ZEISS MyoCare

Summary of clinical data on the effectiveness and safety of the ZEISS MyoCare portfolio.

The first age-related myopia management lens solution by ZEISS.

ZEISS

Seeing beyond

Clinical data on the effectiveness and safety of ZEISS MyoCare lenses

ZEISS MyoCare lenses, a new category of myopia management lenses by ZEISS, are currently undergoing clinical testing in multiple single- and multi-center clinical trials together with leading medical institutes and hospitals across China and in Europe for a comprehensive, representative, and robust evaluation of their safety and effectiveness. The 12-months interim results of the first randomized controlled clinical trial show that ZEISS MyoCare lenses can help to effectively slow down myopia progression in children aged 7 – 12 years.

Randomized controlled clinical trials – the gold standard to confirm safety and effectiveness

The gold standard for the collection of clinical data to confirm the safety and effectiveness of a myopia management intervention are prospective, double-blind, randomized controlled clinical trials (RCTs). Two design variants, ZEISS MyoCare and ZEISS MyoCare S, representing a harder and a softer version of the MyoCare® lens design, are currently being tested in on-going single- and multi-center clinical trials with leading medical institutes and hospitals across China and in Europe to ensure a comprehensive, representative, and robust evaluation of their effectiveness and safety (see Table 1 for an overview of clinical trial registries). These trials are assessing the cumulative absolute reduction in progression of the spherical equivalent refractive error and axial length over the duration of the clinical trial as relevant measure to evaluate their effectiveness for myopia progression control (see Highlight Box Evaluating effect size in myopia control trials: Every diopter matters).

Within an RCT, the study participants are randomly allocated to either a treatment group, wearing in this case one of the two design variants of ZEISS MyoCare lenses, or the control group, wearing ZEISS Single Vision lenses as the current standard of care for myopia correction, for two years, with regular follow ups along the way (Figure 1). Comparing the average change or progression in spherical equivalent refractive error and shows the effectiveness of the myopia intervention. Research community standards ask for 2-year data to establish a myopia control effect.[1] Up to this point, all insights on clinical effectiveness should be considered as preliminary and evaluated within the context of the respective study duration. As compliance highly matters for myopia management, adaptability, wearability, and vision-related quality of life are important secondary objectives.

Lead Investigator of Clinical Trial	Clinical Trial Registration Number
Wenzhou Medical University Eye Hospital, CN	ChiCTR2100054139
Tianjin Medical University Eye Hospital, CN	NCT05288335
Complutense University of Madrid, ES & ISEC Lisboa, PT	EudraCT Number 2022-001696-14
Zhongshan University, CN	NCT05818033
Wenzhou Medical University Eye Hospital, CN	ChiCTR2200065011

Table 1. Overview of clinical trials.

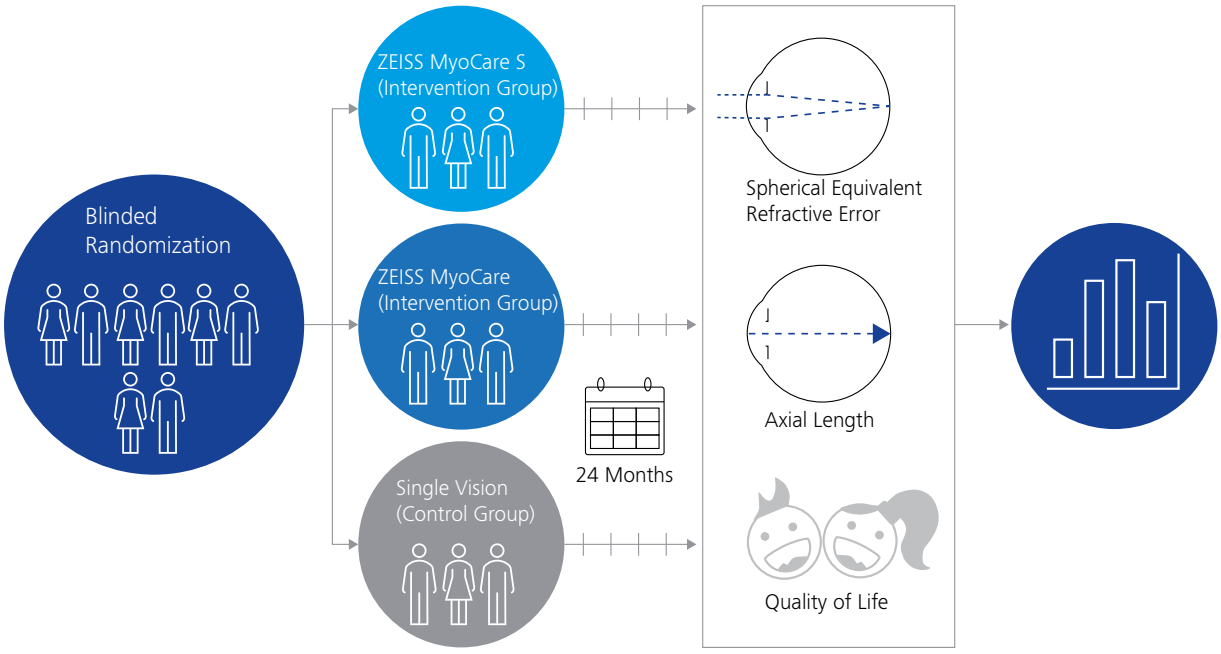


Figure 1. Overview of a randomized controlled clinical trial (RCT) to assess the safety and effectiveness of ZEISS MyoCare and ZEISS MyoCare S lenses to manage myopia progression.

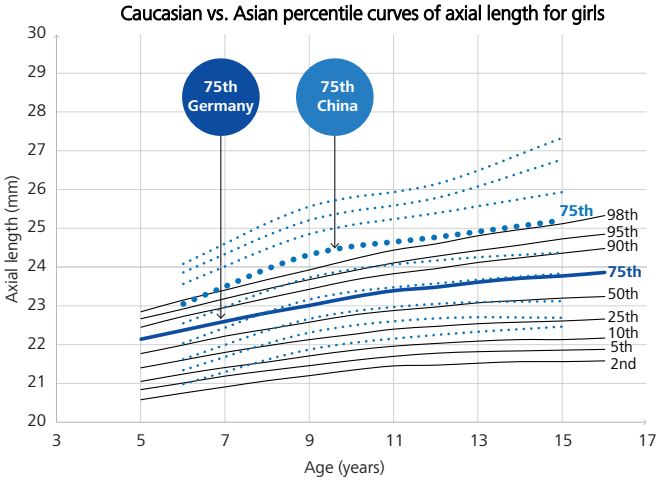
Emmetropic progression - a target for myopia management

To determine the success of any myopia intervention, it is important to consider the exact target of myopia progression management. What management effect is needed to be considered clinically meaningful? Is it the goal to stop all eye growth?

Physiological growth

The first years of a child's life are marked by growth and development with an innate drive to explore, learn, and evolve. On the one hand, children grow physically. On the other hand, they also grow emotionally, as they learn to communicate, think, socialize, and interact with the world around them. Developmental milestones are thereby important markers from infancy on into childhood that help determine if a child is within the range of normal development.[2] Rolling over, crawling, walking, and talking are all considered milestones. All children develop differently, with individual variations in exact timing when the one or other milestone is reached. But overall, there is a normal age range in which children typically reach a specific milestone. The way a child's development progresses in the early years of life can determine an individual's lifelong development. Regular checkups and screenings starting already at young age improve early detection and allow for faster intervention if a child is not developing as expected, which in turn leads to better intervention outcomes. The role of the primary health care providers is therefore critical in recognizing normal and identifying out-of-normal development. This also applies to Optometry and Ophthalmology when it comes to vision development. Like children must learn to walk and talk, they also need to learn how to see. This includes developing basic abilities like visual acuity, accommodation, color vision, depth perception, and how visual information must be processed by the brain to understand the world around them.

