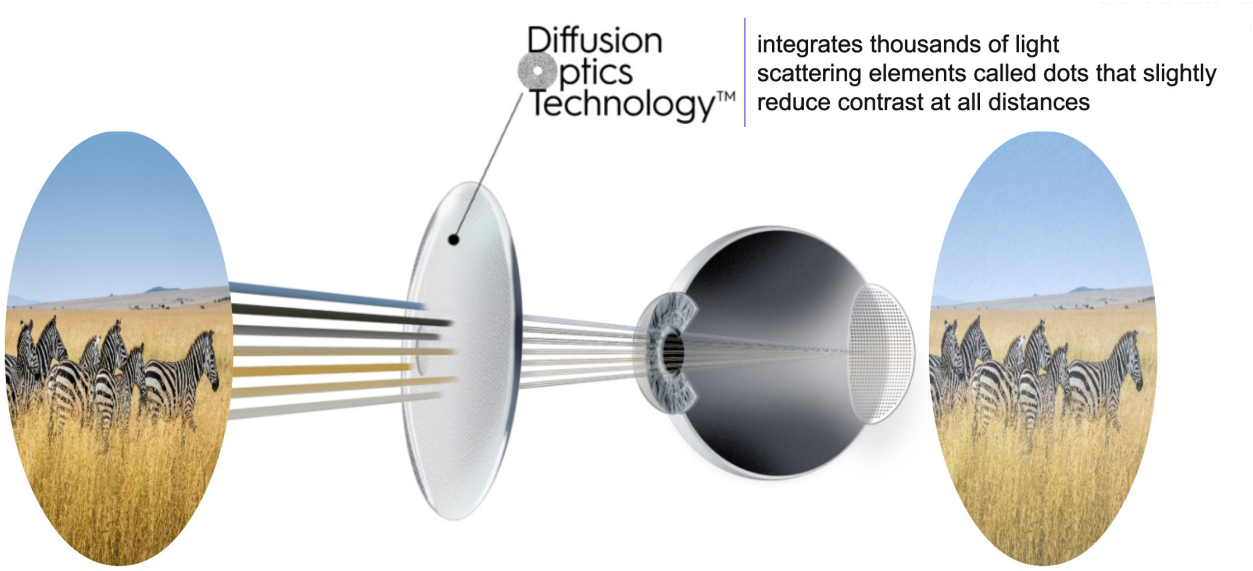



*Figure 6. Diagram illustrating lowering of retinal image contrast with a DOT lens.*

Unique features:

- Demonstrated clinical efficacy in children aged 6 to 14 years.[46]
- Excellent visual acuity when looking through the treatment zone.[47]
- Designed to slightly lower artificial contrast to mimic more natural contrast.
- Does not clinically impact contrast sensitivity compared to a single-vision lens.[46]
- Distance and vergence independent.[46]
- No impact on peripheral visual acuity.[46]

## 4.1.1 Visual Acuity

DOT lenses provide excellent visual acuity through the central clear aperture and the treatment zone. Monocular visual acuity through the treatment zone is slightly reduced by up to approximately half a line (or 2-3 letters) of high -contrast visual acuity (Figure 7).[48] At this level, children with 20/25 best corrected visual acuity would still have acceptable visual acuity per the American Association for Pediatric Ophthalmology and Strabismus's vision screening guidelines.[49]

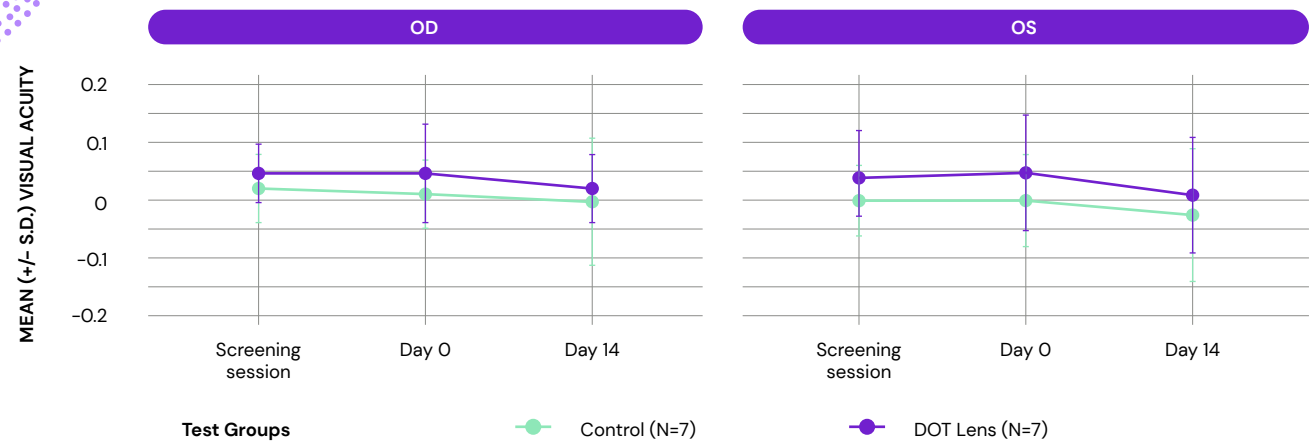



*Figure 7. Mean ±SD logMAR visual acuity at screening, Day 0, and Day 14 visits in right (OD) and left (OS) eyes of children (n=7) when wearing DOT lenses with no clear aperture (purple) and control lenses (turquoise).*

## 4.1.2 Contrast Sensitivity

Although the DOT lens slightly reduces contrast on the retina, this does not result in a significant reduction in contrast sensitivity for the wearer compared to standard single vision lenses, regardless of whether subjects looked through the centre or periphery of the lenses (Figure 8-9).[46]

