Long-term Effect of Dual-focus Contact Lenses on Myopia Progression in Children: A 6-year Multicenter Clinical Trial

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SIGNIFICANCE: Treatment of myopic children with a dual-focus soft contact lens (DFCL; MiSight 1 day) produced sustained slowing of myopia progression over a 6-year period. Significant slowing was also observed in children switched from a single vision control to treatment lenses (3 years in each lens).

PURPOSE: This study aimed to evaluate the effectiveness of DFCLs in sustaining slowed progression of juvenile-onset myopia over a 6-year treatment period and assess myopia progression in children who were switched to a DFCL at the end of year 3.

METHODS: Part 1 was a 3-year clinical trial comparing DFCLs with a control contact lens (Proclear 1 day) at four investigational sites. In part 2, subjects completing part 1 were invited to continue for 3 additional years during which all children were treated with MiSight 1 day DFCLs (52 and 56 from the initially treated [T6] and control [T3] groups, respectively). Eighty-five subjects (45 [T3] and 40 [T6]) completed part 2. Cyclopleged spherical equivalent refractive errors (SEREs) and axial lengths (ALs) were monitored, and a linear mixed model was used to compare their adjusted change annually.

RESULTS: Average ages at part 2 baseline were 13.2 ± 1.3 and 13.0 ± 1.5 years for the T6 and T3 groups, respectively. Slowed myopia progression in the T6 group observed during part 1 was sustained throughout part 2 (mean ± standard error of the mean: change from baseline SERE [in diopters], –0.52 ± 0.076 vs. –0.51 ± 0.076; change in AL [in millimeters], 0.28 ± 0.033 vs. 0.23 ± 0.033; both $P > .05$). Comparing progression rates in part 2 for the T6 and T3 groups, respectively, indicates that prior treatment does not influence efficacy (SERE, –0.51 ± 0.076 vs. –0.34 ± 0.077; AL, 0.23 ± 0.03 vs. 0.18 ± 0.03; both $P > .05$). Within-eye comparisons of AL growth revealed a 71% slowing for the T3 group (3 years older than part 1) and further revealed a small subset of eyes (10%) that did not respond to treatment.

CONCLUSIONS: Dual-focus soft contact lenses continue to slow the progression of myopia in children over a 6-year period revealing an accumulation of treatment effect. Eye growth of the initial control cohort with DFCL was slowed by 71% over the subsequent 3-year treatment period.

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Myopia is predicted to affect more than half of the world's population by 2050,[1] and the prevalence of high myopia (defined as myopic refractive errors higher than –6 D)[2] is also increasing, being present in approximately 3% of the myopic population in 2000 and expected to reach 10% by 2050. The associated retinal and specifically macula pathologies, such as myopic macular degeneration,[3,4] are already leading causes of impaired vision in Europeans younger than 75 years[5] and have become the leading cause of blindness in older Chinese populations.[6]

Although the prevalence of retinal pathologies associated with myopic eye growth increases later in life,[7] the excessive eye growth that results in myopia often begins early in childhood[8] and continues into adolescence.[9] The anomalous growth of the eye can continue over many years[10] and can vary widely in rate—for example, from 0.17 mm to a maximum reported 0.53 mm per year in European children[11]—with earlier onset and faster progression generally resulting in higher levels of adult myopia.[12]

Efforts to delay onset of myopia and slow myopia progression have included modifying a child's visual environment, for example, increased lighting,[13] increased time outdoors,[14–16] and manipulations of visual optics to counteract the external environmental changes. Optical interventions incorporated into soft contact lenses, spectacle lenses, and orthokeratology are designed to introduce some myopic defocus and have shown promise in slowing eye growth.[17]

Assessing the efficacy of myopia control treatments is complicated by the need to monitor eye growth and refractive error over an extended period,[18] coupled with the significant covariate of slowed myopic eye growth with increasing age.[12] The added impact of measurement noise and selection bias may compromise the value of short-term studies.[19] Also, short-duration trials cannot examine important questions of treatment sustainability or satisfactorily reveal the interactions of treatment duration and age. In contrast, longer-term myopia control trials can be expected to evaluate sustained treatment effectiveness, whereas normal age-related

slowing of progression is ongoing during the evaluation period. However, maintaining control groups over long periods without treatment raises ethical and practical considerations.[20,21] Only a few 3-year randomized controlled clinical trials of optical myopia management have been published.[22–25] This is the first study to report myopia control efficacy data in a study cohort over a 6-year period.

After an observed average reduction of –0.73 D in myopia progression over the 3-year part 1 of this randomized control trial,[22] the dual-focus contact lens myopia management option was approved by the U.S. Food and Drug Administration[26] for the indication of slowing the progression of myopia in children. During part 1, standard treatment and control arms were used. However, because of ethical concerns,[20,21] the almost zero chance of placebo effect influencing the data,[27,28] and concerns that families would simply choose to purchase the commercially available treatment lens, subjects from the part 1 control group were all switched into the treatment lens at the start of year 4 (part 2). This protocol shift would enable better retention of subjects. The spherical equivalent refractive error and axial length progression data for both groups during part 2 (years 4 to 6) and the full 6 years of the trial were used to test the following hypotheses: (1) the slowed growth observed during years 1 to 3 in the treatment group would be sustained during years 4 to 6; (2) prior treatment for a period of 3 years will not result in faster progression compared with a newly treated group of the same age; (3) slowed myopia progression is achieved when treatment is initiated in an older cohort of subjects; and (4) faster growing eyes experience greater slowing of growth during treatment.