As children grow, their eyes grow with them, which can best be seen in the drastic increase in axial length, until the eye is fully developed at around 20 years of age.



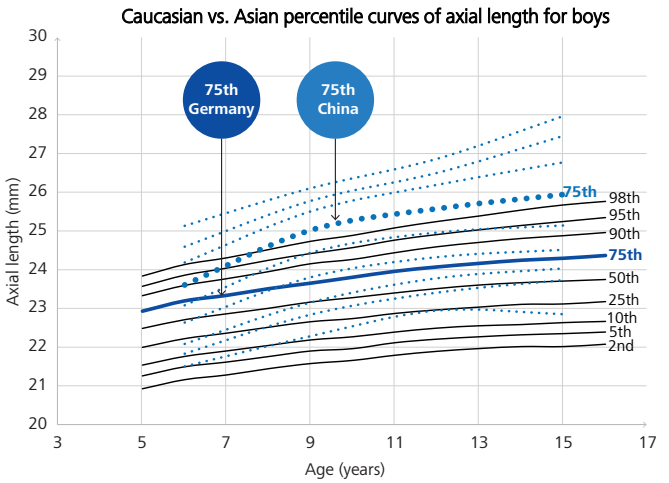


Figure 2. Growth charts with percentile curves of axial length. The solid lines show data from Caucasian children, the dashed lines show data from Chinese children, separated for girls (upper panel) and boys (lower panel). An axial length exceeding the 75th percentile indicates a high risk for the development of high myopia in Caucasian children. Adapted from Truckenbrod et al. 2021.[3]

Growth charts are essential tools typically applied in pediatric practices to track the growth of infants, children, and adolescents. These growth charts typically illustrate with percentile curves the distribution of selected body measures within a population, like in Figure 2 for eye length in German and Chinese children. Knowledge of age-specific normative data on ocular dimensions and growth patterns makes it possible to monitor a child's growth and identify children with out-of-normal development.

As the eyes grow, that means as eye length gradually increases from about 16 to 17 mm in newborns to around 22 to 25 mm on average in young adults,[4], [5] the emmetropization process takes care that the eye's optical power actively matches the axial length so that the unaccommodated eye is focused on far distance. Most of the eye growth thereby occurs in the very first months to the first years of life. Afterwards, the corneal curvature is quite stable while axial elongation is balanced by a flattening of the crystalline lens. When this complicated balancing process is disturbed, mismatches between the ocular components will result in ametropia. Typically, if axial length grows too quickly, the compensation by flattening of the crystalline lens is lost, and the child is developing myopia.

Interestingly, a comparison of the average annual progression of axial length by age in emmetropic children shows that children from different regions of the world, Europe, the United States, and Asia, all have very comparable rates of ocular growth with negligible variations in axial elongation between the age of 6 and 16 years (Figure 3). The comparison is based on 1200 datasets from emmetropic children participating in the LIFEChild study in Germany (3), their validation by Kaymak et al. (2021),[6] 194 datasets of emmetropic children from the US, and 369 emmetropic children from Singapore as published in Chamberlain et al. 2021.[7] Across all regions, the average rate

of eye growth is highest in young children and then declines naturally as children get older. Several studies have shown that before age 10, eye growth is faster, with an average annual growth of 0.12 mm ± 0.24 mm observed in Asian 8-year-old emmetropes,[8] 0.19 mm ± 0.05 mm (range of 0.12 to 0.29 mm) in European 9-year-old emmetropes,[9] and 0.16 mm in 6- to 9-year-olds who remained emmetropic in the large-scale Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study that included emmetropic children of Asian, black, Hispanic, and white ethnicity.[10] In summary, and as can be seen in Figure 3, before age 10, emmetropizing children typically show an eye growth in the range of 0.1 to 0.2 mm per year. Above age 10, the rate of axial elongation slows down, as exemplified in the CLEERE study cohort with an average eye growth of 0.08 mm per year in 9- to 12-year-olds, and 0.02 mm in 11- to 14-year-olds.[10] Fledelius et al. (2014) found a similar average rate of 0.1 mm eye growth per year until age 13 in European emmetropic children, with evidence for a small amount of continued growth thereafter.[11] At age 16, eye growth and axial length typically reaches stabilization.[12] Notably, males typically display longer eyes of about 0.5 mm than females, even though refractive error and axial growth rates are comparable(12).

Overall, this cross-sectional analysis shows that the physiological eye growth at a given age to develop emmetropia, and not end up myopic or hyperopic, seems to be quite stable around the world. Based on this observation, a physiological emmetropic growth curve can be established with an average annual progression or increase in axial length that is normal for a certain age in emmetropic children (Figure 3).

Evaluating treatment success

The physiological emmetropic growth curve defines a target for myopia management: to slow down excessive myopia progression to the age-normal physiological growth that is observed in emmetropic children.

This is also recommended by Dr. Kate Gifford, a clinical optometrist, researcher, peer educator and professional leader from Brisbane, Australia, and co-founder of myopiaprofile.com. According to her clinical expertise, success of myopia control should be measured by how much progression can be slowed down to approach the typical progression in emmetropic children of the same age (13). Hence, a successful intervention for a child under the age of 10 years, who would typically show a myopia progression greater than 0.3 mm per year without treatment, would have an ideal outcome if annual progression can be slowed down to less than 0.3 mm. It would be an excellent outcome of a myopia intervention if annual progression can be slowed down to 0.1 to 0.2 mm, the rate that emmetropes of the same age progress per year. In children older than 10 years, who typically show an average axial elongation of 0.2 mm without treatment, an ideal outcome of myopia intervention would be if progression can be slowed to less than the untreated average. Slowing the progression to less than 0.1 mm per year constitutes an excellent outcome for pre-teens and teenagers, as emmetropes of the same age show on average this rate of axial elongation.

The importance of considering the age of the child when evaluating treatment success was also highlighted by Dr. Fuensanta Vera-Diaz in "A practical guide to managing children with myopia" recently published by the World Council of Optometry.[14] As the expected, physiological progression changes with age, with older children progressing slower than younger children, anticipated intervention goals differ depending on the age of the child.

Emmetropic progression ratio

Taking the age-specific emmetropic growth curve as a treatment reference, the emmetropic progression ratio can be applied as a measure to indicate how close children with an intervention are approaching physiological emmetropic growth in contrast to myopic growth without an appropriate myopia intervention:

Emmetropic progression (Ep) ratio =

$$1 - \left(\frac{\text{Progression with intervention - physiological } \mathbf{Ep}}{\text{Progression without intervention - physiological } \mathbf{Ep}}\right) \times 100\%$$