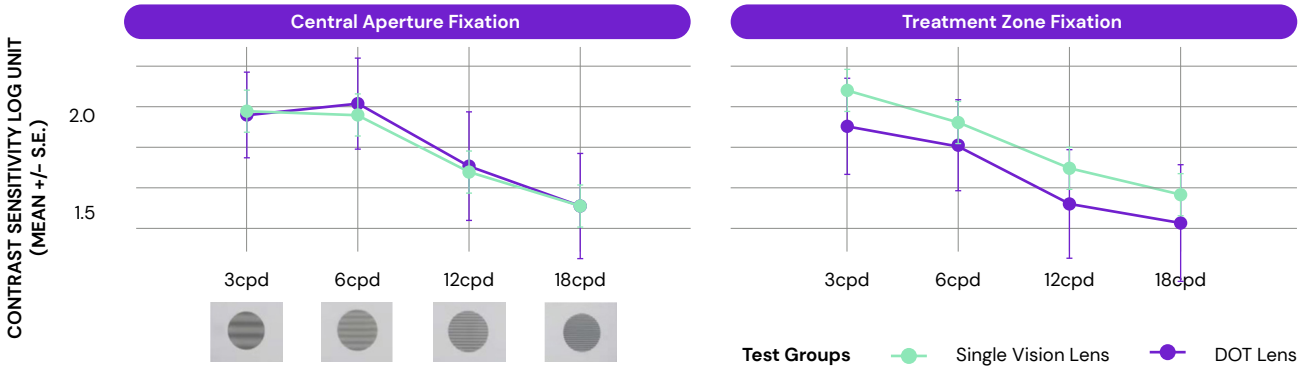



*Figure 8. Mean contrast sensitivity across spatial frequencies (3, 6, 12, and 18 cycles per degree - cpd) in subjects (n=10) with standard single vision lenses and DOT lenses when fixating through the lens centre and periphery (treatment zone of DOT lenses). Error bars represent standard error.*

With on-axis vision through the central aperture, contrast sensitivity was not different between DOT and Single Vision lenses for all spatial frequencies. With off-axis vision through the treatment zone, contrast was reduced at all spatial frequencies with no clinically significant differences between the lenses.[46]

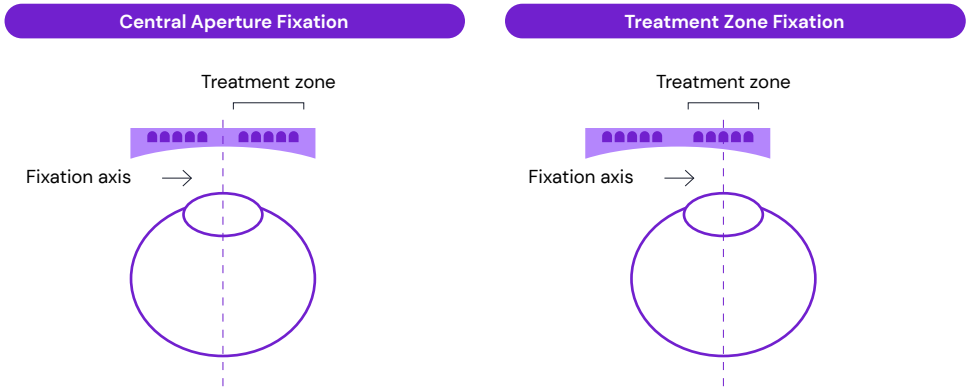



*Figure 9. Schematic diagram of experimental set-up to measure contrast sensitivity through the lens centre and periphery (treatment zone of DOT lenses).*[46]

## 4.1.3 Modulation Transfer Function

Modulation Transfer Function (MTF) analysis quantitatively evaluates the contrast across different spatial frequencies that is transferred by a lens from an object to the lens image. As displayed in Figure 10, DOT spectacle lenses reduce contrast evenly across all spatial frequencies above 25 cycles per mm, regardless of pupil size. DOT lenses generate comparable image quality and visual performance to standard single vision lenses when looking through the central clear aperture or treatment zone (Figure 10).[46]

