A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control

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SIGNIFICANCE: Results of this randomized, double-masked clinical trial demonstrate the effectiveness of the MiSight soft contact lens in slowing myopia progression over multiple years.

PURPOSE: The purpose of this study was to quantify the effectiveness of MiSight daily disposable soft contact lens in slowing the progression of juvenile-onset myopia.

METHODS: Myopic children (spherical equivalent refraction, –0.75 to –4.00 D; astigmatism, <1.00 D) aged 8 to 12 years with no prior contact lens experience were enrolled in a 3-year, double-masked, randomized clinical trial at four investigational sites in four countries. Subjects in each group were matched for age, sex, and ethnicity and were randomized to either a MiSight 1-day contact lens (test) or Proclear 1-day (control; omafilcon A) and worn on a daily disposable basis. Primary outcome measures were the change in cycloplegic spherical equivalent refraction and axial length.

RESULTS: Of the subjects enrolled, 75.5% (109/144) completed the clinical trial (53 test, 56 control). Unadjusted change in spherical equivalent refraction was –0.73 D (59%) less in the test group than in the control group (–0.51 ± 0.64 vs. –1.24 ± 0.61 D, $P < .001$). Mean change in axial length was 0.32 mm (52%) less in the test group than in the control group (0.30 ± 0.27 vs. 0.62 ± 0.30 mm, $P < .001$). Changes in spherical equivalent refraction and axial length were highly correlated ($r = –0.90$, $P < .001$). Over the course of the study, there were no cases of serious ocular adverse events reported. Four asymptomatic corneal infiltrative (one test, three control) events were observed at scheduled study visits.

CONCLUSIONS: Results of this clinical trial demonstrate the effectiveness of the MiSight daily disposable soft contact lens in slowing change in spherical equivalent refraction and axial length.

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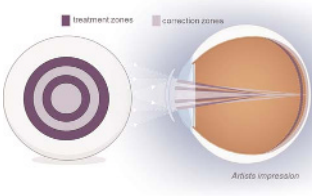

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Myopia represents a growing public health issue, affecting 33% of adults in the United States[1] and markedly higher proportions in Asia.[2–4] Increasing myopia is associated with increased risk of retinal detachment,[5] glaucoma,[6] cataract,[7] and myopic retinopathy.[8] Higher levels of myopia are also associated with increased disability[9,10] and poorer refractive surgery outcomes.[11]

In the past decade, there has been increased research activity aimed at slowing the progression of myopia by optical methods, including overnight corneal reshaping contact lenses (orthokeratology)[12–14] and soft contact lenses incorporating multifocal or aspheric optics,[15–24] and these have shown promise to slow myopia progression.

Studies of the mechanisms that regulate refractive development in nonhuman primates show that hyperopic defocus can induce excessive eye growth and myopia and that myopic defocus can retard or reverse eye growth.[25] Further research has shown that eye growth can be manipulated when defocus, particularly myopic defocus, is presented simultaneously with an additional optical power. These simultaneous optics are typically used with concentric alternating powers in a zonal design within the lens optic and are commonly referred to as "dual-focus optics." Lenses with dual-focus optics have been used in a number of animal models, such as chickens, guinea pigs, marmosets, and rhesus monkeys, with the aim of retarding eye growth. All of these studies[26–32] have consistently shown that adding simultaneous myopic defocus to either hyperopic or plano correction resulted in reduced eye growth when compared with the control animals or fellow control eyes.

This principle of applying myopic defocus via a dual-focus optical design has been studied in clinical trials of human subjects. Anstice and Phillips[15] evaluated a dual-focus soft contact lens in children aged 11 to 14 years. This dual-focus design had a central zone containing the distance correction with concentric peripheral zones, alternating myopic defocus (additional positive power) with distance correction power. The intent of this optical design was to fully correct refractive error but simultaneously create myopic defocus in all directions of gaze. The central correction zone was

made sufficiently large for good visual acuity, but also to ensure that normal accommodation would be stimulated for near work. The zone diameters were designed to achieve constant presentation of myopic defocus to the retina. The dual-focus lens was compared in a contralateral study design with a single-vision soft contact lens. The mean 10-month change in spherical equivalent refraction in the eye wearing the dual-focus lens was significantly less than that in the contralateral eye wearing the single-vision lens (–0.44 vs. –0.69 D). The mean axial elongation was also significantly less with the dual-focus lenses (0.11 vs. 0.22 mm) than with the single-vision lenses.

This dual-focus optical design is the basis for the MiSight soft contact lens (CooperVision, Inc., Pleasanton, CA). Myopia progression was recently studied in 89 children aged 8 to 12 years in a 2-year parallel-group study comparing MiSight with standard single-vision spectacles.[23] In this study, the mean change in spherical equivalent refraction and the mean axial elongation were significantly less in the MiSight group than in the spectacle control group (–0.45 vs. –0.74 D, 0.28 vs. 0.44 mm).

The purpose of the current study is to report the results from a clinical trial of MiSight lenses with dual-focus optics compared with a single-vision contact lens of the same lens material and overall geometry. The clinical trial was designed to quantify the effectiveness of the MiSight lenses for slowing juvenile-onset myopia progression. The primary outcomes for effectiveness were change of cycloplegic spherical equivalent refractive error and axial length over the 3-year period. Additional end points included assessment of best-corrected visual acuity and subjective responses.

METHODS

Study Design

This study was a multicenter, parallel-group, double-masked, randomized clinical trial (ClinicalTrials.gov identifier: NCT01729208) of a daily wear, daily disposable myopia control soft contact lens compared with a standard daily disposable lens. The duration of the study was 3 years.

The study was performed at four investigational sites: University of Minho, Portugal; Aston University, United Kingdom; National University Hospital, Singapore; and the University of Waterloo, Canada. The study was conducted in conformance with the ethical principles in the Declaration of Helsinki, with the International Conference on Harmonization Good Clinical Practice guidelines and all applicable local regulations. The protocol, consent, and assent documents, along with all recruitment materials, were approved by each institution's institutional review board before commencing the study.

The test product, MiSight, and the control lenses, Proclear 1-day (CooperVision, Inc.), are both soft (hydrophilic) contact lenses composed of omafilcon A material. The study contact lenses were identical for both material and lens overall geometry and differed only in the optical design of the contact lens.

To ensure standardized measurements across sites, all sites were provided with the same protocol and trained before study initiation. Identical equipment calibration instructions were implemented for each site.