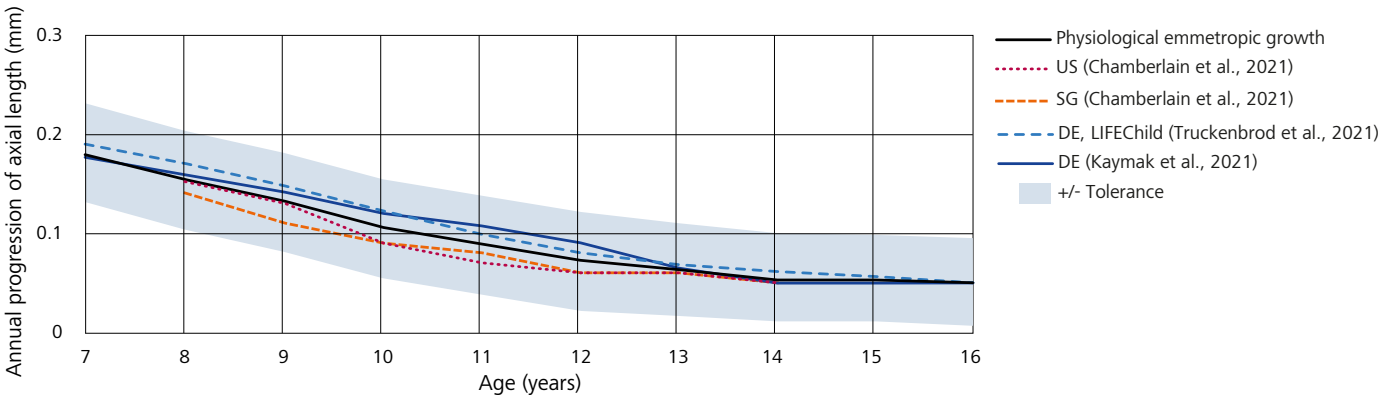


Figure 3. Physiological emmetropic growth curve defined as the average annual progression of axial length by age in emmetropic children from Germany, the US, and Singapore. The grey shaded area around the physiological emmetropic growth curve shows a tolerance range +/- 0.05 mm, which is derived from a recent study investigating the stabilization of axial length progression[12] and also reflects the typical standard error in repeated measurements of axial lengths in the same subject within an RCT.

This relation is displayed in Figure 4. The black curve represents the emmetropic physiological growth curve as defined above. The red curve, labelled "myopic growth", shows an example for the rate of eye growth per year in untreated myopic children at age 7 to 12, i.e., myopic children who only receive myopia correction but no myopia intervention. The green curve, labelled "with myopia management", shows an example of eye growth per year in myopic children aged 7 to 12 receiving an appropriate myopia management intervention. As the physiological growth is known to naturally decline with increasing age, the emmetropic progression ratio is specific for age. As shown in Figure 4, at each specific age, a value that lies on the red curve represents an emmetropic progression ratio of 0%, i.e., myopic growth, and a value that lies on the black curve represents an emmetropic progression ratio of 100%, i.e., physiological emmetropic growth. Everything in between shows the effect of the myopia management intervention to slow down the rate of eye growth per year to come closer to the physiological emmetropic progression in contrast to untreated myopic progression without the intervention.

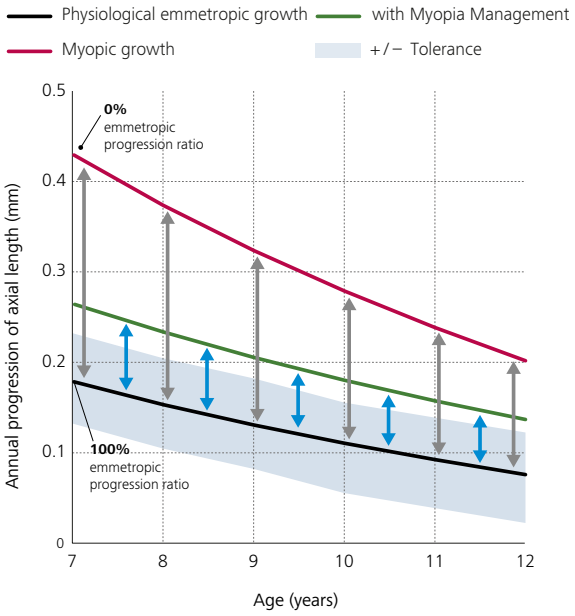


Figure 4. The emmetropic progression ratio indicates how close annual progression with a myopia intervention comes to the physiological emmetropic progression in contrast to untreated myopic progression.

Randomized controlled clinical trial on ZEISS MyoCare lenses at Wenzhou University Eye Hospital WMU

Following the cooperation in lens design ideation and prototype testing, the first of the on-going clinical trials with ZEISS MyoCare lenses takes place at the Wenzhou Medical University Eye Hospital WMU. The primary objective is thereby to investigate the effect of MyoCare® lenses on the progression of the axial length, and the spherical refractive error (SER), assessed by cycloplegic autorefraction, of the juvenile myopic eye. As secondary objective, the adaptability, wearability, and vision-related quality of life will be assessed in children when wearing MyoCare® lenses.

Starting in October 2021, children aged 6 to 13 were enrolled to participate in the clinical trial if they met the following inclusion criteria and gave written informed consent for voluntary participation: objective cycloplegic spherical equivalent refractive error (SER) of -0.75 D to -5.00 D; astigmatism ≤ 1.50 D and a refractive error of ≤ 1.50 D in both eyes after equivalent spherical lenses; and best corrected visual acuity of ≥ 1.0 in both eyes. Exclusion criteria comprised a history of ocular trauma or intraocular surgery; clinically significant slit lamp findings; fundus examination results ≥ grade 2; IOP abnormalities (IOP <10 mmHg or IOP >21 mmHg or bilateral IOP difference ≥5 mmHg); concurrent ocular diseases, such as glaucoma, cataract, fundus disease, ocular tumors, ocular trauma, dominant strabismus, or various inflammatory conditions (for instance uveitis); and any ocular pathology that affects visual function; immunocompromised systemic diseases (e.g., acute or chronic sinusitis, diabetes, Down syndrome, rheumatoid arthritis, psychiatric diseases, or other diseases that the investigator considers unsuitable for wearing spectacle lenses); previous participation in drug clinical trials or any clinical trials on myopia control within three months; patients who meet the inclusion criteria in only one eye; previous or current usage of rigid gas-permeable contact lenses, multifocal lenses, specifically designed myopia control lenses, atropine medication, etc.; and dominant strabismus.

The enrolled study participants were randomly assigned to one of three groups using a randomized block design, either one of two test groups wearing ZEISS MyoCare or ZEISS MyoCare S as myopia intervention, or the control group wearing ZEISS Single Vision lenses for myopia correction only. The clinical trial applies a double-blind design, i.e., neither the investigator nor the study participants know which group an individual was allocated to until data analysis is completed. All study participants are invited for regular follow-up visits every 6 months over a time of 2 years, with a planned interim analysis after 1 year. At each of the follow-up visits, as primary endpoints, objective optometry after cycloplegia and axial length with and without cycloplegia is recorded. Additional measures taken are best corrected visual acuity; uncorrected visual acuity; objective/subjective optometry including corneal curvature; visual function in both eyes; slit lamp examinations; choroidal thickness; frame position, and lens conditions were checked, and it is determined whether lenses need to be changed. Moreover, the occurrence of adverse or serious adverse events is recorded, if applicable.

Figure 5 shows a flow chart summarizing the enrollment, allocation, and follow-ups of the clinical trial. Two hundred forty children were enrolled to the study and 80 children each were randomized to the intervention groups and the control group.