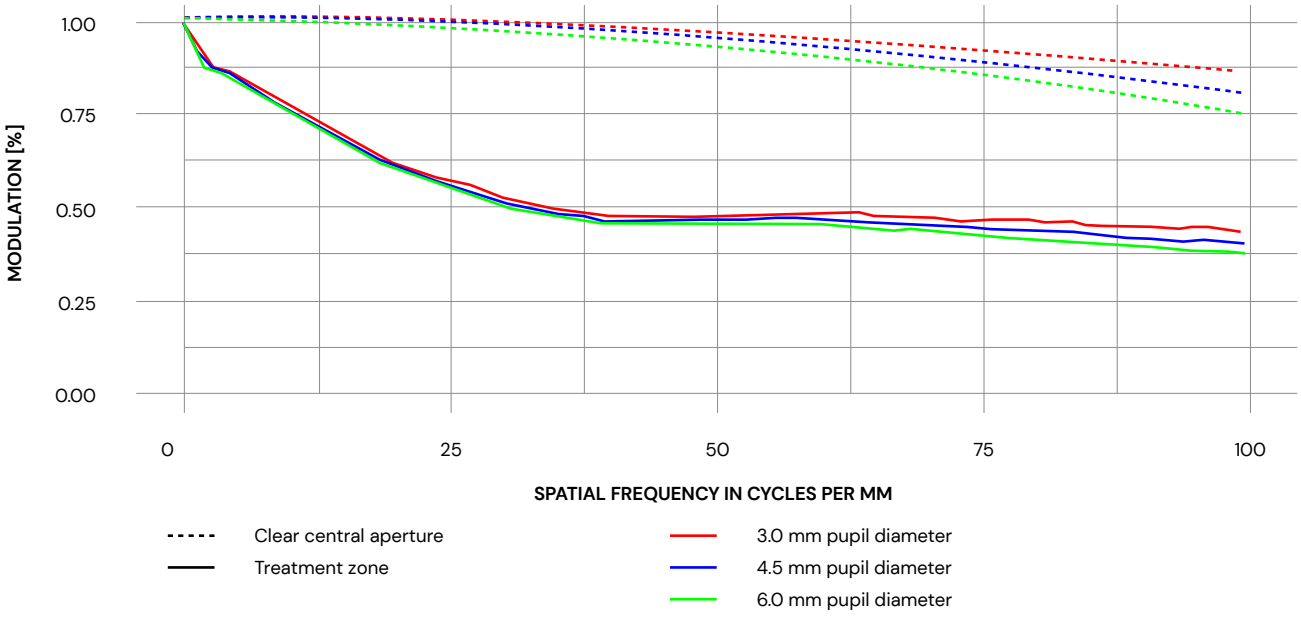



*Figure 10. Simulated Modulation Transfer Function for DOT lens.*

## 4.1.4 Clinical Comparison to Standard Single Vision Spectacle Lenses

A recent study evaluated a range of clinical parameters in 51 children aged 10 to 14 years old, who had worn either DOT lenses or standard single vision lenses for at least 3 years.[50] The results showed that performance with DOT lenses was clinically equivalent to standard single vision lenses across the full range of parameters investigated, demonstrating excellent visual performance with DOT lenses.[41]

| | DOT™ Spectacles | Standard Single Vision Spectacles |
|---|---|---|
| **Visual Acuities:** Central, Peripheral, Low Contrast, Distance, Near | ✓ | ✓ |
| Contrast Sensitivity | ✓ | ✓ |
| Minimal Glare & Halos | ✓ | ✓ |
| Reading Speed | ✓ | ✓ |
| Stereopsis | ✓ | ✓ |
| Color Vision | ✓ | ✓ |
| Safety Profile | ✓ | ✓ |
| MYOPIA CONTROL EFFICACY | ✓ Proven to slow down myopia progression[41] | ✗ Do not slow down myopia progression |

## 4.2 Visualizing Reduced Contrast Compared to Defocus

To help visualize the difference between slightly lowering the contrast of an image and blur, a couple of examples are provided (Figures 11–12). Images with slightly reduced contrast appear to have a softer tone than the original black and white, while the blurred images have distorted, unclear edges. Just as when altering the contrast settings on a computer screen or television set, a slightly reduced contrast does not result in blurry images but maintains form and shape recognition. For example, in Figure 12, all the elements in the classroom are distinguishable with the reduced contrast and can be recognized more easily than with the blur simulation.

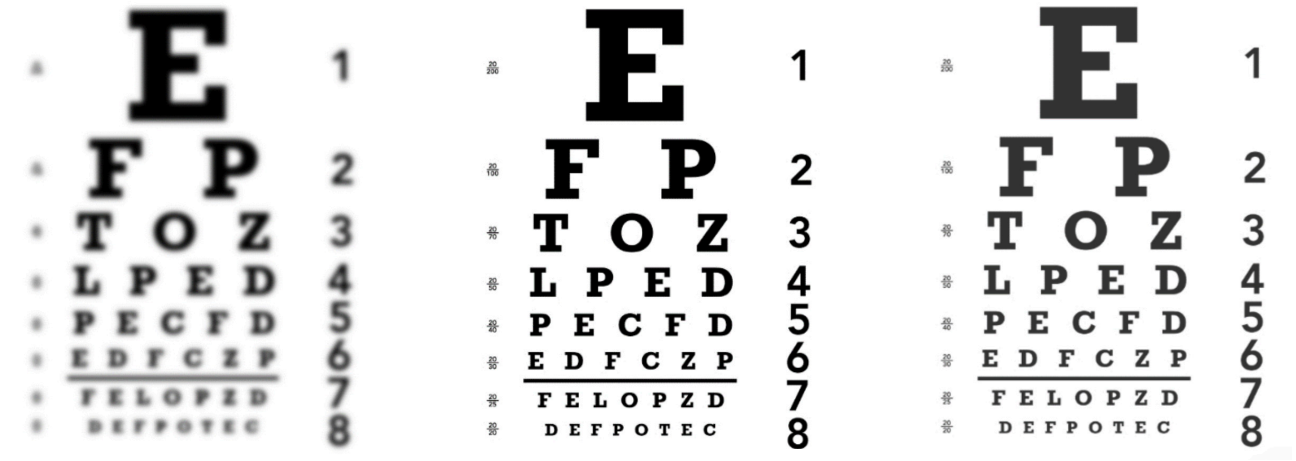



*Figure 11. Visualization of reduced contrast and induced blur for a letter chart. For illustration purposes only.*