METHODS

Part 1 of this multicenter, double-masked, randomized, controlled clinical trial (ClinicalTrials.gov identifier, NCT01729208) compared myopia progression and eye growth in children aged 8 to 12 years at baseline and fitted with either a daily disposable dual-focus myopia control soft contact lens (MiSight 1 day, omafilcon A; CooperVision, Inc., Pleasanton, CA) or a standard single-vision, daily disposable lens (Proclear 1 day, omafilcon A; CooperVision, Inc.). The duration of part 1 was 3 years. Part 2 of the clinical trial was an open-label study with no masking or randomization, as all subjects were refitted with the dual-focus treatment lenses. Subjects remained masked to their previous cohort assignment for part 1. Part 2 was 3 years in duration and registered under the same identifier. Both parts of the study were conducted at the same four investigational sites: University of Minho, Braga, Portugal; Aston University, Birmingham, United Kingdom; National University Hospital, Singapore; and the University of Waterloo, Ontario, Canada. The study was conducted in conformance with the ethical principles in the Declaration of Helsinki, with the International Council for Harmonization guidelines for Good Clinical Practice and all applicable local regulations. This research was reviewed by an independent ethical review board and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research. Standardized measurements were used across sites, under the same protocol with identical equipment calibration instructions to ensure concordance across the study sites.[22] All subjects who successfully completed part 1 were invited to enroll in part 2. Initial visits for part 2 took place immediately after the 36-month exit visit and reconsent. These visits were completed between December 2015 and February 2017.

An assent document was explained to, read, and signed by each potential study subject before enrollment in each part of the study. Similarly, an informed consent document was explained to, read, understood, and signed by a parent or legal guardian of the subject before enrollment.

During the 3-year part 1, cohorts were identified as "control" and "treatment" groups and monitored every 6 months as reported previously.[22] In part 2, however, both cohorts from part 1 received the same treatment lens. Thus, these two cohorts are referred to as T6 (for those children who received 6 years of dual-focus myopia control treatment lenses) and T3 (for the original control group who then received 3 years of treatment in dual-focus myopia control treatment lenses at a later age). Subjects were subsequently monitored in part 2 at 42-, 48-, 54-, 60-, 66-, and 72-month visits. Lens refits for the previously untreated T3 cohort were

TABLE 1. Demographics at part 2 baseline for T6 (6 years of treatment) and T3 (original control group refitted with MiSight 1 day for years 4–6)

Variable	T3 group	T6 group	*P*
Subjects (n)	56	52	
Eyes (n)	112	104	
Age entering part 2 (y)			
Mean	13.0	13.2	.60
SD	1.5	1.3	
Range	11 to 15	11 to 16	
Age range, n (%)			
11–12 y	25 (45)	18 (35)	
≥13 y	31 (55)	34 (65)	
Sex, n (%)			
Male	27 (48)	28 (54)	.57
Female	29 (52)	24 (46)	
Ethnicity of subject, n (%)			
White	34 (61)	28 (54)	.94
East Asian	9 (16)	11 (21)	
South Asian	6 (11)	5 (10)	
Other	2 (4)	2 (4)	
Mixed	5 (9)	6 (12)	
Cycloplegic spherical equivalent refractive error (D)			
Mean	–3.45	–2.52	**<.001**
Median	–3.40	–2.50	
SD	1.14	0.98	
Range	–1.31 to –6.88	–0.19 to –4.93	
Axial length (mm)			
Mean	25.07	24.76	**.002**
Median	25.13	24.77	
SD	0.74	0.66	
Range	23.2 to 26.8	23.2 to 27.2	

Values in bold are significant. SD = standard deviation.

appropriately powered for their subjective refraction at 36 months, and acceptable lens fits were confirmed.

The primary outcome measures of cycloplegic spherical equivalent refractive error and cyclopleged optical interferometric measures of axial length were conducted at baseline and annually over the 6-year study using the Grand Seiko Binocular Autorefractor/Keratometer WR-5100 K or WAM-5500 (Grand Seiko Co., Hiroshima, Japan) and the IOLMaster (Carl Zeiss Meditec, Dublin, CA), respectively.

All measurement protocols used in part 1 were retained for part 2.[22] Other additional outcomes collected but not addressed in this article included subject and parent questionnaires, contact lens overrefraction, and lens fit assessment.

Statistical Analysis

The primary effectiveness aims of this study were twofold: (1) to compare myopia progression during part 1 and part 2 for both groups (Hypotheses 1 and 3) and (2) to compare the rate of myopia progression between the two study groups during part 2 and thus evaluate the impact of treatment history (Hypothesis 2).

Demographic data for the T6 and T3 groups were evaluated by the two-sample *t* test (continuous data), Mann-Whitney *U* test (categorical data), or Fisher exact test (nominal data). Unadjusted data for myopia progression are presented as population means with standard deviation. Mixed-effects models—used to analyze the changes in axial length and spherical equivalent refractive error—