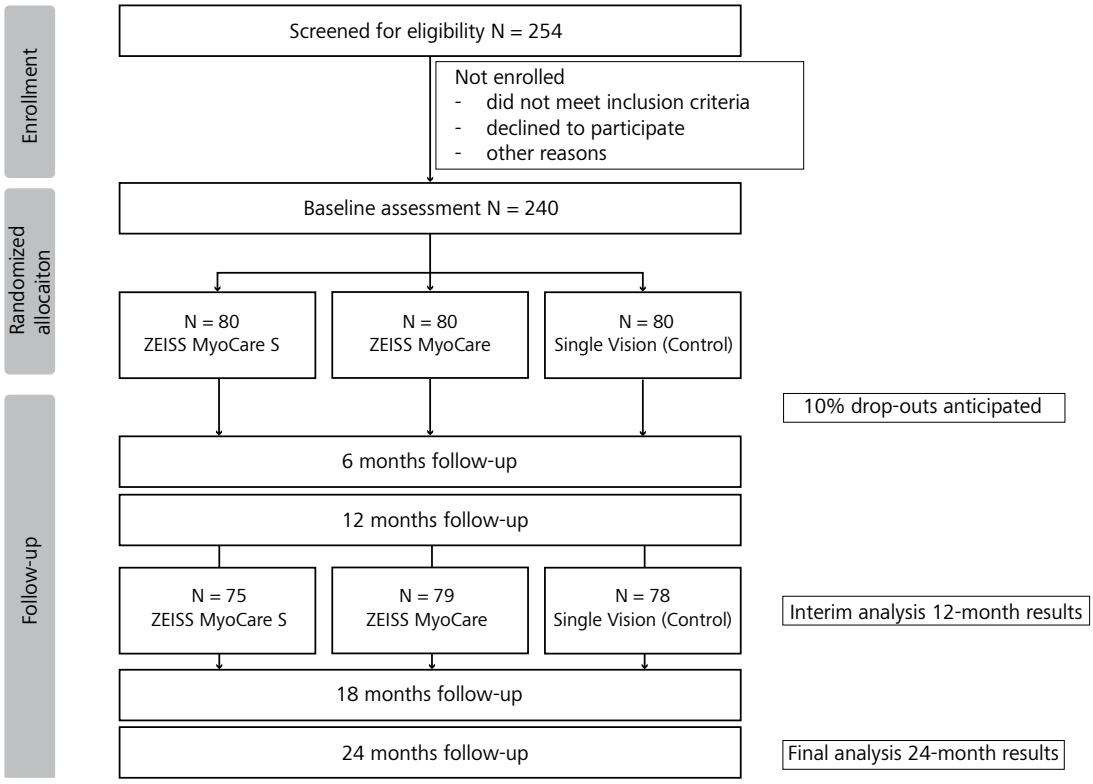


Figure 5. Flow chart of enrollment, allocation, and follow-up in the ZEISS MyoCare RCT lead by Wenzhou Medical University Hospital WMU.

Interim analysis of 12-months results

Study population

Table 2 summarizes the baseline characteristics of the study participants that completed the 12-months follow-up. Two hundred and thirty-two children successfully completed the first year of the clinical trial, 78 (97.5 %) children that were allocated to the control group, 75 (94 %) allocated to the ZEISS MyoCare S group, and 79 (99 %) allocated to the ZEISS MyoCare group. None of the baseline characteristics differed significantly between the three groups at time of enrollment and group allocation. After accounting for children that dropped out of the study and only considering those children that participated at the 12-months follow-up, mean age, gender distribution, and axial length did not differ significantly between the three groups at baseline. Despite the initial randomization, the group of children wearing ZEISS MyoCare S who participated at the 12-months follow-up were on average slightly less myopic, with a significant difference compared to the control group. The difference in cycloplegic spherical equivalent refractive error at baseline between the control group and the ZEISS MyoCare group, as well as between the ZEISS MyoCare S and the ZEISS MyoCare group were not statistically significant. Children aged between 6 and 13 years were enrolled to participate in the study. However, only four children aged 6 years and two children aged 13 years completed the 12-months follow-up, with an uneven distribution across the three groups. Therefore, all statistical analysis in the following were based on the study cohort of 7- to 12-year-olds, and only confirmed in the complete study cohort of 6- to 13-year-olds.
#

	Untreated control group (N = 78)	ZEISS MyoCare S (N = 75)	ZEISS MyoCare (N = 79)
Age (years) at enrollment	9.59 ± 1.54	9.15 ± 1.51	9.44 ± 1.48
Age range (years)	6 - 12	6 - 13	6 - 12
Gender			
Male, N (%)	36 (46.2	26 (34.7)	43 (54.4)
Female, N (%)	42 (53.8)	49 (65.3)	36 (45.6)
Cycloplegic SER (D)	-2.43 ± 0.97	-2.11 ± 0.93	-2.32 ± 0.82
Axial length (mm)	24.6 ± 0.84	24.4 ± 0.88	24.6 ± 0.80
Lens wearing time (h)	12.5 ± 2.5	12.7 ± 2.1	12.7 ± 2.2

Over all groups, children showed good compliance and wore the lenses full time. The mean daily lens-wearing time for ZEISS MyoCare S and for ZEISS MyoCare was 12.7 hours on average, and 12.5 hours on average for ZEISS Single Vision lenses, with no significant differences between the three groups. Further, there were no significant associations between lens wearing time and age or gender.

Changes in AL and SER

Analysis of variance (ANOVA) on the change in axial length from baseline to 12-months follow-up showed a significant effect of group on axial length progression ($F[2,223] = 6.7$, $p = .001$). A post hoc Tukey test revealed a significant group difference between ZEISS MyoCare and the control group ($p <. 001$), while the group difference between ZEISS MyoCare S and the control group showed a statistical trend ($p < .10$).

Interestingly, follow-up analysis on the absolute treatment effect, i.e., the absolute difference in progression from baseline to 12-months follow-up between the intervention groups and the control group, showed that age significantly influenced the relation between the type of intervention and the observed absolute reduction in axial length progression. The comparison of multiple linear regression models with and without an interaction term by applying Akaike's information criterion (AIC)[15] identified the model with an interaction of intervention (ZEISS MyoCare or ZEISS MyoCare S) and age as best-fitting model to explain the absolute difference in axial length change, with lens wearing time and gender accounted for as additional covariates. Inclusion of additional covariates did not further improve the fit of the linear regression model. The linear regression analysis revealed a significant interaction effect of age and intervention type ($p < .005$), explaining in total 9.3% of the variance in the absolute change of axial length progression (adjusted $R2 = 0.093$, $F[5,144] = 4.04$, $p = .002$). As illustrated in Figure 6, younger children showed a higher absolute reduction in axial length progression when wearing ZEISS MyoCare lenses, while older children showed a higher absolute reduction in axial length progression when wearing ZEISS MyoCare S lenses.

Specifically, children aged between 7 and 9 years, showed an age-weighted average absolute reduction of progression in axial length of 0.14 mm after wearing ZEISS MyoCare for 12 months (Figure xy). Likewise, the absolute progression in SER was reduced by -0.22 D on average, weighted for age, in children aged 7 to 9 years.

Children aged between 10 and 12 years, showed an age-weighted average absolute reduction of progression in axial length of 0.13 mm after wearing ZEISS MyoCare for 12 months (Figure 7). Likewise, the absolute progression in SER was reduced by -0.33 D on average, weighted for age, in children aged 10 to 12 years.