Subjects were recruited between November 2012 and April 2014. An assent document was explained to, read, and signed by each potential study subject before enrollment in the study. Similarly, a consent document was explained to, read, understood, and signed by a parent or legal guardian of the subject before enrollment.

All the inclusion and exclusion criteria are listed in Table 1. Children with spherical equivalent refractive error between –0.75 and –4.00 D inclusive with less than 1.00 D of astigmatism or anisometropia were eligible for the study. The study population was children aged 8 to <13 years at the baseline examination with targeted enrollment of a minimum of 50% of the study population in the 8- to 10-year age group.

At baseline, subjects were assessed for eligibility, which included ocular characteristics such as refraction, visual acuity, binocular status, and ocular health (Table 1). Subjective refraction was performed using a phoropter and projector chart at 6 m. Cycloplegic autorefraction and axial length measurements were performed as described in detail hereinafter.

Eligible subjects were sequentially randomized into either the MiSight or control group (1:1 ratio). The randomization procedure was stratified by clinical site and age group using a random permuted block design to achieve the 50% target of the younger-age group. The randomization log was created centrally by the contract research organization using a random number–generating computer program. Each clinical site was given a randomization log to assign the order in which subjects were dispensed the lens types. The randomization log was stored in the study documentation, so all investigators could access it, but the study product was coded (lens A and lens B) and the randomization log only had the lens codes listed on it. This code was also the only identifying feature on the study product. Participants and their parents were masked.

A lens-fitting procedure was performed where the contact lens power for the subject was finalized, and acceptable lens fitting was confirmed. The subject was dispensed once he/she had successfully completed training for insertion and removal of the contact lenses. Both the MiSight and control lenses were used following a daily wear, daily disposable modality. Progress was monitored at follow-up visits at 1 week, 1 month, and 6, 18, 24, 30, and 36 months.

Cycloplegic spherical equivalent refraction and axial length were assessed at baseline and at the annual follow-up visits. Cycloplegia was produced by first instilling one drop of anesthetic, either 0.5% proparacaine or 0.4% benoxinate, in each eye. One minute later, one drop of 1% tropicamide was instilled in each eye, followed by a second drop 5 minutes later. The examiner waited at least 25 minutes before conducting further assessments.

Cycloplegic refraction was measured using the Grand Seiko Binocular Auto-refractor/Keratometer WR-5100K or WAM-5500 (Grand Seiko Co., Hiroshima, Japan). Subjects were instructed to view a 4-m distance target one line larger than their best acuity; subsequently, 10 measurements were taken per eye and later averaged. Axial length was measured using the IOLMaster (Carl Zeiss Meditec, Dublin, California), with the subject fully cyclopleged. Subjects were instructed to view the internal fixation target, and 10 measurements were taken of each eye.

Visual acuity was assessed using ETDRS Revised 2000 Series Charts (Precision Vision, Woodstock, IL) using by-letter scoring (0.02 logMAR). The charts were standardized to a luminance of 85 cd/m^2. With the subject wearing the appropriate distance vision correction and left eye covered, the subject began at 20/50 line, reading the first letter on each successive line until he/she made an error. When the subject made an error, he/she was asked to read progressively larger lines until the subject was able to correctly

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Be between 8 and 12 y of age inclusive at baseline examination	Current or prior contact lens wear
The participant has been given a clear explanation, then read, understood, and signed the informed assent form.	Subject is currently or within 30 d before this study has been an active participant in another clinical study
The participant has been given a clear explanation, then read, understood, and signed the informed assent form.	Parent/guardian or close relative is a member of the office staff, including the investigator(s)
The parent or legal guardian has been given a clear explanation, then read, understood, and signed the informed consent form.	Current or prior use of bifocals, progressive addition lenses, atropine, pirenzepine, or any other myopia control treatment
Willingness to adhere to protocol, agreement to maintain the visit schedule	Birth earlier than 30 wk or <1500 g (3.3 lb) at birth
Along with their parent or guardian, agree to maintain the visit schedule and be able to keep all appointments as specified in the study protocol for the duration of the study	Regular use of ocular medications, artificial tears, or wetting agents
Acceptance of either the control or test lens as assigned by randomization	Current use of systemic medications, which may affect contact lens wear, tear film production, pupil size, accommodation, or refractive state
Agreement to wear the assigned contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the duration of the 3-y study. Agreement to inform the study investigator if this schedule is interrupted	A known allergy to fluorescein, benoxinate, proparacaine, or tropicamide
Possess wearable and visually functional eyeglasses	A history of corneal hypoesthesia (reduced corneal sensitivity), corneal ulcer, corneal infiltrates, ocular viral or fungal infections, or other recurrent ocular infections
Be in good general health, based on his/her and parent's/guardian's knowledge	Strabismus by cover test at distance or near wearing distance correction
Best-corrected visual acuity by manifest refraction of +0.10 logMAR (20/25) or better in each eye	History of ocular or systemic diseases, including those that could influence refractive development
Meet the following refractive criteria determined by cycloplegic autorefraction at baseline: (*a*) Spherical equivalent refractive error: between –0.75 and –4.00 D inclusive (*b*) Astigmatism: ≤–0.75 D (*c*) Anisometropia: <1.00 D	Keratoconus or an irregular cornea
	Contraindications for contact lens wear including giant papillary conjunctivitis of grade 2 or worse and allergic or seasonal conjunctivitis
	Subject seems to exhibit poor personal hygiene (that in the investigator's opinion might prevent safe contact lens wear) or the investigator for any reason considers that it is not in the best interest of the subject to participate in the study

identify all five letters on a line. The subject continued reading until three or more letters were missed on a given line. Visual acuity was recorded in logMAR to the nearest letter, including the final read line. Near visual acuity was measured in logMAR notation with Near Point Flip Charts (Precision Vision) held at 40 cm. The same protocol for measuring distance vision was used to assess near vision under the same lighting conditions. Refractive status was assessed at each visit before cycloplegia. A change in lens power was provided at any study visit when subjective overrefraction was equal or greater than 0.50 D or a clinically meaningful improvement in visual acuity could be achieved (greater than ½ line). Lens fit and ocular health were also assessed at these visits.

Subjective feedback was obtained from both the participants and the parents via questionnaires at each follow-up visit. Questionnaires targeted information for lens handling along with assessments of comfort, vision, and overall satisfaction. Each question offered five Likert-type responses. The subjects were given ample time and asked to complete the questionnaire by themselves. A member of the site staff was available to answer any queries and to help the subject understand the question but was instructed not to help the subject with the answer.