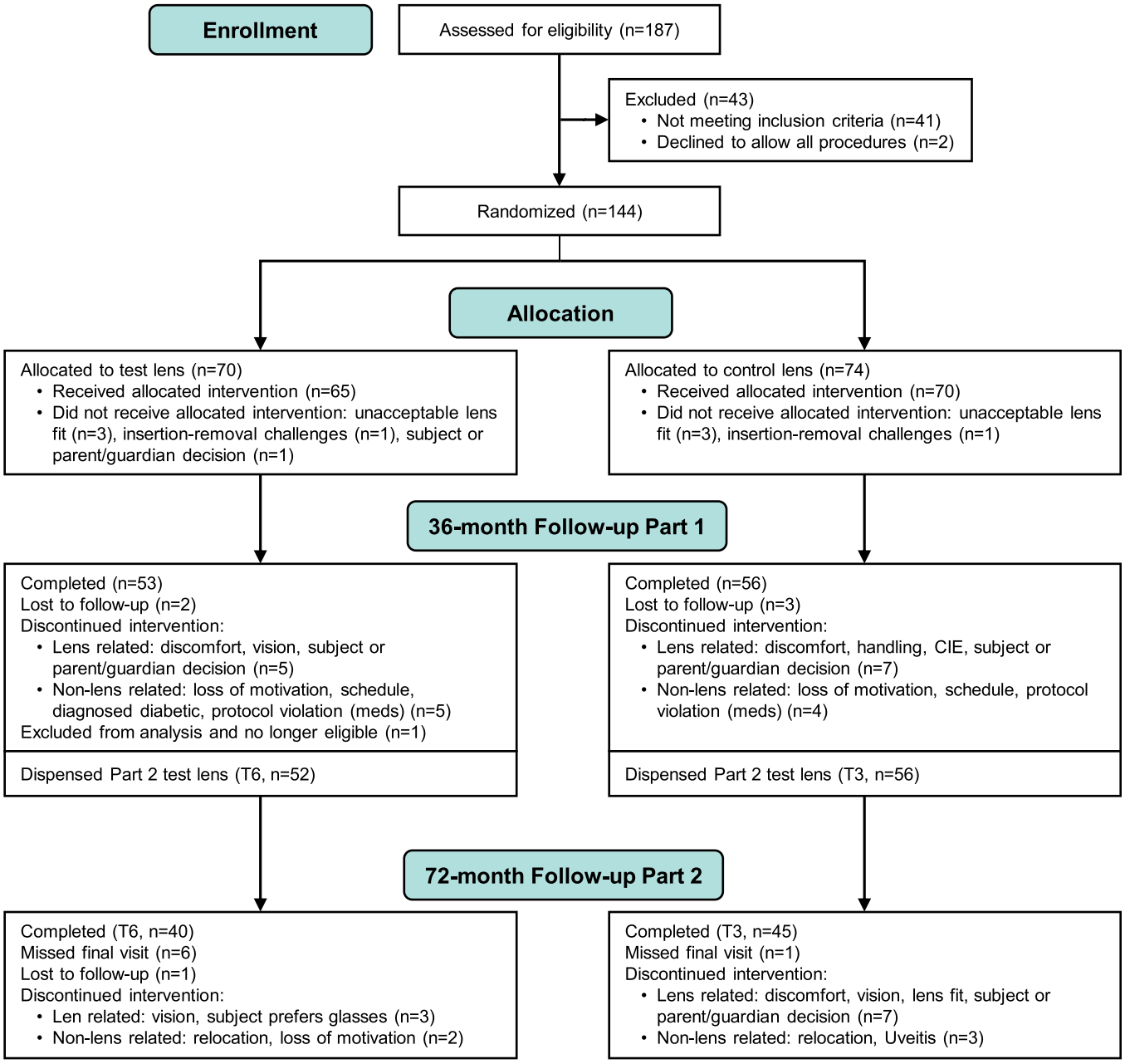

FIGURE 1. Flowchart showing treatment allocations and subject numbers for parts 1 and 2. Discontinuations are detailed as lens related, not lens related, and lost to follow-up.

TABLE 2. Mean spherical equivalent refractive error (in diopters) and axial length (in millimeters) progression with SD for the T6 (6 years of treatment) and T3 (original control then treated in years 4–6) cohorts

Study period	Group	n	Δ Spherical equivalent refractive error, mean ± SD (D)	Δ Axial length, mean ± SD (mm)
Baseline to 36 mo (part 1)	T6	104	–0.51 ± 0.64	+0.30 ± 0.28
	T3	112	–1.24 ± 0.61	+0.62 ± 0.30
36 to 72 mo (part 2)	T6	80	–0.45 ± 0.41	+0.22 ± 0.17
	T3	90	–0.29 ± 0.52	+0.18 ± 0.23
Baseline to 72 mo (parts 1 and 2)	T6	80	–0.92 ± 0.87	+0.49 ± 0.39
	T3	90	–1.55 ± 0.81	+0.81 ± 0.43

Progression during part 1, part 2, and parts 1 and 2 combined is shown.
SD = standard deviation.

included group, visit, part, site, and the interactions group by site, group by visit, group by part, and group by visit by part as fixed effects; age at part 1 baseline, part 1 baseline myopia (spherical equivalent refractive error or axial length), and ethnicity were included as fixed covariates; and subject (nested in site) and eye (nested in subject) were included as random effects. The model was used to estimate the mean change from part 1 baseline for each lens group by visit (least squares means and standard error of the mean) and their differences.

The analyses for testing efficacy end points were performed on all evaluable subjects' dispensed lenses at 36 months and subjects who did not have a protocol deviation that was deemed to render data unsuitable for inclusion in the analysis. Safety end points were assessed on all eyes with an evaluable visit, including unscheduled visits, from part 1 dispensing to the 72-month visit.

Comparisons of individual T3 subjects' eye growth rates from part 1 baseline to 36 months with those from 36 to 72 months used Deming regression and cluster analysis (Hypothesis 4).

RESULTS

In part 1 of the study, 144 subjects were enrolled and 135 were dispensed lenses, and 109 subjects completed the 36-month visit.[22] Of these, 108 remained eligible and were dispensed the dual-focus treatment lens for part 2 (52 from the original test group [T6] and 56 from the original control group [T3]). Eighty-five (85) subjects completed part 2 with eligible final visits, 45 in the T3 group and 40 in the T6 group. One subject in the T3 group and six in the T6 group attended a final visit but were not included in the final analysis, as the visits were outside of the allowable visit window.