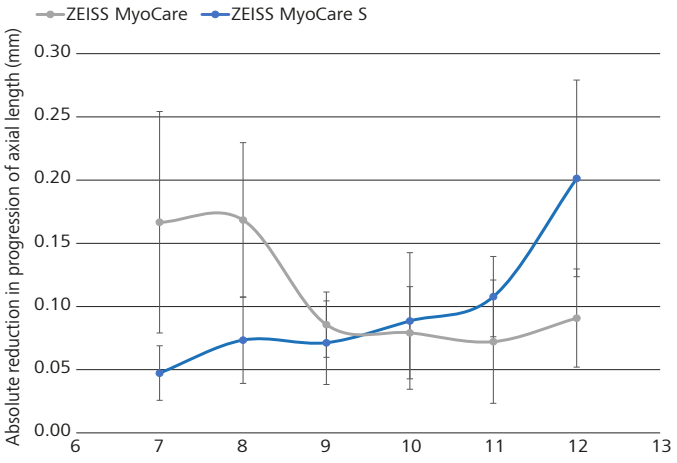
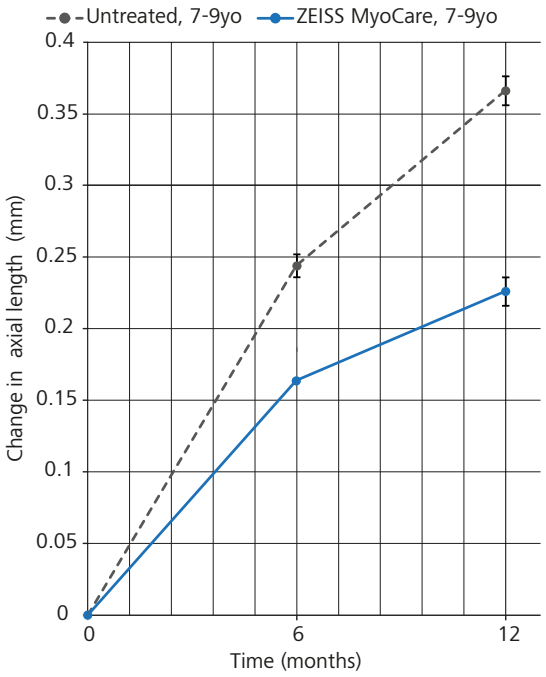
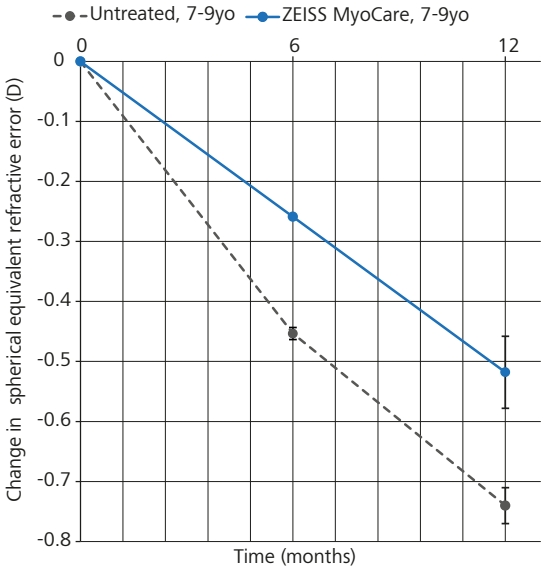


Figure 6. Younger children showed a higher absolute reduction in axial length progression when wearing ZEISS MyoCare lenses, while older children showed a higher absolute reduction in axial length progression when wearing ZEISS MyoCare S lenses. Mean ± SE is displayed.





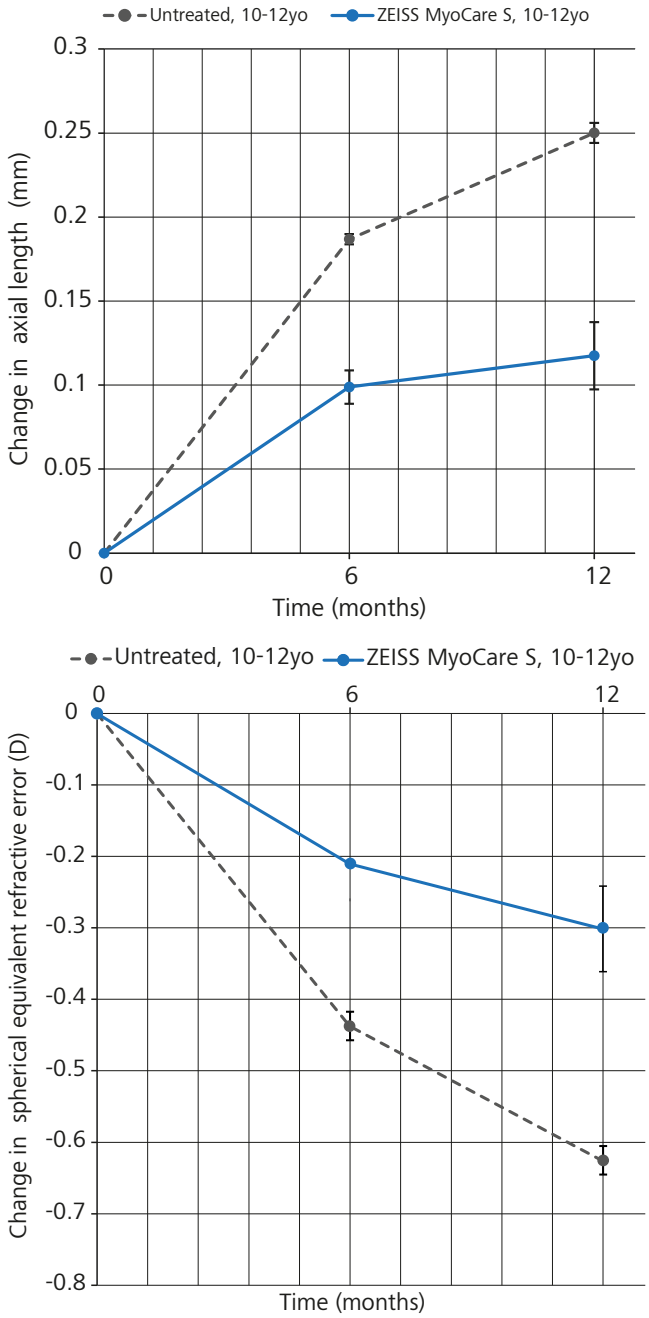


Figure 7. Age-weighted mean and SE of myopia progression (change in SER) and change in axial length from baseline to 12 months for ZEISS MyoCare lenses in 7- to 9-year-olds and for ZEISS MyoCare S lenses in 10- to 12-year-olds.

Emmetropic progression ratio

As outlined above, for the evaluation of treatment effectiveness, the physiological emmetropic growth curve provides a reference measure to rate the success of a myopia intervention. Figure 8 shows the annual progression of axial length, i.e., the observed change in axial length between the baseline and the 12-months follow-up, by age in the three groups of the clinical trial: the untreated control group wearing ZEISS Single Vision lenses, labelled as "myopic growth" in red, the ZEISS MyoCare group with the solid blue line, and the ZEISS MyoCare S group with the dashed blue line. As can be seen in this graph, both ZEISS MyoCare designs can help to significantly slow down progression of axial length and spherical equivalent refractive error compared to ZEISS Single Vision lenses (as indicated by the red curve) to come closer to the physiological growth curve of emmetropic children (as indicated by the black curve) for all age groups. The course of the ZEISS MyoCare curve thereby shows an almost parallel shift to the emmetropic progression curve across the age range, indicating that ZEISS MyoCare works well for all age groups. As already highlighted above, with increasing age, ZEISS MyoCare S shows a stronger treatment effectiveness, approaching emmetropic progression more and more above age 10.

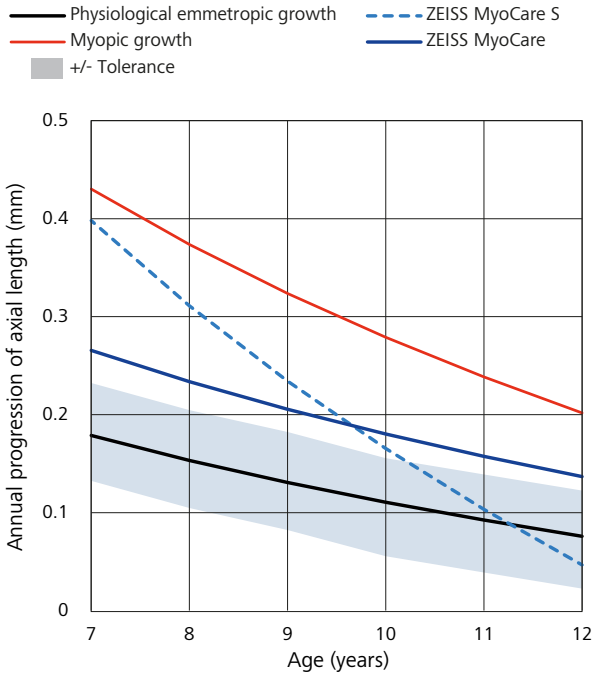


Figure 8. Both ZEISS MyoCare designs can help to significantly slow down myopia progression compared to the untreated control group (myopic growth) to come closer to the physiological growth curve of emmetropic children.