For the purposes of demonstrating the general acceptance of the contact lenses in this trial population, this publication will present findings only for lens handling and overall satisfaction from the extensive questionnaire. Subjects were invited to rate their contact lens handling experience to choose from the following: really easy, kind of easy, neither easy nor hard, kind of hard, or really hard. For the overall satisfaction rating for wearing both their spectacles and contact lenses, the following choices were given to the subjects: I like them the best, I kind of like them, neither like them nor do not like them, I do not like them, and I cannot stand them.

Wearing time was collected by asking participants their typical lens insertion and removal times on a typical weekday and weekend and how many days in a week the lenses were typically worn. The wear time was calculated from these responses for each participant.

The primary outcomes for safety were assessed using slit-lamp biomicroscopy findings and ocular adverse event rates between

the MiSight and control groups. Adverse events were classified and reported according to a pre-determined list detailed in the study protocol. Slit-lamp signs were graded using a 0- to 4-point scale developed from the guidance illustrated in the regulatory standard ISO11980, with 0 representing none or absent findings and 4 representing severe. Unique supplementary descriptions were added to this scale for specific tissue grading.

Sample Size Estimation

The target effect size for sample size calculation was specified as "0.25 D per year (i.e., 0.75 D for 3 years)." This therefore produced two aims for the primary effectiveness end point; the first was to detect 0.25 D between groups for each year of the study. Using 0.25 D per year as a target and assuming a standard deviation of 0.50 D, it was estimated that 87 subjects per group would be needed (two-sample t test with equal variance, $\alpha = 0.05$, power = 90%). The protocol anticipated an enrollment target of 150 eligible subjects per group to account for attrition (14%, or 42 subjects per year) over the 3-year period.

However, because of a longer-than-expected recruitment period, it was evident that the number of subjects enrolled would be smaller than this target. As a consequence, the sample size requirements for the second aim, which was to detect a 0.75-D difference between the groups for 3 years, were applied. Assuming a standard deviation of 0.50 D, 22 subjects (11 per group) would have been needed (two-sample t test, $\alpha = .05$, power = 90%) to complete the study. As such, the final sample size of 144 eligible subjects was more than adequate to detect the primary effectiveness end point.

Statistical Methods

Baseline data for the MiSight and control groups were evaluated by the two-sample t test (continuous data), Mann-Whitney U test (categorical data), or Fisher exact test (nominal data). Imbalances of potentially confounding variables that were identified between the two groups were addressed by including them as covariates in the final analysis. All inferences were carried out with the type I error rate controlled at 5%.

Data were pooled from all sites based on three factors: (1) common protocol, (2) common data collection procedures, and (3) closely monitored protocol compliance. As specified in the protocol, an analysis of the interaction of lens type by site was performed and found not significant ($P > .10$) for the primary outcome variables.

The primary outcome measures for effectiveness were checked for normality and first compared between treatment groups using a t test. These primary outcomes were also compared using linear mixed models. Comparisons between the MiSight and control lenses were carried out using two-sided confidence interval constructed least-square mean differences at each follow-up visit. The model included treatment (lens type), visit, site, and the interactions: visit by treatment and site by treatment as fixed effects; age, sex, weekday wearing time, weekend wearing time, and baseline value as fixed covariates; and subject (nested in site) and eye as random effects. The inclusion of eye as a random effect accounts for any correlation between eyes. The analyses included all evaluable subjects who did not have a protocol deviation that rendered data unsuitable for inclusion. If a subject missed a primary outcome visit, no data were included for that visit, but all other visits with evaluable data for that subject were included. Data from discontinued subjects were included up to the point of their discontinuation. A statistical difference was concluded if the 95% confidence limit of the mean difference was greater than zero (test minus control). The questionnaire responses were compared with linear mixed models. The model included treatment (lens type), visit, site, and the interactions.

The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Data

Table 2 summarizes the demographics for all enrolled subjects. There were no statistically significant differences between the MiSight and control groups with respect to the critical demographic factors that have been associated with myopia progression. At baseline, the mean cycloplegic spherical equivalent refractive errors were –2.02 ± 0.77 D for the MiSight lens group and –2.19 ± 0.81 D for the control lens group. Axial length was also similar between the groups: 24.42 ± 0.70 and 24.46 ± 0.66 mm for the MiSight and control lens groups, respectively.

Subject Accountability

Fig. 1 shows the flow of participants through the clinical trial from recruitment to study completion and analysis. Of the 187 subjects who were screened, 144 were eligible and randomized. This number comprised 21 subjects in Portugal, 28 in the United Kingdom, 31 in Singapore, and 64 in Canada. The main reasons for ineligibility were spherical refractive error (15), cylinder (7), and anisometropia (5). Of those allocated treatment, six had unacceptable lens fits (three MiSight and three control), and two had challenges with lens insertion and removal, whereas one control subject elected to withdraw from the study during the first week.

TABLE 2. Subject demographics at baseline

Variable	Control (n = 74)	MiSight (n = 70)	*P*
Age (y)	10.1 ± 1.4	10.1 ± 1.3	.83
Range	8–12	8–12	
<10	42 (57%)	40 (57%)	
10–12	32 (43%)	30 (43%)	
Male	37 (50%)	38 (54%)	.62
Female	37 (50%)	32 (46%)	
White (European)	40 (54%)	39 (56%)	.79
East Asian	18 (24%)	16 (23%)	
West Asian	7 (9%)	5 (7%)	
Other	4 (5%)	2 (3%)	
Mixed	5 (7%)	8 (11%)	
	(n = 148 eyes)	**(n = 140 eyes)**	
Cycloplegic spherical equivalent (D)	–2.19 ± 0.81	–2.02 ± 0.77	.08
Range	–0.83 to –4.00	–0.77 to –3.77	
Cylinder (D)	–0.40 ± 0.21	–0.40 ± 0.21	.82
Range	0.00 to –0.75	0.00 to –0.75	
Axial length (mm)	24.46 ± 0.70	24.42 ± 0.66	.90
Range	23.0 to 27.0	22.7 to 26.0	