Table 1 summarizes the demographics for all subjects continuing into part 2. Because most subjects completed part 1, the two cohorts for part 2 continued to be well matched for age, sex, and ethnicity. Owing to differences in their myopia progression during part 1, T3 subjects were, on average, about one diopter more myopic and had longer eyes than T6 subjects at the start of part 2 ($P < .001$ and $P = .002$, respectively).

The age range for subjects entering part 2 of the study was 11 to 16 years, resulting in more than half (60%) of the subjects being older than any subject initiating treatment during part 1 (i.e., 60% were older than 13 years).

Subject Accountability

Fig. 1 shows the flow of participants throughout the clinical trial, from recruitment for part 1 to study completion of part 2.

Of the 108 eligible subjects who consented and were enrolled into part 2, 18 were in Portugal, 23 in the United Kingdom, 18 in Singapore, and 49 in Canada. Ninety-two subjects attended a final 72-month visit. Of these, seven subjects (T6, 6; T3, 1) were 33 or more days late for the 72-month visit (primarily because of scheduling conflicts) and were excluded from the efficacy analysis. Therefore, 85 subjects had eligible final visits, 45 in the T3 group and 40 in the T6 group.

During part 2, 16 subjects discontinued: 6 in the T6 group and 10 in the refitted T3 group. Of those 16 subjects, 7 were discontinued at or soon after the baseline visit (T6, 2; T3, 5). The primary reasons for discontinuing were unacceptable vision (4), preference for spectacles (3), and relocation (3). Overall, the retention rate for those subjects enrolled and dispensed lenses in each part of the study was 81% (109 of 135) for part 1 and 85% (92 of 108) for part 2.

Reported daily hours of wear during weekdays was consistent and high across all 6 years of the study: means ± standard deviations at the 6-month point of part 1 were 12.9 ± 1.3 hours for the T3 group and 12.8 ± 1.2 hours for the T6 group, increasing slightly to 13.9 ± 1.4 and 13.9 ± 1.7 hours for the T3 and T6 groups, respectively, at 72 months. Mean ± standard deviation wearing times reported for weekends were slightly lower at 72 months, 12.9 ± 2.4 and 12.5 ± 1.3 h/d for the T3 and T6 groups, respectively. There were no significant differences

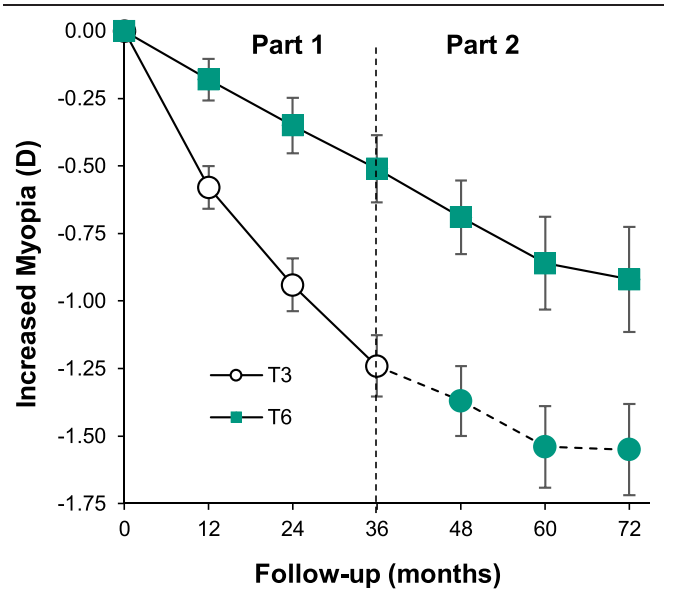

FIGURE 2. Mean change from baseline in cycloplegic spherical equivalent refractive error with 95% confidence intervals. Includes only those subjects enrolled in part 2. Unfilled symbols represent subjects in the control intervention, filled symbols represent subjects in the test intervention.

TABLE 3. Comparison of least squares mean cycloplegic spherical equivalent refractive error progression (in diopters) between part 1 and part 2, and between the T3 and T6 cohorts during part 2

Comparison	Spherical equivalent refractive error, LSM (SEM) (D)	95% CI	Mean difference	95% CI of difference	*P*
T6 group					
Part 1	–0.52 (0.076)	–0.67 to –0.37	0.01 (0.075)	–0.14 to 0.16	.87
Part 2	–0.51 (0.076)	–0.66 to –0.36			
T3 group					
Part 1	–1.32 (0.077)	–1.47 to –1.17	0.98 (0.071)	0.84 to 1.12	<.001
Part 2	–0.34 (0.077)	–0.49 to –0.19			
T6 vs. T3 (part 2)					
T6	–0.51 (0.076)	–0.66 to –0.36	–0.17 (0.094)	–0.35 to 0.02	.08
T3	–0.34 (0.077)	–0.49 to –0.19			

CI = confidence interval; LSM = least squares mean; SEM = standard error of the mean.

between treatment groups for wear time at weekdays or weekends in either part of the study ($P = .19$). However, statistically significantly longer wear times were observed in part 2 compared with part 1 ($P < .001$). During part 2, subjects reported that lenses were worn at least 6.5 d/wk for both lens groups.