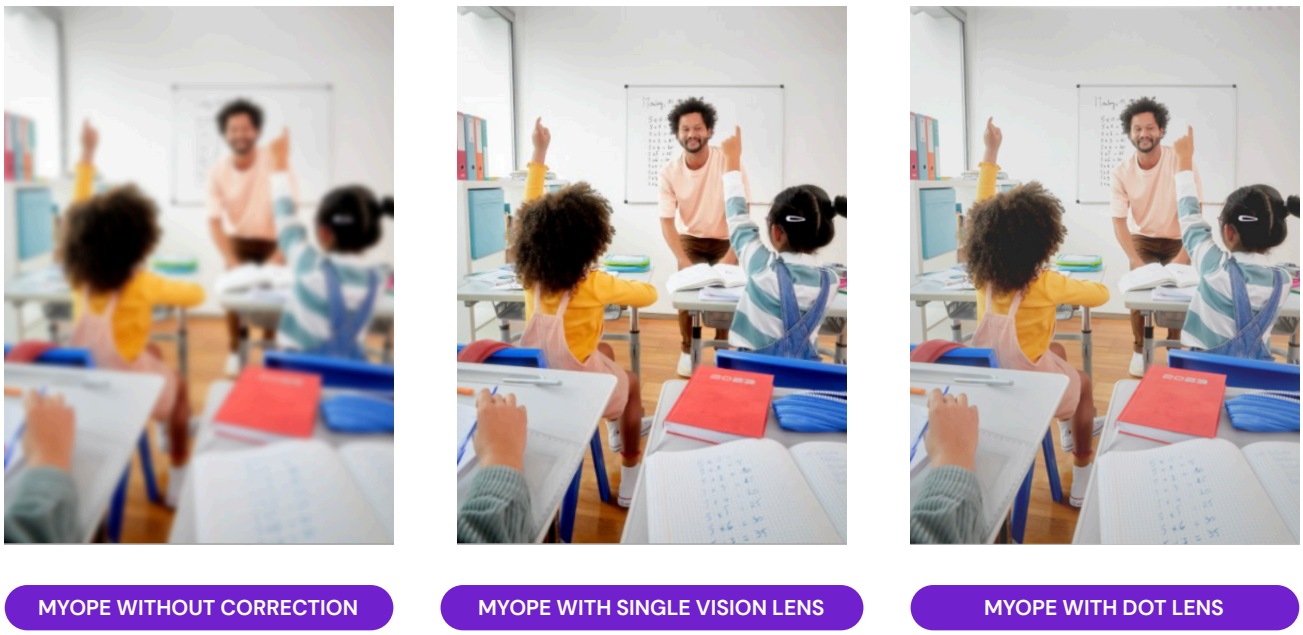


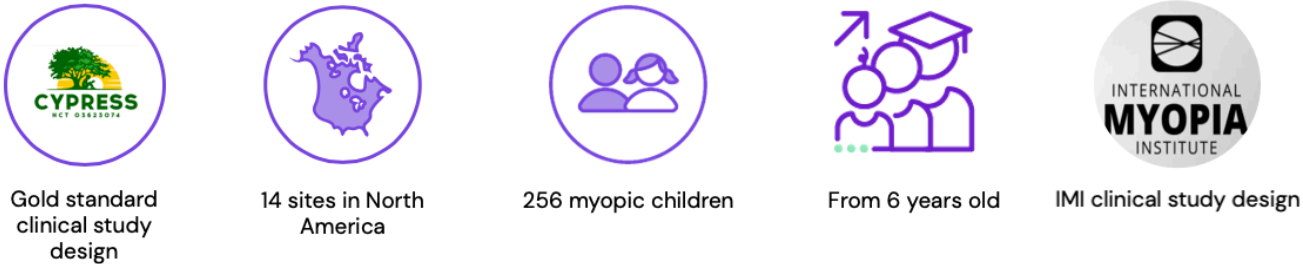

*Figure 12. Visualization of reduced contrast and induced blur for a classroom setting. For illustration purposes only.*

# 5. CLINICAL RESULTS OF CYPRESS STUDY

To evaluate the safety and efficacy of DOT lenses, a large multi-center study was conducted. This is a 3 year study with another 1 year follow up to 48m, but for ease of comparison with other myopia control spectacle lenses' published literature, 24m data is presented here.

## 5.1 Study Purpose and Design

The CYPRESS clinical study (Control of Myopia Using Peripheral Diffusion Lenses: Efficacy and Safety Study – NCT03623074) is a 3-year double-masked, randomized, controlled, parallel group clinical trial conducted at 14 sites in North America. In total, 256 myopic children aged 6 to 10 years old were enrolled. Randomisation was stratified for age and baseline myopia. Children were divided into one of three groups: the Test 1 group to assess DOT 0.2 (currently being commercialized), the Test 2 group to assess DOT 0.4 which is a denser pattern (no longer used), and the control group wore a standard single vision lens (with a slight green tint to aid masking; ~95% light transmission).




## 5.2 Subject Accountability at 24 Months

The total enrolment was 265 subjects, of whom 258 were dispensed study product (ITT population). However, two subjects were dispensed but were subsequently found to be ineligible and, therefore, the efficacy analysis is based on 256 subjects (mITT population).

Of the dispensed subjects, 215 (84%) completed the 24-month visit: 78/88 (89%), 48/75 (64%), and 89/95 (94%) for the Test 1, Test 2, and control groups, respectively. The relatively higher discontinuation rate in the Test 2 arm was partially driven by lens-related reasons, including lens appearance and difficulty adapting. This was less evident in the Test 1 arm, where a majority of discontinuations were unrelated to study lenses (Figure 13).