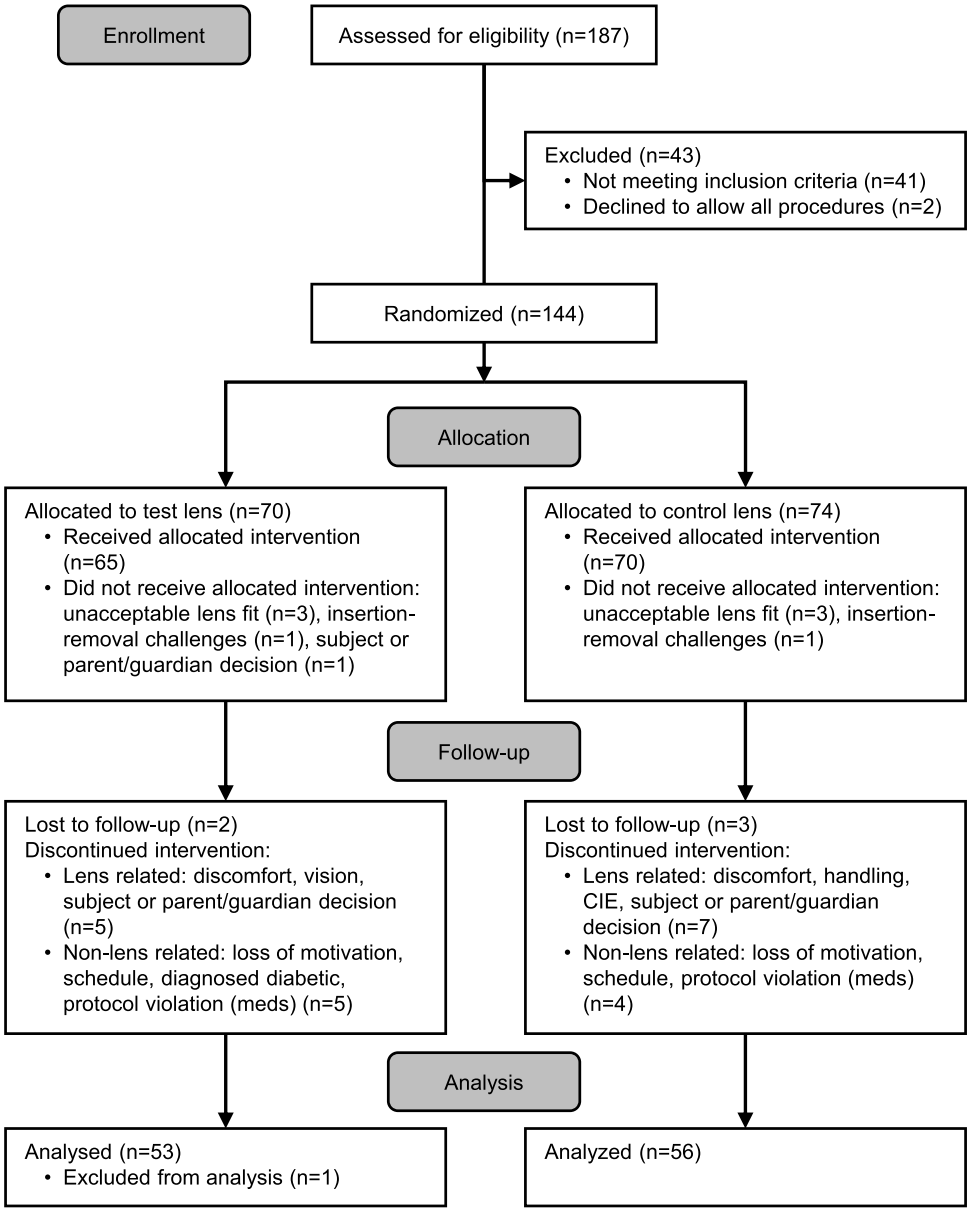

FIGURE 1. Flowchart to indicate the disposition of subjects from screening to study completion.

Thus, 135 subjects were dispensed the allocated intervention, ranging between 21 and 60 subjects per site.

One hundred nine subjects completed the 3-year clinical trial (53 MiSight and 56 control). One subject in the MiSight group was excluded from the 36-month analysis because the subject began a course of growth hormone treatment during the last 6 months of the study. The total retention rate for the study was 75.5%.

Compliance to the protocol-specified wearing time was high. The mean wearing times reported for weekdays at the 36-month visit were 13.3 ± 1.5 hours per day for the control group and 13.7 ± 1.5 for the MiSight group, and this difference was not significant. The mean wearing times reported for weekends were slightly lower but were 12.4 ± 0.9 and 12.1 ± 1.2 hours per day for the control and MiSight groups, respectively. The linear mixed model showed no differences between lens types for wear time at weekdays or weekends ($P > .05$). Subjects also reported the number of days per week that lenses were worn. The mean reported wearing times were at least 6.5 days per week for both lens groups. None of the above measures were significantly different between the groups.

Refractive Error Progression

The MiSight group exhibited less progression in cycloplegic spherical equivalent refraction than did the control group at each of the annual follow-up visits (Fig. 2, Table 3). In comparison with the control group, the changes in cycloplegic spherical equivalent refraction were on average 0.40 D less (–0.58 vs. –0.18 D) with MiSight at 12 months, 0.54 D less at 24 months,

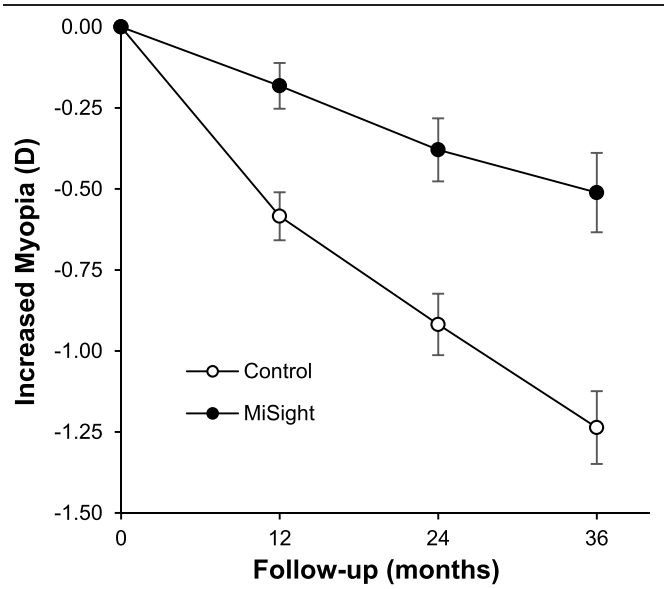

FIGURE 2. Mean unadjusted changes in spherical equivalent refractive error (D) for the test (MiSight) and control (Proclear 1-day) study groups. The filled and open symbols represent the MiSight and control groups, respectively, for the 36-month study period. The error bars denote the 95% CI of the mean changes. The mean unadjusted differences were 0.40 D less with MiSight at 12 months, 0.54 D less at 24 months, and 0.73 D less at 36 months. CI = confidence interval.

and 0.73 D less at 36 months. These differences were statistically significant at each time point (Student *t* test, $P < .0001$), representing myopia control effects of 69%, 59%, and 59%, respectively.