Myopia Progression

To quantify change in myopia, differences were calculated between spherical equivalent refractive error, and axial length measured at part 1 baseline and those measured at each annual time point. This normalization process captures the myopia progression during the full study duration (Table 2, Fig. 2). Across the 6 years of assessment, the T3 group (untreated in part 1) progressed by an average of –1.55 ± 0.81 D. This compares with the T6 group who progressed by an average of –0.92 ± 0.87 D. Within the T6 group, 23% of eyes showed no clinically meaningful change in spherical equivalent refractive error (defined as –0.25 D or less) across the full 6 years of treatment.

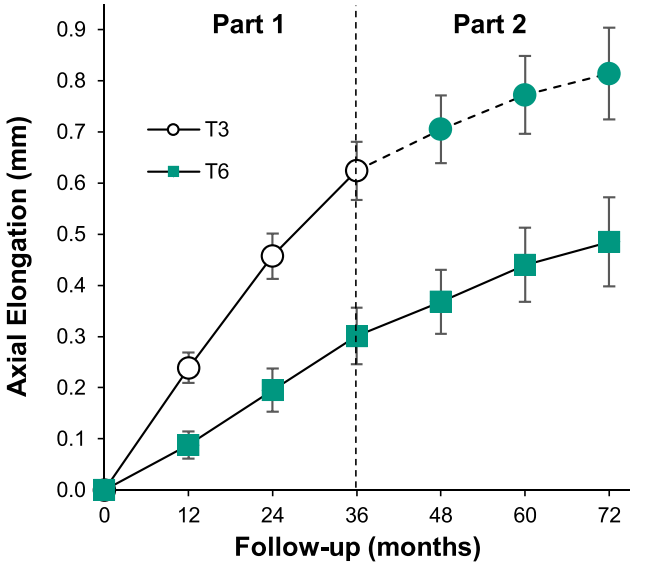

FIGURE 3. Mean change from baseline in axial length with 95% confidence intervals. Includes only those subjects enrolled in part 2. Unfilled symbols represent subjects in the control intervention, filled symbols represent subjects in the test intervention.

The T6 group showed similar spherical equivalent refractive error progression during each of the consecutive 3-year periods, part 1 and part 2, progressing by an average –0.51 ± 0.64 D and –0.45 ± 0.41 D, respectively. During part 2, in which both groups were treated with the dual-focus lens, the T6 and T3 group mean ± standard deviation progression rate was –0.45 ± 0.41 versus –0.29 ± 0.52 D, respectively. The T3 group experienced significant slowing of progression during part 2, slowing from a mean progression of –1.24 D during part 1 to –0.29 D during part 2.

After adjusting for the impact of potential covariables outlined in the statistical analysis plan, the least squares mean estimated progression in spherical equivalent refractive error was calculated. During part 2, no significant difference was observed in progression rate between the two groups at any follow-up visit. Differences in least squares mean refractive progression during part 1 and part 2 were not significant for the T6 group but highly significant for the T3 group (Table 3).

Table 2 and Fig. 3 summarize mean axial length progression for both cohorts. Across the 6 years of assessment, axial lengths in the T3 group increased by an average of 0.81 ± 0.43 mm, whereas axial length in the T6 group increased by an average of 0.49 ± 0.39 mm.

Axial length growth in the T6 group slowed from 0.30 mm in part 1 to 0.22 mm in part 2. This contrasts with the much larger slowing observed in the T3 group as they were switched from control to treatment lenses (0.62 mm in part 1 to 0.18 mm in part 2). During part 2, least squares mean analysis revealed no significant difference in axial length progression between the two groups (Table 4). When comparing axial length growth between parts 1 and 2, the T3 group experienced an average slowing of growth of 0.46 mm ($P < .0001$), whereas the T6 group slowed by only 0.05 mm ($P = .13$; Table 4).

Analysis of Axial Length Changes of Individual Eyes Switched from Control to Test Lenses (T3 Group)

Extending the study for 3 years without a control group did not allow further treatment-versus-control comparison used to establish efficacy in part 1. However, switching the T3 group from a single-vision control lens to a dual-focus treatment lens provided a unique opportunity for longitudinal analysis of eye growth and

TABLE 4. Axial length progression

Comparison	Axial length, LSM (SEM) (mm)	95% CI	Mean difference	95% CI of difference	*P*
T6 group					
Part 1	0.28 (0.033)	0.22–0.34	–0.05 (0.033)	–0.11 to 0.01	.13
Part 2	0.23 (0.033)	0.17–0.30			
T3 group					
Part 1	0.64 (0.033)	0.58–0.71	–0.46 (0.031)	–0.52 to –0.40	<.001
Part 2	0.18 (0.033)	0.12–0.25			
T6 vs. T3 (part 2)					
T6	0.23 (0.033)	0.17–0.30	0.05 (0.040)	–0.03 to 0.13	.25
T3	0.18 (0.033)	0.12–0.25			

Least squares mean estimates and differences comparing progression during part 1 and part 2, and between the T3 and T6 cohorts during part 2. CI = confidence interval; LSM = least squares mean; SEM = standard error of the mean.

myopia development in individual children transitioning from untreated to treated status.

