APPENDIX

EMERGING THERAPIES

a. Blue light therapy

Outdoor light is typically towards the blue end of the spectrum and there is some evidence that blue light can make axial length shorter and the choroid thicker [1] [2] both of which are thought to be helpful to retarding myopic progression. Clinical trials are now underway to test the longer-term effects of blue-light therapy, using a smartphone inserted into a virtual reality headset (REF: MyopiaX, Dopavision: NCT04967287)

Exposure to ambient light is recognized for its protective effect against the development and progression of myopia. Studies suggest a positive dose-response relationship between the amount of time spent outdoors and the prevention of myopia. Blue light is a part of the visible light spectrum with shorter wavelengths. It is not only emitted by natural sunlight but artificial sources like digital screens (smartphones, computers, tablets). Blue light is commonly associated with digital eye strain, but it is not directly known to cause myopia. Blue light exposure inhibited the effect of hyperopic defocus and resulted in a reduction in axial length in both defocused eyes and non-defocused eyes in an experimental study from India [3]. The short-term exposure to blue light resulted in a significant reduction in axial length and the authors postulated non-chromatic mechanisms such as blue cone-mediated ON-pathway, reduced levels of retinoic acid, role of intrinsically photosensitive retinal ganglion cells (ipRGCs), in-focus/out-of-focus image, and increased depth of focus due to decreased pupillary size to be responsible [4] [5].

Keeping in mind the photosensitive retinal ganglion cells, the blind spots of both eyes of 10 emmetropes and 10 myopes, were stimulated locally for 1-minute with blue flickering light with a 460 nm peak wavelength in a study from Australia[Error! Bookmark not defined.]. Significant choroidal thickening after blue light stimulation occurred in emmetropes but not in myopes as compared to sham and red-light exposure. Hence blue light exposure may have a significant impact on eye growth. However, the impact of artificial blue light on myopia development remains unclear.

b. Emerging spectacle lens technologies

i. Technologies of Competing Defocus

Since ophthalmic lenses seem to be the least invasive option for myopic progression, another spectacle lens was introduced by ZEISS. ZEISS MyoCare technology integrates two advanced lens concepts to slow myopic progression and optimize visual performance actively. The lens design incorporates a central zone for vision correction. Surrounding this central zone is a treatment zone, that includes Cylindrical Annular Refractive Elements, (C.A.R.E). These elements have relatively more positive power compared to the base surface power, are arranged in concentric rings, and are alternated between the clear zones to enhance the performance of the lens. Due to the distinct geometry of the cylindrical elements, light passing through the C.A.R.E. elements do not refract to a single point. Instead, it creates a blended distribution of myopic defocus in front of the retina. Furthermore, ZEISS MyoCare technology features a non-spherical back surface design that incorporates a point-by-point optimization and referred to as ZEISS ClearFocus design. In contrast to a traditional single vision spectacle lens where myopic eyes experience hyperopic defocus due to lens aberrations especially towards the lens periphery, the ClearFocus design of the ZEISS MyoCare lens aims to minimize these aberrations and allow for visual clarity and myopic defocus across all gaze directions.

Whilst it is crucial to provide a sizeable treatment zone to ensure that competing myopic defocus is present across a substantial region of the retina, the size of the central zone is significant for visual performance. Additionally, the strength or the dioptric power of the cylindrical annual refractive elements as well as the proportion of the surface area occupied by these elements are also important for myopia management. Following wearability and visual performance assessments, two design variants ZEISS MyoCare and MyoCare S were selected for efficacy evaluations. ZEISS MyoCare incorporates a 7 mm central zone, while the softer ZEISS MyoCare S incorporates a 9 mm central zone. Furthermore, the nominal power of the cylindrical annual refractive elements for ZEISS MyoCare is +9.2D that translates to a mean relative surface power of +4.6D, whereas with ZEISS MyoCare S, the nominal power is +7.6D and translates to a mean relative surface power of +3.8D.