After adjusting for factors detailed in Statistical Methods, the least-square estimated mean progression was calculated. The estimated mean progression and differences are shown in Table 4. The adjusted differences in progression rate remained statistically significant at all follow-up visits.

Fig. 3 shows the distribution of individual subject's change in spherical equivalent refraction after 36 months. Among the MiSight lens–wearing eyes, 41% showed no clinically meaningful change in spherical equivalent refraction (defined as –0.25 D or less change) in comparison to 4% of the eyes in the control lens group. Conversely, 62% of the control lens–wearing eyes had progressed by more than –1.00 D compared with 18% of the MiSight eyes.

Axial Elongation

The MiSight group exhibited less axial length growth than did the control group at each of the annual follow-up visits. At 12 months, the change in axial length was 0.24 mm in the control group versus 0.09 mm in the MiSight group, representing on average a 0.15-mm less growth in the MiSight lens group. At 24 and 36 months, the change in axial length growth was 0.24 and 0.32 mm less in the MiSight lens group, respectively (Fig. 4, Table 3). These differences were statistically significant at each time point, representing myopia control effects of 63%, 53%, and 52%, respectively.

After adjusting for factors detailed in Statistical Methods, the least-square estimated mean change in axial length was calculated. The estimated mean change and differences between groups are shown in Table 4. The differences in axial length were statistically significant at all follow-up visits.

TABLE 3. Myopia progression for spherical equivalent and axial length

Visit	Study group	n (Eyes)	Spherical equivalent (D ± SD)	Change (D)	95% CI
Baseline	Control	148	–2.19 ± 0.81		
	MiSight	140	–2.02 ± 0.77		
12 mo	Control	120	–2.80 ± 1.01	–0.58 ± 0.41	–0.51 to –0.66
	MiSight	116	–2.17 ± 0.85	–0.18 ± 0.39	
24 mo	Control	120	–3.13 ± 1.08	–0.92 ± 0.53	–0.82 to –1.01
	MiSight	110	–2.33 ± 0.92	–0.38 ± 0.52	
36 mo	Control	112	–3.45 ± 1.14	–1.24 ± 0.61	–1.12 to –1.35
	MiSight	104	–2.52 ± 0.98	–0.51 ± 0.64	
			Axial length (mm)	**Change (mm)**	**95% CI**
Baseline	Control	148	24.42 ± 0.66		
	MiSight	140	24.46 ± 0.70		
12 mo	Control	120	24.68 ± 0.66	0.24 ± 0.15	0.21 to 0.27
	MiSight	116	24.52 ± 0.69	0.09 ± 0.13	
24 mo	Control	120	24.88 ± 0.70	0.45 ± 0.23	0.41 to 0.50
	MiSight	110	24.60 ± 0.64	0.21 ± 0.22	
36 mo	Control	112	25.07 ± 0.74	0.62 ± 0.30	0.57 to 0.68
	MiSight	104	24.76 ± 0.66	0.30 ± 0.27	

CI = confidence interval.

TABLE 4. Least-square mean estimates for spherical equivalent and axial length progression

Visit	Study group	Spherical equivalent change (D ± SD)	Difference (D ± SD)	95% Confidence interval	*P*
12 mo	Control	–0.64 ± 0.07	0.38 ± 0.09	0.21 to 0.55	<.0001
	MiSight	–0.27 ± 0.07			
24 mo	Control	–0.99 ± 0.07	0.52 ± 0.09	0.35 to 0.69	<.0001
	MiSight	–0.47 ± 0.07			
36 mo	Control	–1.31 ± 0.08	0.67 ± 0.09	0.49 to 0.84	<.0001
	MiSight	–0.65 ± 0.07			
		Axial length change (mm)	**Difference (mm)**	**95% Confidence interval**	***P***
12 mo	Control	0.23 ± 0.03	–0.13 ± 0.04	–0.21 to –0.05	<.002
	MiSight	0.10 ± 0.03			
24 mo	Control	0.45 ± 0.03	–0.22 ± 0.04	–0.30 to –0.14	<.0001
	MiSight	0.23 ± 0.03			
36 mo	Control	0.62 ± 0.03	–0.28 ± 0.04	–0.36 to 0.20	<.0001
	MiSight	0.34 ± 0.03			

Factors Impacting Progression

Statistically significant factors affecting refractive error progression and axial length elongation included lens type, investigative site, study visit, age, and sex (Table 5). Ethnicity and baseline myopia (refractive error or axial length) were not significant. There was a significant interaction of lens type and visit for refractive error progression and axial elongation, suggesting that the rate of change of the two lens types is different over the years. There was no significant interaction between lens type and site, suggesting that the myopia progression for both lens types was independent of investigative sites. The interaction of lens type with age, sex, or baseline myopia was not significant and was removed from the model. The absence of significant interactions of lens type with age, sex, baseline myopia, or investigative site demonstrates that the myopia control effect is independent of these factors in this study population.