**Subject Disposition**

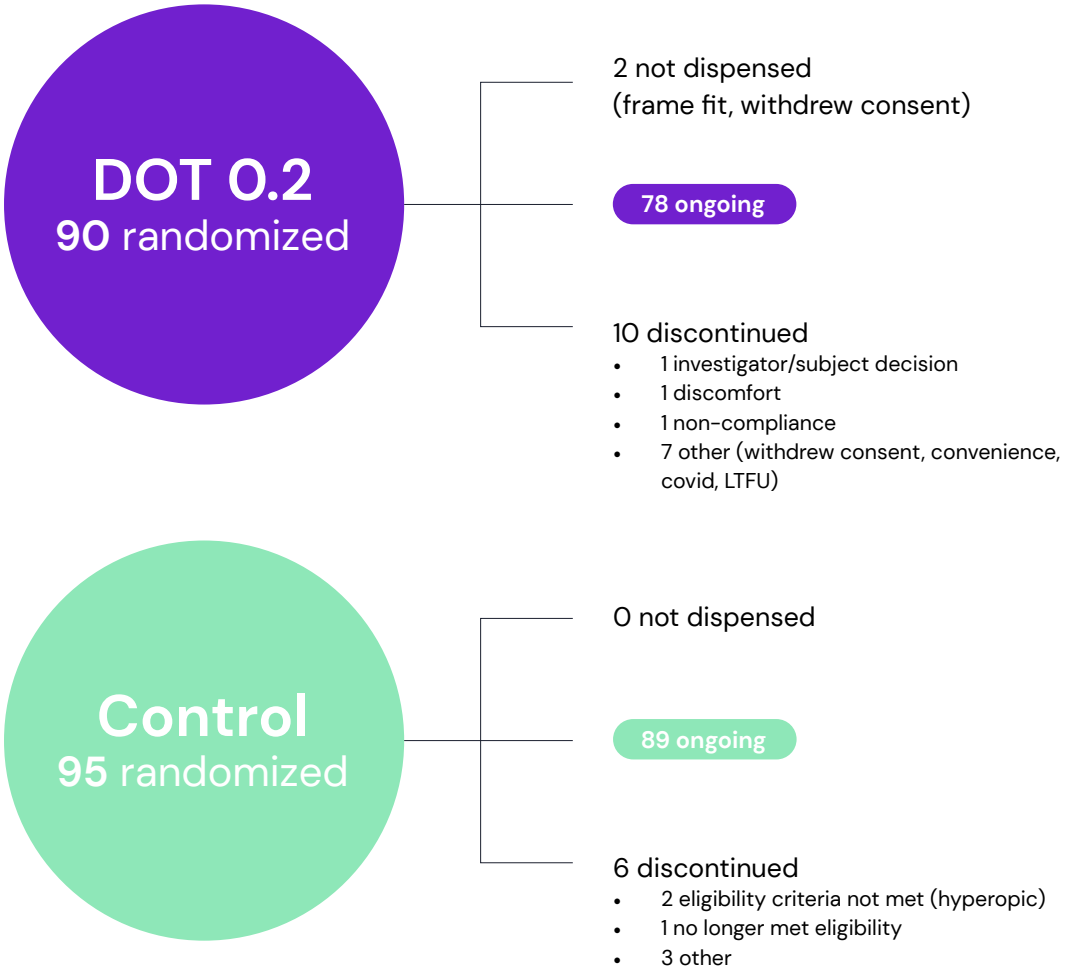



*Figure 13. Participant disposition.*

After 2 years, **89%** of the children were successfully wearing DOT 0.2 spectacle lenses and remained in the clinical study.[46]

## 5.3 Subject Baseline Characteristics

Of the 256 eligible and dispensed subjects, 58% were female. The mean age at baseline was 8.1 years (SD ± 1.2). The age range was 6 to 10 years. The study population mostly consisted of White participants, followed by Black or African American and east Asian participants, reflecting the demographics in North America – unlike many studies in which most participants are Asian.

Randomisation was stratified for age and baseline myopia. The baseline characteristics of subjects were comparable between the test and control groups (Table 1).

**Table 1. Baseline subject characteristics by lens group.**

| | | Control (n=93) | Test 1 (n=88) |
|---|---|---|---|
| **Age (Years)** | Mean (SD) | 8.2 (1.16) | 8.0 (1.17) |
| | Range | 6 to 10 | 6 to 10 |
| **Axial Length (mm)** | Mean (SD) | 24.03 (0.78) | 24.09 (0.82) |
| | Range | 22.13 to 25.72 | 22.03 to 26.25 |
| **Cycloplegic Spherical equivalent refractive error (SER, D)** | Mean (SD) | -1.95 (1.02) | -2.00 (0.93) |
| | Range | -4.94 to -0.38 | -4.52 to -0.19 |

| | | |
|---|---|---|
| Female, n (%) | 54 (58.1%) | 49 (55.7%) |

| Race* n (%) | Control (n=93) | Test 1 (n=88) |
|---|---|---|
| White | 71 (76.3) | 64 (72.7) |
| Black or African American | 17 (18.3) | 19 (21.6) |
| American Indian or Alaska Native | 2 (2.2) | 2 (2.3) |
| Asian Indian | 2 (2.2) | 1 (1.1) |
| Chinese | 3 (3.2) | 2 (2.3) |
| Filipino | 3 (3.2) | 2 (2.3) |
| Japanese | 1 (1.1) | 0 (0) |
| Other | 0 (0) | 1 (1.1) |

**Proportions may not sum to 100% as subjects selecting more than one race will be counted multiple times.*

## 5.4 Myopia Progression

DOT 0.2 spectacle lenses significantly reduced both axial length and cycloplegic SER progression compared to the control lenses. The proportion of children whose myopia progressed by less than 0.25 D during the 24 months was significantly greater among children wearing DOT 0.2 than among children wearing the control spectacle lens (Figure 14). At 12 months, myopic progression was limited to <0.25 D for 65% of children wearing DOT 0.2 and only 23% of children wearing the control. At 24 months, myopic progression was limited to <0.25 D and <0.50 D for 41% and 56% of children wearing DOT 0.2 respectively and 17% and 28% of children wearing the control respectively.