Part 1 and part 2 axial length growth data from the T3 group were used to assess whether a common pattern of slowed eye growth exists in this group of children across the observed range of progression rates in part 1. Specifically, did treatment produce either a fixed amount of slowing[19] for each eye irrespective of the pre-treatment growth or a slowing that scaled with the magnitude

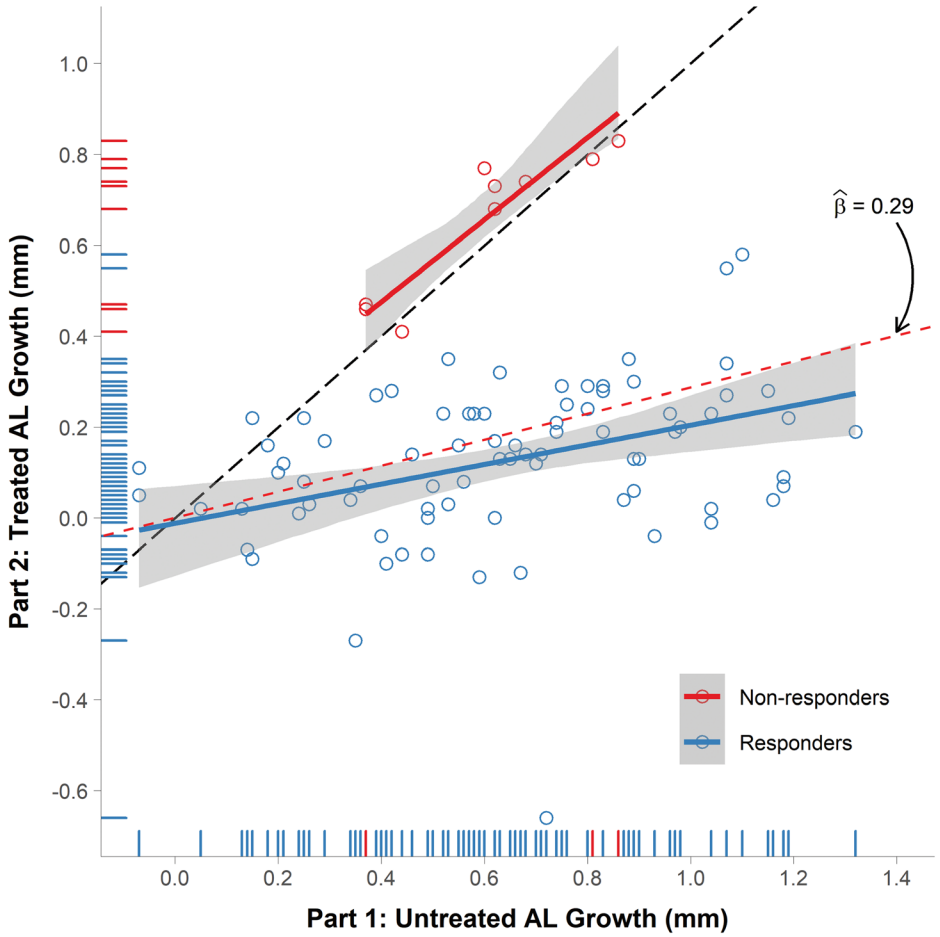

FIGURE 4. Axial length growth of T3 eyes observed over the 3 years of part 2 treatment (*y* axis) compared with growth observed during the part 1 untreated 3-year period (*x* axis). Red dashed line represents the fitted single-parameter model with slope $\hat{\beta} = 0.29$. Symbols represent individual eyes, blue for the main subgroup (81 eyes) and red for the identified subgroup of "nonresponders" (9 eyes). Solid red and blue lines are best-fit Deming regression lines for each subgroup, gray shaded areas represent a bootstrapped 95% confidence interval on the fitted model, and the black dashed line represents the $Y = X$ values. Red and blue tick marks on the axes reveal the distribution of AL growths during parts 1 and 2. AL = axial length.

of the eye growth seen before treatment (a proportional treatment effect in which eyes that were growing faster before treatment experienced the largest reduction in growth rate)?[29]

Fig. 4 shows a comparison of T3 axial length progression between parts 1 and 2. A Deming regression fit to the full sample of 90 eyes produced an estimated slope of +0.32 and intercept of –0.03, with jackknife 95% confidence intervals (CIs) of 0.06 to 0.59 and –0.19 to 0.14, respectively. A single-parameter model with the intercept set at zero produced a slope of $\hat{\beta}$ +0.29 with 95% CI of 0.21 to 0.37. Importantly, neither fit is consistent with a fixed treatment effect ($Y = X - k$) model. This single-parameter model indicates a 71% slowing of eye growth for the T3 group in part 2.

A subgroup of nine eyes was identified based on statistical criteria for outlier detection and by applying multiple unsupervised learning algorithms to the full N = 90 data set (Fig. 4). Good agreement was found among the best-fitting solutions obtained with two-dimensional kernel density estimation, Gaussian finite mixture modeling, and K-means iterative descent clustering. It is notable that most of these data points (6 of 9) were categorized statistically as "outside" values[30] in the treatment period only; that is, these points were larger than the upper quartile plus 1.5 times the interquartile range. Separate Deming regression of the two subgroups revealed a slope of 0.22 (95% CI, 0.08 to 0.35) and intercept of –0.01 (95% CI, –0.10 to 0.08) for the main group of 81 eyes (90%), with best-fit slopes of 0.90 (95% CI, 0.56 to 1.24) and intercept of 0.11 (95% CI, –0.09 to 0.32) for the nine-eye subgroup. Thus, parameter estimates for the model fitted to the main group data are consistent with a proportional treatment effect ($Y = kX$), whereas the ones from the model fitted to the small subgroup are inconsistent with slowed growth (nonresponding eyes, $Y = X$). Eight of the nine eyes classified as nonresponders were right-left pairs from four subjects. Two eyes of one subject in the main group were significantly shorter after 3 years of treatment (Y values of –0.27 and –0.66 mm). These reduced axial lengths were observed to accumulate annually during the 3 years of treatment. The growth ratios (years 4 to 6/years 1 to 3) were highly correlated for right and left eyes ($R = 0.89$; 95% CI, 0.81 to 0.94).