Correlation between Changes in Axial Length and Refractive Error

There is a strong relationship between increasing myopia with increasing axial length. With the MiSight and control combined

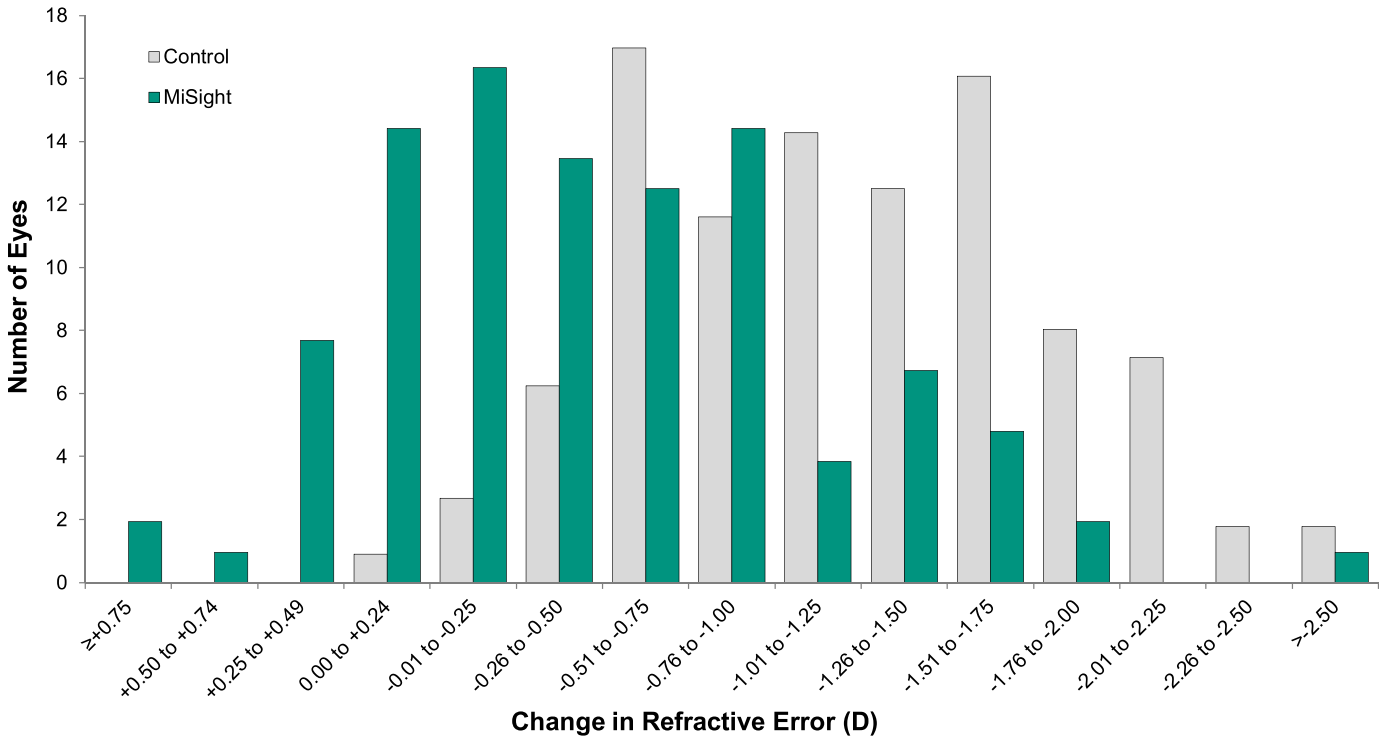

FIGURE 3. Frequency distribution of change in refractive error from baseline to 36 months. The filled and open bars represent the MiSight and control groups, respectively.

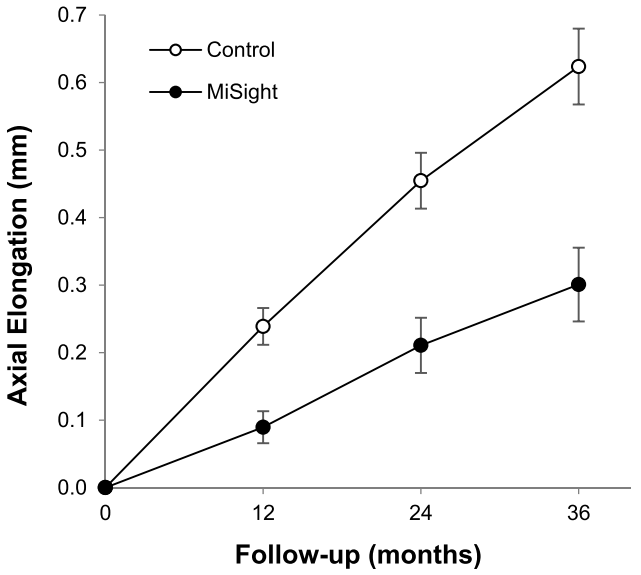

FIGURE 4. Mean unadjusted changes in axial length (in millimeters) for the test (MiSight) and control (Proclear 1-day) study groups. The filled and open symbols represent the MiSight and control groups, respectively, for the 36-month study period. The error bars denote the 95% CI of the mean changes. The mean unadjusted differences were 0.15 mm less with MiSight at 12 months, 0.24 mm less at 24 months, and 0.32 mm less at 36 months. CI = confidence interval.

data, there were statistically significant correlations at each of the follow-up visits ($P < .0001$). These correlations became stronger as the study progressed. At 12 months, the correlation coefficient (R) was –0.77; at 24 months, the R value was –0.86; and at 36 months, the R value was –0.90.

The correlations were also statistically significant at each follow-up visit when considered separately for the MiSight and control groups. At 36 months, the correlation coefficients were –0.89 ($P < .0001$) for the MiSight group and –0.85 ($P < .0001$) for the control group.

The slope for all subjects at 36 months was –0.42 (95% confidence interval, –0.45 to –0.39), showing that a 0.1-mm change in axial length corresponded to 0.24-D change in myopia in this study population. The slope did not vary significantly between treatment groups or among sites.

Contact Lens Visual Acuity

At the dispensing visit, mean distance visual acuity with contact lenses was within one letter for the MiSight lenses and control lenses (–0.03 ± 0.06 vs. –0.05 ± 0.07 logMAR). Mean visual acuity with contact lenses varied slightly at follow-up visits, possibly due to refractive error changes that occurred since the last visit, but did not differ by more than two letters at any visit. With spherical overrefraction, best-corrected visual acuity with contact lenses remained similar for the two lens types and within one letter at each visit. Near visual acuity remained within one letter for the MiSight and control lenses at each visit. The data for visual acuity are shown in Table 6.

Subjective Responses

Responses to the question "How easy is it to put the lenses on your eye?" were obtained. At the 1-month visit, a large proportion of children (>80%) in each group described insertion of lenses as "kind of easy" or "really easy" (top 2 box responses). Over the remainder of the study period, more than 90% of subjects rated within the top 2 box category. There was no difference between study groups in the response to this question ($P = .64$). With respect to lens removal, the responses to "How easy is it to take the lenses out of your eye?" remained in the top 2 boxes for more than 90% of the subjects throughout all visits of the study; again, there was no difference between study groups for this response ($P = .99$).