In both Asia and Europe, multiple trials are currently in progress to assess the safety, efficacy, and subjective performance of ZEISS MyoCare technology through both single-centre and multi-centre randomised clinical trials. In China, approximately 1400 children are enrolled in these trials [6] and in Europe, a multi-centre clinical trial with 300 participants is ongoing [7]. Based on interim data from a prospective clinical trial at Wenzhou University Eye Hospital involving 240 children randomized to ZEISS MyoCare, MyoCare S or single vision spectacles, all children reported adaptation to their lenses within a day. This was regardless of whether they wore test or control lenses. At 3 months of lens wear (first visit after dispensing), 97.5% or more of children wearing MyoCare or MyoCare S reported their vision for distance, near, during sporting activities, perception of moving objects and going up and down stairs to be very good (on a scale of 1-4 where 1 = very poor and 4 = very good). Additionally, an interim analysis was conducted on the 12-month efficacy of these lenses. The performance was benchmarked against the eye growth of an emmetropic eye using the "emmetropic progression ratio". With this metric, a value of 100% indicates eye growth like that of an emmetropic eye, while 0% indicates eye growth like that of a myopic eye wearing single vision spectacle lens. Both ZEISS MyoCare and MyoCare S slowed eye growth across all ages assessed. In younger children aged 7 to 9 years, ZEISS MyoCare demonstrated an emmetropic progression ratio of 63% and in older children aged 10 to 12 years ZEISS MyoCare S demonstrated an emmetropic progression ratio of 86%.

**The results published in the article by Liu et al [8] titled "One-year myopia control efficacy of cylindrical annular refractive element spectacle lenses" and published in Acta Ophthalmologica, 101(6), 2023 do not refer to or reflect the performance of ZEISS MyoCare or MyoCare S. The design used in the published article refers to an earlier prototype that served as a starting point for optimization [9].

ii.Shamir myopia control lenses (Focus flow technology) Focusflow™

Shamir myopia control lens implements the defocus in a unique back surface design. Rather than a concentric design, the defocus is in a U-shape, creating a clear central vertical canal and a continuous defocus toward the periphery. The vertical canal is symmetrically located around the center point in the horizontal meridian, with a width of 10 mm. In the vertical meridian, the canal extends up to the lens periphery, while it measures 10 mm inferiorly. The relative positive power gradually increases from approximately 0.5 D at the canal's edge to 3.00 D at 17.5 mm from the center horizontally and

1.50 D at 16 mm from the center in the inferior meridian. Depending on the frame size, the relative positive power at the inferior rim ranges from 1.00 to 1.50D. Implementing a gradual defocus in the lens aims at inhibiting axial elongation. Additionally, a central vertical canal provides the patient's optimal prescription and is kept distortion-free. A controlled randomized, double- masked trial was conducted to evaluate the effectiveness of the Shamir myopia control spectacle lens vs the control group wearing a standard single-vision lens (Shamir Aspheric Ophthalmic Lenses (Optimee©) for Myopic Control Clinical Trial) [10]. The trial included 126 participants,aged between 6 and 13 years, with cycloplegic objective spherical equivalent refractive error ranging from –0.50 D to –6.00 D in at least 1 eye, and astigmatism not exceeding –1.50 D. At 12 months, the adjusted mean progression in axial length and Spherical equivalent were 0.32 mm and 0.64 D in the control group and 0.21 mm and 0.48 D in the Shamir lens group, respectively. A statistically significant ($p < .05$) effect was found in axial length adjusted mean progression but not in spherical equivalent adjusted mean progression, however in children aged 6-10 years and in children with two myopic parents, more statistically significant differences were obtained. Overall, the lenses slowed axial progression by 35% and spherical error progression of 25% as compared to the control group. The technology has some ergonomic advantages minimizing stress on the child's head, neck, and upper body muscles.

c. Emerging Contact Lens Technology

i.Concentric annular zones with noncoaxial relative plus power (RingBoost™ technology)

In contrast to the typical coaxial dual-focus or multifocal soft contact lens designs, the non-coaxial ring focus contact lens generates a ring focus that falls in front of the retina but off the line of sight, enabling a larger treatment zone and the incorporation of a higher add power while maintaining comparable visual performance. A multisite randomised clinical trial compared 2 prototypes of RingBoost™ technology with dual focus contact lens and single vision contact lens. Both prototypes consist of two concentric, annular treatment zones of +7.00 D non-coaxial plus power with the EE (enhance efficiency) design having the plus power positioned closer to centration and featuring an additional +10 D coaxial treatment zone for greater efficacy without compromising visual acuity. At 6 months, the EE lens (commercialised as Johnson and Johnson Vision ACUVUE Abiliti™) produced the most significant effect with a mean difference in axial length elongation being 0.11mm compared with the control [11].

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