The emmetropic progression ratio provides a measure to indicate how close children with the intervention are approaching physiological emmetropic growth in contrast to myopic growth. On average, 7- to 9-year-olds wearing MyoCare® come 63 % closer to the normal growth of the eye in emmetropic children of the same age. With MyoCare® S, eye length growth comes on average 86 % closer to normal physiological development of the eye in 10- to 12-year-olds. Table 3 shows the results for the emmetropic progression ratio by age for ZEISS MyoCare and ZEISS MyoCare S lenses.

Age (years)	Emmetropic progression ratio, %
ZEISS MyoCare	
7	65
8	64
9	61
ZEISS MyoCare S	
10	67
11	92
12	100

Table 3. Emmetropic progression ratio for defined age-groups with ZEISS MyoCare and ZEISS MyoCare S.

Individual analysis of myopia progression

To analyse individual treatment response, the number of individual study participants was assessed that showed less than 0.05 mm progression in axial length and less than -0.125 D progression in SER, respectively, between baseline and the 12-months follow-up. Overall, on average across both designs and all age groups, 16 % of study participants did not show myopic progression of axial length over the first 12 months of the RCT when wearing ZEISS MyoCare or ZEISS MyoCare S lenses, compared to 7 % wearing ZEISS Single Vision lenses. When analysed for SER, on average across both designs and all age groups, 13 % of study participants did not show myopic progression of SER over the first 12 months of the RCT when wearing ZEISS MyoCare or ZEISS MyoCare S lenses, compared to 10 % wearing ZEISS Single Vision lenses. Follow-up analyses in the defined age-groups showed that 9 % of 7- to 9-year-olds did not progress in axial length as well as in SER in 12 months when wearing MyoCare® lenses, compared to 2 % and 7 % of study participants wearing ZEISS Single Vision lenses, respectively. Within the older age group, 35 % of 10- to 12-year-olds did not show any myopic progression of axial length and 17 % no progression of SER over the first 12 months of the RCT when wearing MyoCare® S lenses, compared to 8 % and 14% of study participants wearing ZEISS Single Vision lenses, respectively.

Adaptation and wearability

All children participating in the clinical trial reported that they adapted to their lenses within 1 day, regardless of whether they were wearing ZEISS MyoCare, ZEISS MyoCare S, or ZEISS Single Vision lenses. Furthermore, far distance vision, near distance vision, perception of moving objects, vision while doing sports, and vision while going up and down the stairs were rated as "very good" for both designs by 97.5 % or more study participants at the 3-months follow-up (see Figure 9 for detailed results). All measures were as good as or even better than the ratings made by the control group wearing ZEISS Single Vision lenses. Stratification for age and type of intervention showed that 98 % or more of 7- to 9-year-olds rated their vision in all instances as "very good" and otherwise as "good" with ZEISS MyoCare lenses. Of the 10- to 12-year-olds, 100 % rated their vision with ZEISS MyoCare S lenses in all instances as "very good". Interestingly, vice versa, children aged 10 and above rated their vision with ZEISS MyoCare lenses slightly less high than with ZEISS MyoCare S lenses, while children younger than 10 years of age rated both designs equally high.
No treatment-related adverse events were reported during the clinical trial.

Conclusion & Outlook

The 12-months interim results of the first clinical trial with ZEISS MyoCare and ZEISS MyoCare lenses, led by the Wenzhou Medical University Eye Hospital, confirm that both MyoCare® designs can help to significantly slow down myopia progression compared to ZEISS Single Vision lenses. Evaluation of the treatment effectiveness in reference to the physiological emmetropic growth curve indicates that ZEISS MyoCare works well for all age groups. Age significantly impacts the treatment effectiveness of ZEISS MyoCare S lenses, with children aged 10 and above benefitting more from ZEISS MyoCare S than ZEISS MyoCare lenses.

Potential reasons underlying this observation are currently under further investigation. Differences in wearing habits, lens wearing

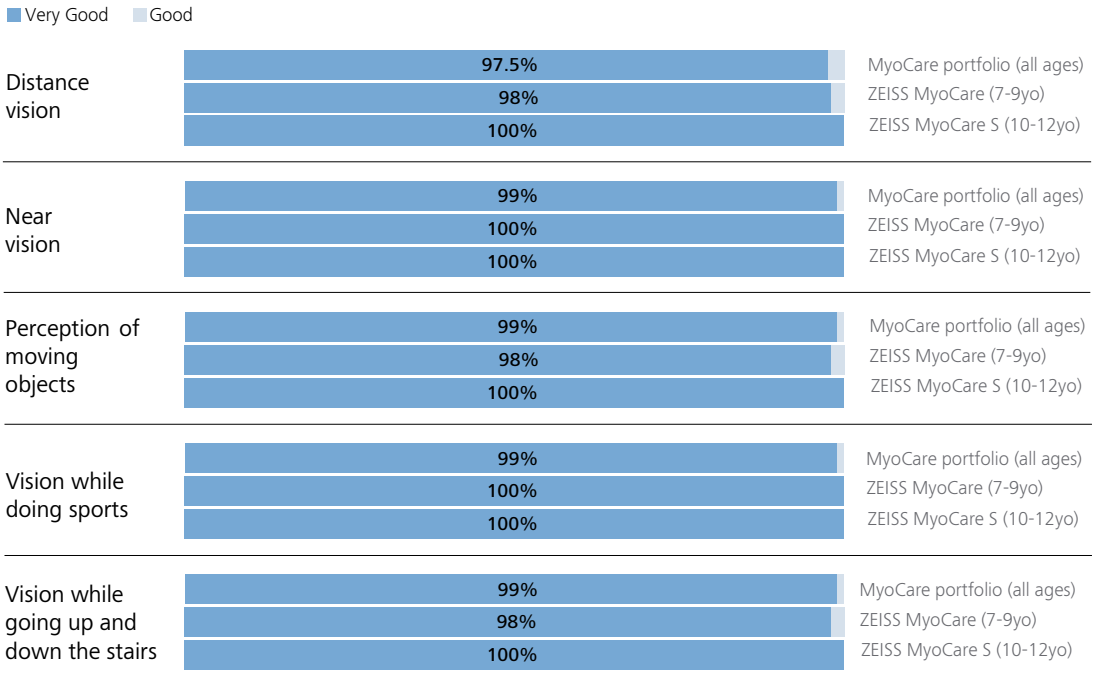


Figure 9. Detailed results on wearability ratings.

parameters, and wearability ratings might be important factors that influence treatment efficacy with age. The first decade of life is characterized by rapid development, with no other period in life where physiology and anatomy changes in a similar extent. With growth and development, facial morphology changes, with most substantial differences at the age between 7 and 14.[16] Likewise, the eyes are growing physiologically, accompanied by the emmetropization process that takes place in parallel. It is well established that axial elongation is faster at younger ages, with a physiological average progression between 0.1 and 0.2 mm in children younger than 10, and a slower progression in children 10 years and older of less than 0.1 mm, as reported by the various studies outlined above. Pupil size and pupil dynamics, accommodation, and further vision dynamics are all continuously changing and evolving as vision fully develops. Together, there are plenty of developmental changes in anatomy and physiology during vision development that might have an influence on the specific interaction between the lens design and its respective clinical treatment effect for myopia management. Together with our experts internally and with our external research partners we are already looking further into this topic, to see if and how wearing habits, but also changes in anatomy and physiology might influence treatment efficacy.

Outlook – Validation in multi-center clinical trials and with real-world-evidence

It is very difficult or not even possible to predict from one RCT how successful an intervention will be for an individual child. Therefore it is essential to extend the basis for evaluation, extend the number of children, age groups, living environments, ethnicities, etc., in multi-center clinical trials to allow for a generalization of the observed effects.