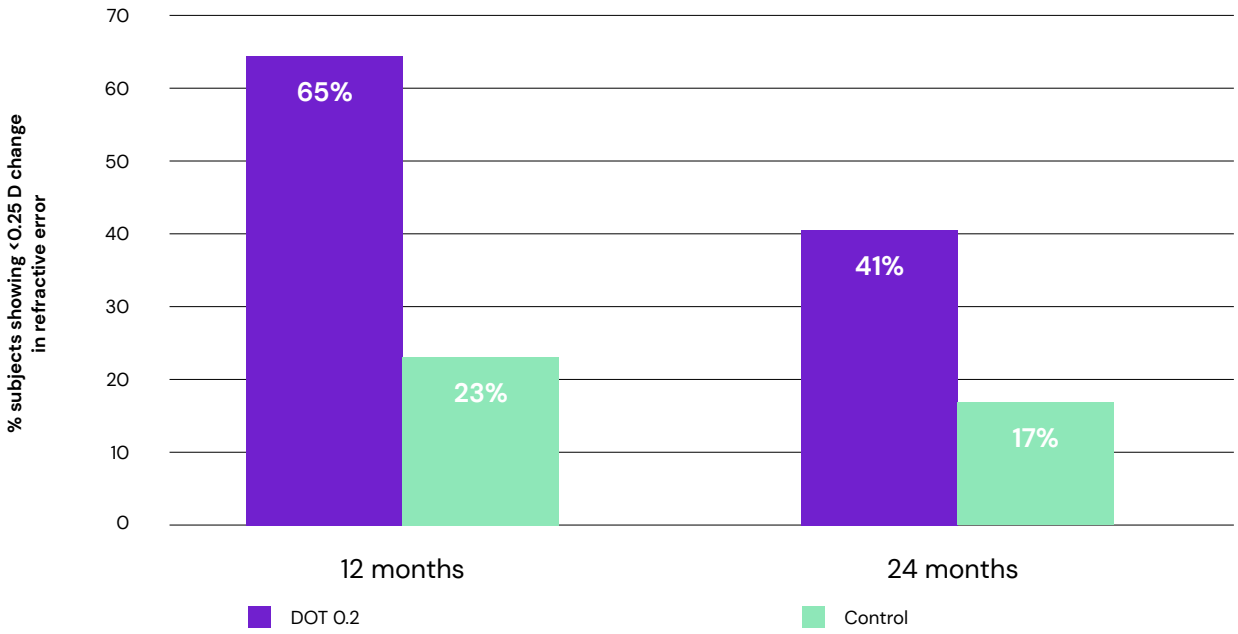



*Figure 14. Proportion of children in the DOT 0.2 and Control group who experienced less than a 0.25 D myopic shift in refraction at 12 months and 24 months.*

## 5.4.1 Full-Time Wearers

The effectiveness of DOT 0.2 is particularly apparent when analyzing those children who were compliant with wearing their glasses for near-vision activities (Figure 15). Unlike contact lenses, spectacles can be easily removed and replaced, allowing for more flexible wear behavior. Nonetheless, most participants reported that, for most of the study, they wore their lenses for at least 10 hours per day. These full-time wearers of DOT 0.2 showed significantly less progression of SER and less axial elongation than those wearing the control lenses. At 24 months, children who used their DOT 0.2 spectacles for near work showed 0.52 D (59%) and 0.21 mm (38%) less myopic progression than full-time wearers in the control group.

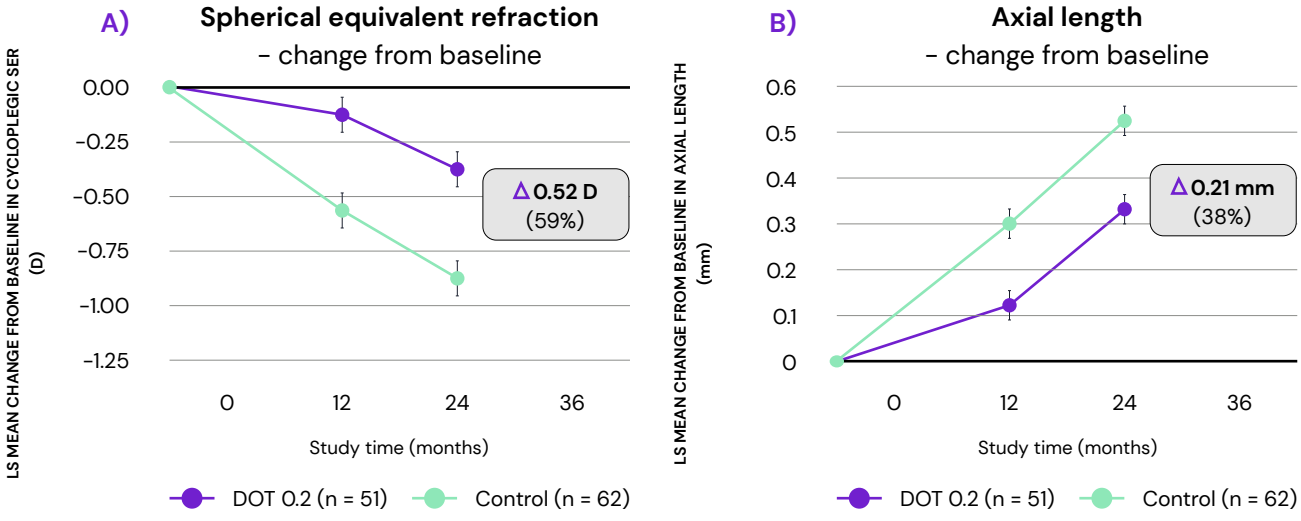



*Figure 15. Least square mean changes from baseline in A) cycloplegic spherical equivalent refraction (D) and B) axial length (mm; right) at 12 and 24-month visits among full-time wearers in the Test 1 (DOT 0.2; n=51) and control groups (n=62). Error bars represent standard error.*

## 5.4.2 Correcting Axial Length Changes for Physiological Eye Growth

Childhood myopic eye axial elongation may consist of a physiological component (observed even in persistent emmetropic eyes due to eye growth in co-ordination with body growth) and a myopic element that causes a myopic shift in refractive error.[51] Physiological eye growth is most rapid in children under 10 years old.[52] Age-matched emmetropic eye growth (considered physiological eye growth) can be subtracted from total myopic eye growth to isolate the myopic or pathological component of eye growth in an age-independent manner. Subtracting age-matched emmetropic eye growth from the axial length measurements of full-time lens wearers in the CYPRESS study produces an estimated slowing of 83% at 24 months for those children wearing DOT 0.2 lenses compared to control.