A positive response to the general experience of wearing contact lenses was also observed. For the question "How much do you like wearing your contact lenses?" an average of 97% of children chose one of the top 2 responses across all visits of the study. There was no difference between study groups in the response ($P = 1.00$). This was compared with a less positive response for spectacles, with an average of 57% choosing one of the top 2 responses to the question "How much do you like wearing your spectacles?" across all visits. The difference between groups approached statistical significance ($P = .05$), In general, this was due to higher variation in the response across the groups, throughout the study period.

TABLE 5. Tests of fixed effects for primary variables

	Refractive error			Axial length		
Model term	***df***	***F***	***P***	***df***	***F***	***P***
Lens type	1, 106	44.31	<.0001	1, 106	33.29	<.0001
Site	3, 104	13.26	<.0001	3, 106	4.90	.003
Visit	2, 209	119.89	<.0001	2, 209	245.13	<.0001
Age	1, 103	7.78	.006	1, 108	13.75	.0003
Sex	1, 103	9.20	.006	1, 122	4.43	.04
Ethnicity	4, 104	0.59	.67	4, 106	0.11	.98
Baseline spherical equivalent/axial length	1, 361	2.22	.14	1, 364	0.26	.61
Lens type × site	3, 105	1.08	.36	3, 107	1.70	.17
Lens type × visit	2, 209	9.03	.0002	2, 209	14.89	<.0001
Site × visit	6, 209	2.21	.05	6, 209	5.31	<.0001
Lens type × site × visit	6, 209	1.14	.34	6, 209	0.81	.56

TABLE 6. BCVA with contact lenses

	n (eyes)	Presenting contact lens VA	BCVA with spherical overrefraction	Presenting contact lens near VA
Control				
Dispensing	148	–0.05 ± 0.07	–0.05 ± 0.07	–0.07 ± 0.11
12 mo	120	+0.01 ± 0.13	–0.07 ± 0.08	–0.11 ± 0.11
24 mo	120	+0.00 ± 0.13	–0.07 ± 0.08	–0.11 ± 0.09
36 mo	112	+0.00 ± 0.10	–0.05 ± 0.07	–0.10 ± 0.08
MiSight				
Dispensing	140	–0.03 ± 0.06	–0.03 ± 0.06	–0.05 ± 0.10
12 mo	116	–0.04 ± 0.09	–0.07 ± 0.06	–0.09 ± 0.10
24 mo	110	–0.04 ± 0.10	–0.07 ± 0.08	–0.11 ± 0.09
36 mo	104	–0.01 ± 0.11	–0.05 ± 0.07	–0.09 ± 0.09

All values are in logMAR (mean ± SD). BCVA = best-corrected visual acuity; VA = visual acuity.

Safety Evaluation

There were no serious (events that are vision-threatening and result in permanent impairment of a body function or permanent damage to a body structure) or significant (events that usually are symptomatic but are non–vision-threatening and result in temporary impairment of a body function or temporary damage to a body structure) ocular adverse events reported in the 3-year study. There were 18 events (11 subjects) in subjects wearing the MiSight lens and 12 (10 subjects) with the control lens. Seven events (six subjects) with the test lens and seven events (five subjects) with the control lens were considered lens related. Four of these were asymptomatic corneal infiltrative events, one in the MiSight lens and three in the control lens group. The remainder of these events included foreign body, bilateral allergic reaction, unilateral mild pannus (requiring temporary discontinuation), superficial punctate corneal staining, a unilateral subconjunctival hemorrhage, and a case of irritation with the lens located under the eyelid. There were no reports of loss of best-corrected visual acuity.

There was only one instance of a slit-lamp finding of grade 3 or more. Grade 3 palpebral roughness was recorded in a MiSight lens–wearing eye at the 1-month visit. This was attributed to a

TABLE 7. Summary of previous studies of soft contact lenses on myopia progression

Authors	Duration (mo)	Analyzed test/ control	Discontinued (%)	Study design	Treatment lens	Control lens	Age (y)	Entry Rx range (D)	Treatment effect for axial length: Axial length difference (mm)	Treatment effect for axial length: Myopia control (%)
Anstice and Phillips[15]	10	35/35*	13	Randomized paired eye, crossover	Dual focus	Soft lenses	11–14	–1.25 to –4.50	0.11	49
Sankaridurg et al.[16]	12	43/39	18	Prospective	Progressive periphery	Spectacles	7–14	–0.75 to –3.50	0.15	38
Fujikado et al.[18]	12	11/13	0	Randomized masked, crossover	Menicon low-addition (Nagoya, Japan)	Soft lenses	10–16	–0.75 to –3.50	0.05	25
Aller et al.[21]	12	39/40	9	Randomized, masked	Acuvue Bifocal (Vistakon, a division of Johnson & Johnson Vision Care, Jacksonville, FL)	Soft lenses	8–18	–0.50 to –6.00	0.19	79
Cheng et al.[22]	12	53/59	16	Randomized, masked	Positive spherical aberration	Soft lenses	8–11	–0.75 to –4.00	0.14	39
Walline et al.[17]	24	27/27	33	Historical control	Proclear multifocal	Soft lenses	8–11	–1.00 to –6.00	0.12	29
Allen et al.[24]	24	45/50	33	Randomized masked	Aberration controlled monofocal	Soft lenses	14–22	–0.75 to –10.00	–0.01	–0.1
Lam et al.[19]	24	65/63	42	Randomized, masked	Custom concentric bifocal	Soft lenses	8–13	–1.00 to –5.00	0.12	32
Paune et al.[20]	24	19/21	44	Prospective	Radial refractive gradient	Spectacles	9–16	–0.75 to –7.00	0.14	27
Ruiz-Pomeda et al.[23]	24	41/33	7	Randomized, masked	MiSight	Spectacles	8–12	–0.75 to –4.00	0.17	36
Present study	36	52/56	19	Randomized, masked	MiSight	Soft lenses	8–12	–0.75 to –4.00	0.32	52

Rx = refraction.

foreign body and was not noted at subsequent follow-up visits. Palpebral roughness was graded from 0 to 4 as follows: 0 (none), uniform satin appearance of the conjunctiva; 1 (trace), slight conjunctival injection without texture; 2 (mild), mild or scattered papillae/follicles less than 1 mm in diameter; 3 (moderate), (*a*) significant papillae/follicles less than 1 mm in diameter and/or marked conjunctival injection and (*b*) staining of the top of one papilla; and 4 (severe), (*a*) localized or generalized papillae/follicles 1 mm or more in diameter and (*b*) staining of the top of more than one papilla.