Even though clinical research is key to provide the evidence and confirmation of the efficacy and safety of myopia management interventions, it obviously has its limitations. These include the controlled environment in which the lenses are being tested, e.g., with regards to the regional setting of the trial, but also to how lenses are prescribed, how tests are done and who is following-up with the children. No matter the sample size, clinical studies will never reflect the diversity seen in the real world; even more so as specific inclusion and exclusion criteria are needed to allow for a proper statistical evaluation of the treatment effects. In contrast, in the real world, there is an enormous diversity of patients from clinical practice, with diverse baseline characteristics, and who are treated and refracted according to practice norms. In addition to clinical testing, it is therefore essential to follow up on how lens performance and its application transfers into the real world.

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Evaluating effect size in myopia control trials: Every diopter matters

Although it is the central component of any evaluation, so far little attention has been paid to the interpretation of efficacy in myopia control trials. Typically, clinical trials investigating the effectiveness and safety of myopia control interventions assess the change in refractive error, axial length, or both as primary endpoint, which is then compared between the intervention group and the control group. As primary endpoint, these are consequently the relevant measures taken to evaluate the effect size of the intervention.

In the following, the outcomes are however mainly communicated in the form of a relative reduction of progression expressed as a percentage treatment effect. This is typically calculated from the reduction in mean progression in the intervention group compared to the control group and is often further averaged as progression over time to show an annualized treatment effect.
But is percentage efficacy a valid key performance criterion for myopia control trials, to measure the success of a myopia control intervention? As Brennan and colleagues recently pointed out, while this currently seems to be common practice, it is important to reconsider if a percentage efficacy on its own is in fact the appropriate concept to describe, evaluate, interpret, and compare efficacy in myopia control studies (H1).

Study-specific baseline parameters significantly influence percentage evaluation of efficacy

A major weakness of such a relative assessment is its dependency on study-specific baseline parameters. Age at study onset, parental myopia, seasonal effects, and lifestyle are all known to have a profound effect on myopia progression, to name just a few examples (H2-H4). Although strict inclusion and exclusion criteria contribute to standardization, there remain influencing factors that cannot be controlled by the research team, such as seasonal variations in progression or effects due to extreme lifestyle changes as for example it was the case by pandemic home confinement. A consistent body of evidence already shows the influence of home confinement during the COVID-19 outbreak on myopia progression, with an average increase in annual progression by -0.25 D (H5).
The impact of these study-specific baseline parameters becomes apparent when comparing the change in refractive error within the control groups of published myopia control studies, which reveals a wide spread in myopia progression as shown in Figure H1.

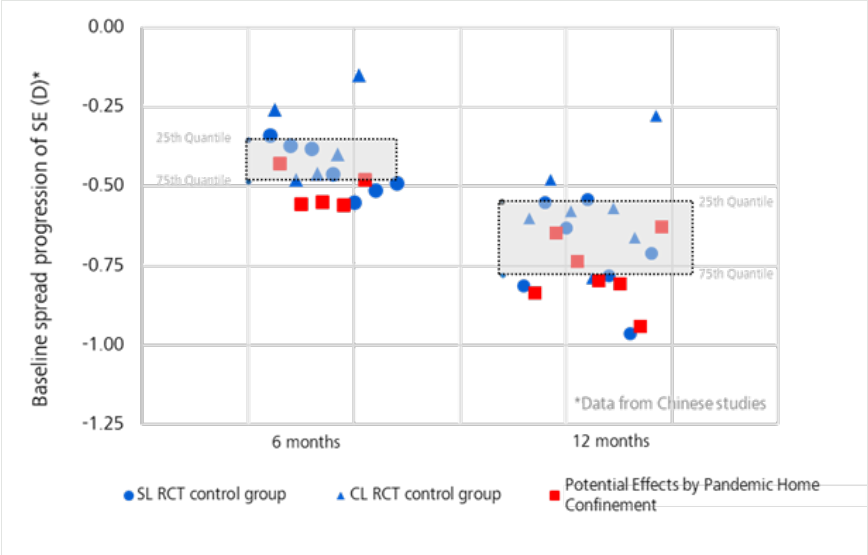

Figure H1. Baseline spread in absolute progression of spherical equivalent (SE; in diopters (D)) within the control groups of randomized controlled clinical trials (RCT) investigating single vision (SV) or contact lens (CL) interventions for myopia management in Chinese children (H6). New studies show that pandemic home confinement during the COVID-19 pandemic led to an average increase in annual progression by -0.25 D.

As the relative or percentage evaluation of a treatment effect takes the control group as its baseline, the spread in the absolute progression within the control groups has a major impact on the respective percentage outcome. This means that for two studies with the same amount of absolute reduction over the same period, a difference in the progression within the control group will result in a remarkable difference in percentage efficacy. This becomes even clearer with a calculation example, as shown in Figure H2. This example shows 2 studies comparing the annual progression between an intervention group – shown in dark blue – and a control group – shown in light blue. Both studies find that with the applied intervention, the difference in annual progression, or effect size, between control group and treatment group is -0.3 D, meaning that the intervention groups show 0.3 D less myopia progression than the control group. The calculation of the percentage efficacy however results in an efficacy of 50% for study 1 and an efficacy of only 40% for study, even though the absolute effect is identical. The reason for this is that the myopia progression within the control group is taken as the baseline.

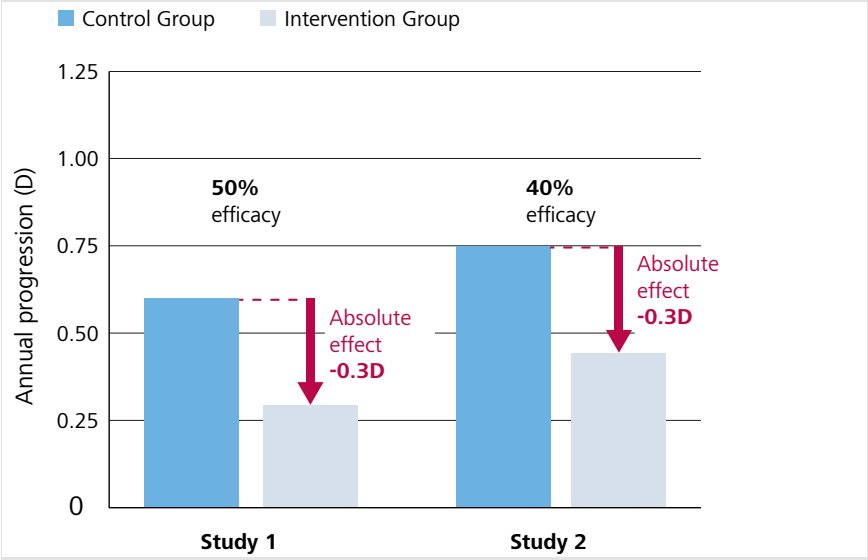

Figure H2. Example showing that a difference in the progression within the control group leads to a remarkable difference in percentage efficacy for two studies with an identical absolute reduction.

Variations in baseline progression, that cannot be ruled out even by strict inclusion or exclusion criteria, have a major impact on the respective relative percentage outcome. Reporting a relative or percentage efficacy on its own gives a misleading picture of the treatment effect in myopia control interventions.

Optical interventions show absolute and not proportional effects on myopia progression rates

Only reporting a percentage efficacy makes it difficult to generalize observed effects and compare results from different trials, because of the reference to the control group within the clinical trial. But what about its meaning with respect to what a patient can expect from the intervention?

Do optical interventions really produce percentage, that is proportional reductions in myopia progression? A true percentage effect would produce a greater reduction in progression rate in fast progressors, which would be a major benefit for those really at risk to develop higher myopia. And then again, there would be a reason to talk about percentage efficacy.