## 5.4.3 Younger Population (6–7 Years Old)

DOT 0.2 was especially effective for children who entered the study at a young age (Figure 16). The planned subgroup analysis of children aged 6 to 7 years at baseline showed that these younger wearers of DOT 0.2 had significantly less progression of cycloplegic SER and less axial elongation than the control lenses. For this age group, myopic progression at 24 months was 0.77 D and 0.27 mm less in the DOT 0.2 group than in the control group.

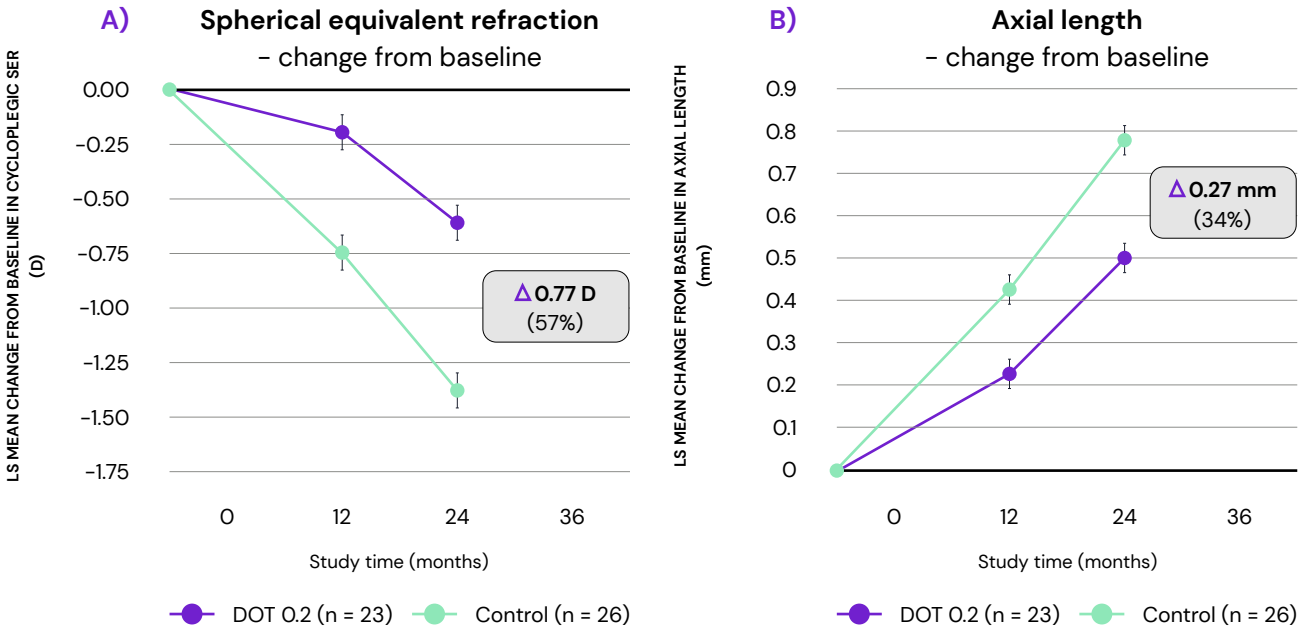



*Figure 16. Least square mean changes from baseline in A) cycloplegic spherical equivalent refraction (D) and B) axial length (mm) at 12 and 24-month visits among 6–7-year-old wearers in the Test 1 (DOT 0.2; n=23) and control groups (n=26). Error bars represent standard error.*

## 5.5 Visual Performance

Visual performance with the DOT 0.2 lens was excellent and similar to that with the single vision control lens. For both DOT 0.2 and Control lenses, high contrast visual acuity was 0.00 logMAR (20/20) or better at each study visit over 2 years. This is consistent with participant responses to a question about the quality of their vision, with 8/10 children wearing DOT 0.2 lenses reporting very clear distance and near vision.

## 5.6 Visual Artifacts

At the baseline and follow-up visits, the children were asked how much they noticed three types of visual disturbance: glare, halos, and hazy vision. At the baseline visit, subjects answered this question referencing their habitual spectacles.

The experience of glare and hazy vision was similar between the DOT 0.2 and Control groups and remained stable across 24 months. As expected, based on the light scattering features, slightly high reporting of halos was evident in the DOT 0.2 group, however average severity was low (graded 0.5 by DOT 0.2 lens wearers and 0.3 by Control lens wearers, on a 0 to 3 scale where 1 = mild, 2 = moderate and 3 = severe).

There were no adverse events in the study relating to visual symptoms. Overall satisfaction was high with DOT 0.2, similar to subjects' habitual spectacles and the control spectacles used in the study. For most subjects, subjective responses indicated no evidence of issues with tolerability or function with DOT 0.2 lenses.

## 5.7 Safety

As expected, the spectacle lenses demonstrated excellent overall safety. Additionally, neither headache nor visual discomfort were reported with the DOT lenses.

### 5.7.1 Adverse Events

Results from the CYPRESS clinical trial demonstrate the safety of the DOT spectacle lens (Table 2). The frequency of adverse events was low and similar between groups. Two non-ocular adverse events were classified as device-related: one participant experiencing three cases of headaches in the Control group, and one case of skin irritation from a spectacle nose pad (Test 1 subject). During the 24 months of follow-up among the 163 subjects randomized to the DOT lenses, there were no spectacle lens-related ocular adverse events.