Additional Outcomes

Visual Acuity

During part 2, mean ± standard deviation distance visual acuities were –0.02 ± 0.07 and –0.03 ± 0.07 logMAR at the dispensing visit for the T3 and T6 groups, respectively. At the final 72-month follow-up, acuities were –0.02 ± 0.08 and –0.02 ± 0.10 respectively, with no significant differences between cohorts across the follow-up visits ($P = .34$).

Rate of Adverse Events and Biomicroscopic Findings

The safety end points—rate of adverse events and biomicroscopic findings >grade 1—have been discussed in detail in a recent publication.[31]

DISCUSSION

Demonstrated efficacy of the dual-focus treatment lens during years 1 to 3 of the 6-year study created ethical and practical reasons to switch from a two-arm randomized control design to one in which all subjects wore the treatment lens for years 4 to 6. This change eliminated the treatment versus control comparisons that were the primary efficacy indicators during part 1 of the study, but it revealed three key results: (1) a sustained rate of slowed eye growth and myopia progression in children who had already experienced 3 years of treatment and (2) a similar rate of myopia progression in a cohort of children introduced to MiSight 1 day contact lenses at an older age, compared with the matched T6 group who had already experienced 3 years of treatment. Eliminating speculation that longer treatment duration will result in a faster progression rate and thus reduced efficacy, compared with a newly treated age-matched population and (3) in the group new to MiSight, significantly reduced myopia progression relative to that experienced during the prior 3-year use of conventional daily disposable contact lenses.

For the originally treated cohort (T6), there was little difference between the least squares mean myopia progression for part 1 and part 2 (mean difference, 0.01 D and 0.05 mm). This suggests that the myopia control treatment with dual-focus contact lenses shows a sustained slowed eye growth over time and supports the value of a prolonged treatment through childhood and into adolescence. However, this sustained slowed eye growth may not directly translate to efficacy, given that older age can also result in slower eye growth in untreated eyes. During part 2, the group new to MiSight 1 day (T3) experienced slightly slower progression (not statistically different) to that observed in the demographically matched T6 group, suggesting that treatment efficacy is not significantly affected by prior treatment. Also, this similar progression of the T3 group occurred despite their generally higher myopia levels and longer eyes after an absence of treatment in part 1.

Average spherical equivalent refractive error progression of the T3 cohort was slowed by nearly a diopter (0.98 D) in part 2, and axial length growth was reduced by 0.46 mm. This significant slowing of eye growth was observed in all but nine of the eyes newly treated with MiSight 1 day in part 2 who were older (age, 13 to 15 years) than the age range of subjects enrolled into part 1 (8 to 12 years). Overall, these results provided evidence of treatment efficacy in children who were, on average, 3 years older than those recruited into the original treated cohort.

The within-eye comparisons of growth during and before treatment of the T3 cohort (Fig. 4) are consistent with a proportional effect for myopia control across the progression range and revealed growth rates during part 2 that were, on average, 29% of the rate observed during part 1. The 29% result cannot be interpreted as a 71% treatment effect because increasing age in itself would account for some slowing of growth during part 2. Analysis using published eye growth models[10] shows that, if left untreated, axial length growth for untreated myopes in the older age range would, on average, be approximately 76% of that observed in the 3-year-younger, original control group enrolled in part 1. In other words, approximately one-third of the slowing of eye growth observed during part 2 can be attributed to age.

Comparisons of axial length growth between parts 1 and 2 of the T3 cohort also provided the opportunity to identify any potential "nonresponders," an advantage provided by switching the T3 group, whose myopia progression before treatment had been well defined, into treatment lenses. Nonresponders could not be identified in part 1 because faster progressors in the treatment group may have progressed more than average because they did not respond to treatment or because they did respond to treatment, but their growth rate, if left untreated, would have been even faster. Applying statistical outlier detection to the data identified 10% (9

of 90) of eyes as belonging to the subgroup for whom the treatment lens did not slow eye growth.

Although Deming regression analysis (Fig. 4) of the majority subgroup reveals that growth during treatment was, on average, 22% of that before treatment, many subjects experienced approximately zero growth during treatment, whereas others grew at up to 30 to 50% of the pre-treatment rate. Although the data support a proportional treatment model over a model in which treatment slows growth in all children to a low level that is independent of their pre-treatment growth, the CI for a Deming regression of the "responder" subgroup overlaps with that of $Y =$ constant model over a significant range of values of untreated axial length growth. The data do not support a fixed treatment effect where slowed progression is fixed number of millimeters regardless of part 1 progression rate.

Finally, it should be noted that this study represents one of the longest prospective interventional trials of pediatric soft contact lens wear. As such, the clinical and, in particular, safety end points are worthy of note. The previously reported low rate of significant biomicroscopic findings[31] further illustrates the minimal impact on ocular physiology in this younger population with full-time, daily disposable contact lens wear and is an important finding for eye care professionals considering recommending contact lens myopia control for children.

In conclusion, these 6-year data provide compelling evidence of an accumulating myopia control effect of a dual-focus contact lens as treatment duration is extended and beneficial effects even when treatment is commenced at an older age. The data for the refit T3 cohort are consistent with the hypothesis that treatment effect is proportional to pre-treatment growth rates and thus larger for fast-growing eyes. As such, this result emphasizes the added value of treatment to the fast progressors, who are at the greatest future risk of maculopathy.[4]

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REFERENCES

1. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016;123:1036–42.

2. Flitcroft DI, He M, Jonas JB, et al. IMI—Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. Invest Ophthalmol Vis Sci 2019;60:M20–30.