To answer this question, instead of only comparing the observed mean change of the control group and the treatment group, we have to look at how the progression changes in each individual patient within the two groups. The change in the overall distribution or frequency of progression changes shows, whether the treatment produces a proportional or an absolute effect. This relation is shown schematically in Figure H3. The dark blue curve in the first figure panel shows the distribution or frequency of individual progression changes over two years for a group of untreated children. A treatment with a true percentage efficacy, producing a percentage reduction in each individual progression rate, would rescale the shape of the progression distribution, making it overall narrower as the negative and positive refractive changes would be proportionally reduced. This is illustrated in the second figure panel by the grey curve, showing how the distribution of progression changes would look in the same group of children with an intervention that has a a 50% percentage efficacy. In contrast, an absolute effect, which reduces the progression rate for all myopic children by a constant amount, would not affect the shape of the distribution, but simply shift it along the progression axis towards less negative values, as illustrated by the light blue curve in the third figure panel.

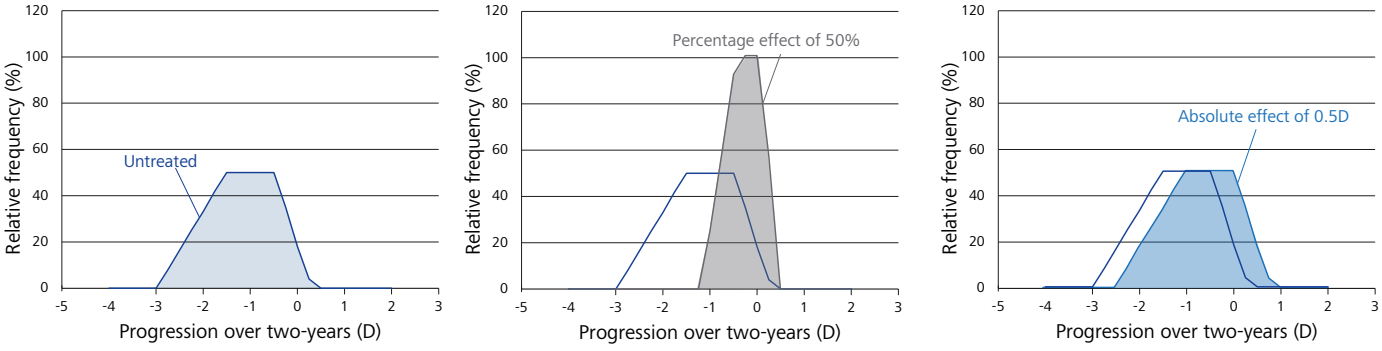

Figure H3. Schematic illustration of the effects of percentage and absolute effects on the frequency distribution of progression in a group of myopic children.

Charman and Radhakrishnan (2021) recently re-analyzed the data of two existing optical interventions, one spectacle lens solution and one contact lens solution, to exactly find out if myopia control treatments rather produce proportional or absolute effects (H7). The evaluation of the frequency distribution of the individual refractive changes in untreated and treated myopic children revealed that the treatment effect appears to be approximately the same for all myopic children across the progression range, and not a percentage of the original rate for the individual child. Based on this observation, Charman and Radhakrishnan (2021) argue that it is important to consider absolute differences in the rates of myopia progression as compared to those found in control groups to describe the treatment effect of optical myopia interventions, rather than using proportional descriptions.

Cumulative Absolute Reduction of Progression as relevant measure of effect size

Importantly, these considerations show that a mere percentage evaluation makes not only the comparison of different clinical trial outcomes and the generalization of the results more difficult, but also the prognosis for an individual patient. For an individual patient, it is not the comparison of a relative percentage measure of efficacy that matters most, but the absolute number of diopters and millimeters saved.

Putting this finding into context, Figure H4 shows the cumulative absolute reduction of progression assessed for the spherical equivalent and axial length over 6 to 24 months of different myopia management interventions. Looking at the clinical trial outcomes from micro-structured spectacle lens interventions, contact lens interventions, and atropine comprehensively shows that within the same type of intervention, a scattering of results is evident. This scattering can be observed for all interventions. Interestingly, efficacy results are spread over the same range across the different interventions.

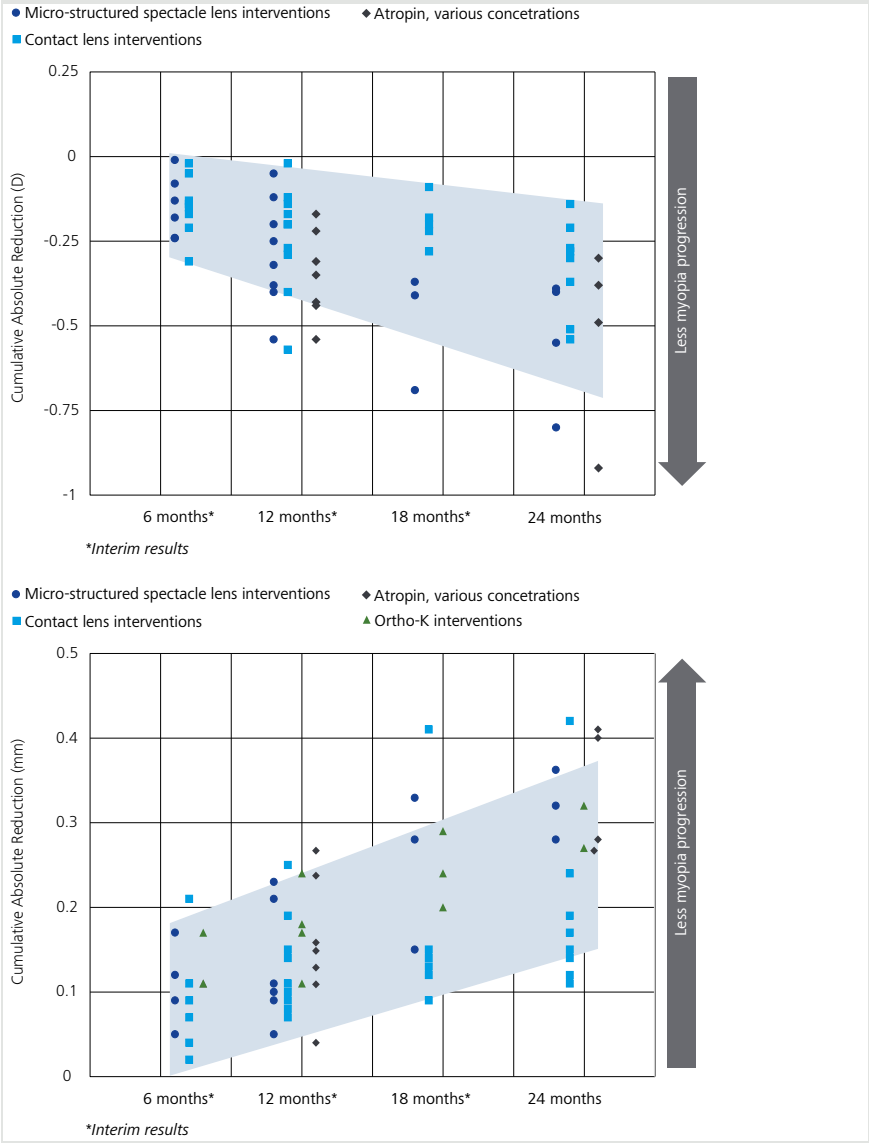

Figure H4. Overview of the cumulative absolute reduction of progression of the spherical equivalent (A) and axial length (B) over 6 to 24 months from various myopia management interventions

While a percentage efficacy relates to individual study statistics, the cumulative absolute reduction of progression relates to the observed treatment effect. **That's why the "Cumulative Absolute Reduction of Progression" is the relevant measure of effect size to describe, evaluate and compare myopia management interventions.**

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