DISCUSSION

The findings of this 3-year randomized clinical trial demonstrate that myopia progression is significantly slowed by the MiSight soft contact lens. MiSight lenses showed less unadjusted refractive error change by 0.40 D at 12 months, 0.54 D at 24 months, and 0.73 D at 36 months compared with the single-vision control contact lens. This was closely mirrored by a reduction in axial elongation of 0.32 mm at 36 months in the MiSight group. The strong correlation between axial elongation and refractive error progression demonstrates that the lenses slow myopia progression by reducing the rate of axial growth.

Table 7 presents a summary of other clinical trials that utilized soft contact lenses for myopia control, arranged by trial duration. This current clinical trial presents 3-year results, whereas all of those summarized in Table 7 are 1- or 2-year studies. The reduction in myopia progression reported here approaches the greatest observed effect size from previously published studies. However, the absence of studies of similar duration makes comparison of effect size difficult.

Ruiz-Pomeda et al.[23] recently published results of a 2-year clinical trial assessing myopia progression with the MiSight lens compared with a control group wearing single-vision spectacles. Although the study used a different control group and different statistical methods for accounting for imbalances between groups at baseline compared with the current study, overall the results of the studies are similar. In the study by Ruiz-Pomeda et al., the mean change in axial length at the 12-month visit was 0.12 mm for the MiSight lens and 0.24 mm for the control group, for a difference in elongation of –0.12 mm. At the 24-month visit, the difference in axial elongation was –0.16 mm (0.28 vs. 0.44 mm). These findings are within the 95% confidence intervals (Table 4) for adjusted axial length differences of this current study (95% confidence intervals, –0.21 to –0.05 [year 1] and –0.30 to –0.14 mm [year 2]).

The current clinical trial used a soft contact lens as the control group. This is in line with the recommendation of the Food and Drug Administration Public Workshop on Controlling the Progression of Myopia.[33] The lenses were matched for all parameters, with the exception of the dual-focus optical design of MiSight. This way, if physiological effects are produced in either a myopic or hyperopic direction, whatever the underlying etiology, they should be identical in the two groups, and thus, any refractive and axial length differences between the two groups can be attributed to the optical design.

The study was conducted in four countries and recruited an ethnically diverse sample. Although myopia progression showed variation among investigational sites, the reduction in myopic progression with MiSight was statistically significant at all sites. Some studies, although not all, have noted a difference in myopia progression as a function of ethnicity.[34–36] This study found no such effect; furthermore, the interaction of lens type with ethnicity or lens type with site when assessing spherical equivalent refraction and axial length progression was not significant, which implies generalizability of the myopia control treatment across different regions and populations.

The high level of wearing time compliance (both hours and days per week) for both groups did not provide sufficient variation to evaluate the effect of wearing time on myopia progression reported by some investigators.[19]

In line with other research, myopia progression varied with age, with younger subjects progressing faster. However, the degree of myopia control with MiSight was not impacted by this factor, suggesting that MiSight works with similar treatment effect in younger and older subjects. A similar finding is observed with sex, where female participants display higher myopia progression than do male participants, also observed by Hyman et al.,[36] but again, the interaction with treatment effect was not significant.

For both refractive error progression and axial elongation, there was a persistence of myopia control effect across the 3 years of the study. The magnitude of the effect was highest in the first year of wear but continued to accrue across the period of observation. In other 2-year studies of myopia control with multifocal soft contact lenses (Table 7), the myopia control effect persisted and accrued over the 2 years.[17,19,20] This is in contrast to the 3-year Correction of Myopia Evaluation Trial (COMET) trial of progressive addition spectacles,[37] where the adjusted treatment effect was 0.18 D with minimal to no accrual in the subsequent 2 years.

A significant proportion of the MiSight group (41%) showed no meaningful progression in spherical equivalent refraction (–0.25 D or less change) over the duration of the trial. In contrast, only 4% of control eyes showed a similar lack of progression (absolute risk reduction, 37%). The number of eyes needed to treat (=1/absolute risk reduction) to achieve this benefit is approximately three eyes (95% confidence interval, 2.1 to 3.6). Therefore, for every three eyes treated in this cohort, one eye will show no meaningful myopic progression over a 3-year period.

Questionnaire responses collected throughout the study align with previous studies[38,39] that have shown that soft contact lenses are well accepted by children. The children in this study showed that they were able to achieve full-time wear, were able to handle the lenses confidently, and had a positive response to contact lens wear. Only one child discontinued for vision quality reasons over the 3-year period. The overall retention rate compares very favorably with previous studies (Table 7).

No serious ocular adverse events were observed during the 3-year clinical trial, including no cases of microbial keratitis. Only four nonsignificant corneal infiltrative events were reported over the 3-year period, all asymptomatic and noted at scheduled visits. The absence of serious or significant ocular adverse events supports the growing acceptance that soft contact lenses are safe for use by children.[40]

Limitations

Enrollment was lower than the target because of recruitment difficulties at some of the sites; however, subject retention was high, and the sample size was sufficiently large to show differences between the two lens types for the primary efficacy end point of 0.75 D at 3 years.

Subjects in this clinical trial were not withdrawn from treatment to assess the extent to which the benefit is sustained. Some myopia treatments with atropine have been shown to be susceptible to post-treatment acceleration.[41] Finally, the investigators had access to the

randomization codes. Although these randomization codes were only identified as "lens A" and "lens B," theoretically an examiner could have identified whether lens A was the experimental or control assignment.

Summary

This 3-year randomized clinical trial, designed to evaluate the safety and effectiveness of a soft contact lens intended to slow myopia progression in children, demonstrates the following:

- The progression of refractive error in children is significantly reduced by the MiSight lens compared with a single-vision soft contact lens.
- The axial elongation that underlies and is correlated with refractive error progression is significantly less with the MiSight lens compared with a single-vision soft contact lens.
- No safety concerns were evident for this population of children who started daily disposable soft contact lens wear between 8 and 12 years of age.
- The high subject retention, long wearing time, and favorable subjective ratings show that contact lens acceptance was sustained across 3 years. This work supports previous findings[38,39] that soft contact lenses are well accepted by children. Children as young as 8 years are able to achieve full-time wear, handle the lenses confidently soon after initial fitting, and achieve good comfort.

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