3. Tideman JW, Snabel MC, Tedja MS, et al. Association of Axial Length with Risk of Uncorrectable Visual Impairment for Europeans with Myopia. JAMA Ophthalmol 2016;134:1355–63.

4. Flitcroft DI. The Complex Interactions of Retinal, Optical and Environmental Factors in Myopia Aetiology. Prog Retin Eye Res 2012;31:622–60.

5. Klaver CC, Wolfs RC, Vingerling JR, et al. Age-specific Prevalence and Causes of Blindness and Visual Impairment in an Older Population: The Rotterdam Study. Arch Ophthalmol 1998;116:653–8.

6. Tang Y, Wang X, Wang J, et al. Prevalence and Causes of Visual Impairment in a Chinese Adult Population: The Taizhou Eye Study. Ophthalmology 2015;122:1480–8.

7. Xiao O, Guo X, Wang D, et al. Distribution and Severity of Myopic Maculopathy among Highly Myopic Eyes. Invest Ophthalmol Vis Sci 2018;59:4880–5.

8. Chua SY, Ikram MK, Tan CS, et al. Relative Contribution of Risk Factors for Early-onset Myopia in Young Asian Children. Invest Ophthalmol Vis Sci 2015;56:8101–7.

9. COMET Group. Myopia Stabilization and Associated Factors among Participants in the Correction of Myopia Evaluation Trial (COMET). Invest Ophthalmol Vis Sci 2013;54:7871–84.

10. Jones LA, Mitchell GL, Mutti DO, et al. Comparison of Ocular Component Growth Curves among Refractive Error Groups in Children. Invest Ophthalmol Vis Sci 2005;46:2317–27.

11. Tideman JL, Polling JR, Vingerling JR, et al. Axial Length Growth and the Risk of Developing Myopia in European Children. Acta Ophthalmol 2018;96:301–9.

12. Chua SY, Sabanayagam C, Cheung YB, et al. Age of Onset of Myopia Predicts Risk of High Myopia in Later Childhood in Myopic Singapore Children. Ophthalmic Physiol Opt 2016;36:388–94.

13. Zhou Z, Chen T, Wang M, et al. Pilot Study of a Novel Classroom Designed to Prevent Myopia by Increasing Children's Exposure to Outdoor Light. PLoS One 2017;12:e0181772.

14. Wu PC, Chen CT, Lin KK, et al. Myopia Prevention and Outdoor Light Intensity in a School-based Cluster Randomized Trial. Ophthalmology 2018;125:1239–50.

15. He M, Xiang F, Zeng Y, et al. Effect of Time Spent Outdoors at School on the Development of Myopia among Children in China: A Randomized Clinical Trial. JAMA 2015;314:1142–8.

16. Xiong S, Sankaridurg P, Naduvilath T, et al. Time Spent in Outdoor Activities in Relation to Myopia Prevention and Control: A Meta-analysis and Systematic Review. Acta Ophthalmol 2017;95:551–66.

17. Walline JJ, Lindsley KB, Vedula SS, et al. Interventions to Slow Progression of Myopia in Children. Cochrane Database Syst Rev 2020;1:CD004916.

18. Mutti DO, Hayes JR, Mitchell GL, et al. Refractive Error, Axial Length, and Relative Peripheral Refractive Error Before and After the Onset of Myopia. Invest Ophthalmol Vis Sci 2007;48:2510–9.

19. Brennan NA, Toubouti YM, Cheng X, et al. Efficacy in Myopia Control. Prog Retin Eye Res 2021;83:100923.

20. Ashcroft R. Equipoise, Knowledge and Ethics in Clinical Research and Practice. Hum Exp Res 2017;13:433–45.

21. Gupta U, Verma M. Placebo in Clinical Trials. Perspect Clin Res 2013;4:49–52.

22. Chamberlain P, Peixoto-de-Matos SC, Logan NS, et al. A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control. Optom Vis Sci 2019;96:556–67.

23. Cheng D, Woo GC, Drobe B, et al. Effect of Bifocal and Prismatic Bifocal Spectacles on Myopia Progression in Children: Three-year Results of a Randomized Clinical Trial. JAMA Ophthalmol 2014;132:258–64.

24. Gwiazda J, Hyman L, Hussein M, et al. A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children. Invest Ophthalmol Vis Sci 2003;44:1492–500.

25. Walline JJ, Walker MK, Mutti DO, et al. Effect of High Add Power, Medium Add Power, or Single-vision Contact Lenses on Myopia Progression in Children: The Blink Randomized Clinical Trial. JAMA 2020; 324:571–80.

26. U.S. Food and Drug Administration (FDA), Pre-market Arroval: Medical Devices. MiSight 1 Day (Omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P180035. Accessed October 29, 2021.

27. Evans SR. Clinical Trial Structures. J Exp Stroke Transl Med 2010;3:8–18.

28. Bassler D, Montori VM, Briel M, et al. Early Stopping of Randomized Clinical Trials for Overt Efficacy Is Problematic. J Clin Epidemiol 2008;61: 241–6.

29. Anstice NS, Phillips JR. Effect of Dual-focus Soft Contact Lens Wear on Axial Myopia Progression in Children. Ophthalmology 2011;118:1152–61.

30. Tukey JW. Exploratory Data Analysis. Reading, MA: Addison Wesley Pub. Co.; 1977.

31. Woods J, Jones D, Jones L, et al. Ocular Health of Children Wearing Daily Disposable Contact Lenses over a 6-year Period. Cont Lens Anterior Eye 2021; 44:101391.