**Table 2. Adverse events by lens group.**[46]

| CATEGORY | DOT 0.2 (n=88) | | Control (n=95) | |
|---|---|---|---|---|
| | N (%) subiects* | No. of events | N (%) subiects* | No. of events |
| **Any event** | 17 (19.3%) | 28 | 22 (23.2%) | 31 |
| **Related AEs** | 1 (1.1%) | 1 | 1 (1.1%) | 3 |
| **Not Related AEs** | 17 (19.3%) | 27 | 21 (22.1%) | 28 |

**Subject level counts across sub-categories may not add up to the total for the subjects could have events in >1 sub-categories*
*^NONR - Non-ocular not related AE (e.g, common cold, influenza, broken wrist)*

## 5.7.2 Safety for Physical Activities

The study data suggest that DOT lenses are as safe for outdoor activities as other spectacle lenses. The children were typically compliant with wearing their spectacles outside. Responding to a questionnaire, most children agreed that they never had a problem with their glasses when playing outdoors, and this appeared to be similar between DOT 0.2 and control groups. It is important to remember that DOT lenses, just like other standard lenses, should not be used as protective eyewear, especially for high impact sports.

## 5.8 Summary of CYPRESS Findings

DOT 0.2 lenses have shown efficacy in both co-primary endpoints (change in cSER and axial length) in a gold-standard, double-masked, multi-center, randomized controlled clinical trial. Coupled with an excellent safety profile, high tolerability, and good visual performance, DOT lenses are an excellent first choice of intervention for young myopic children.

# 6. CONCLUSION

Contrast management is a revolutionary approach to managing myopia and the result of a theory based on genetic observations. Through the groundbreaking work of Professors Maureen and Jay Neitz, contrast management spectacles are now pioneering a new path to reducing myopia progression from an early age. The CYPRESS study has demonstrated the efficacy of DOT spectacle lenses for slowing myopia progression, especially among the youngest patients, who would typically have the fastest progression. DOT spectacle lenses are the first spectacle lens that have been clinically proven to be safe and effective at reducing myopia progression from 6 years old, in a multi-center clinical trial.

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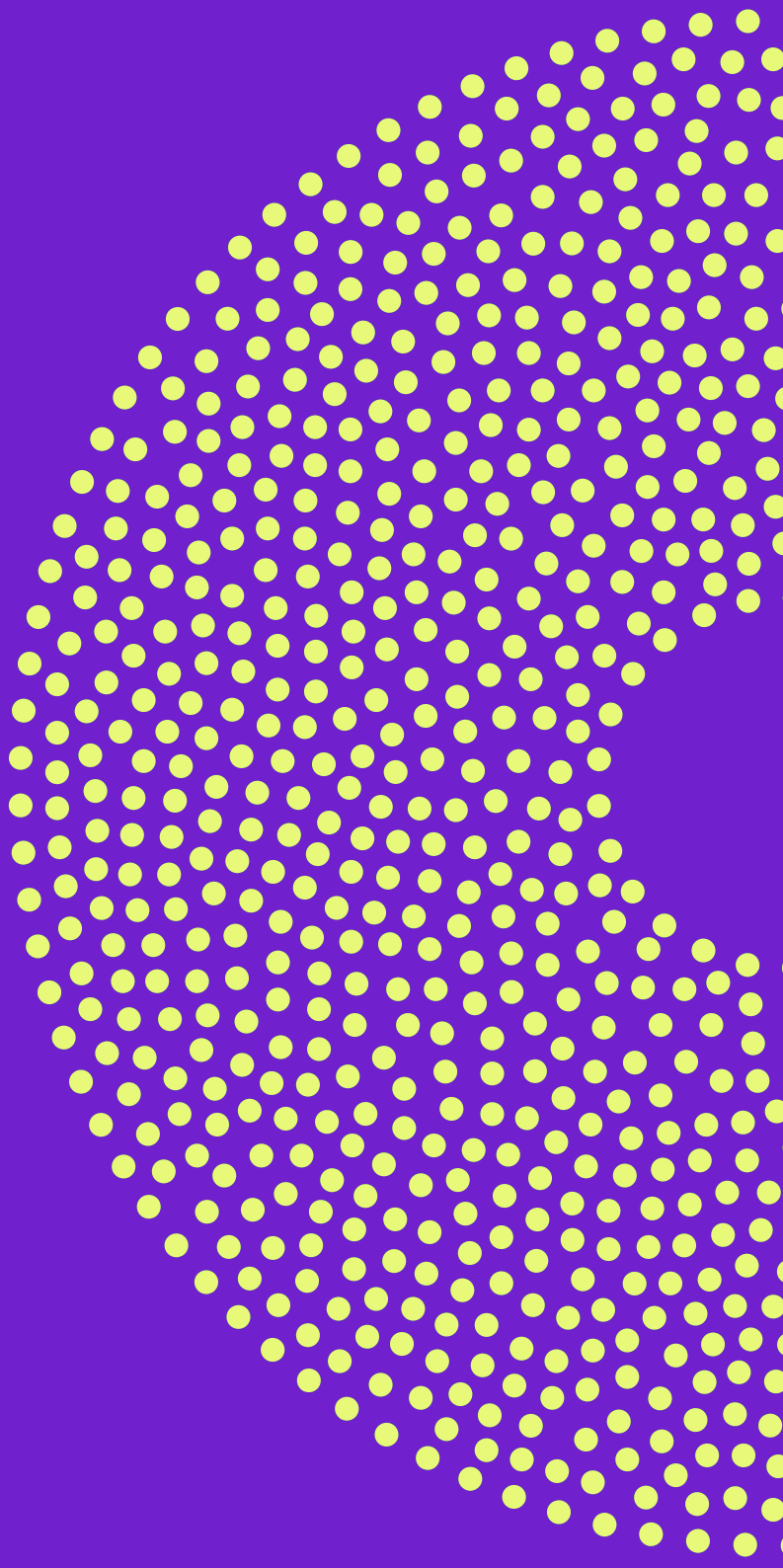


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