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Randomized trial of soft contact lenses with novel ring focus for controlling myopia progression

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Abbreviations and acronyms
AL (axial length), 95%CI (95% confidence interval), DF (dual-focus contact lens design), EE (prototype contact lens design intended to enhance efficacy), EV (prototype contact lens design intended to enhance vision), LSM (least-square mean) MMRM (mixed models with repeated measures), pCLUE (pediatric Contact Lens User Experience), SD (standard deviation), SE (standard error), SECAR (spherical equivalent cycloplegic autorefraction), SV (single-vision contact lens design), VA (visual acuity).

Key words
Pediatric, Myopia progression, Myopia control, Soft contact lenses, Axial length, Vision

Financial Support
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Abstract

Purpose: To evaluate efficacy and vision with two prototype myopia control soft contact lenses with non-coaxial ring-focus designs (EE, for enhancing efficacy and EV, enhancing vision) compared to dual-focus (DF) and single-vision (SV) designs.

Design: Multi-center, 6-month, randomized, controlled, double-masked clinical trial.

Participants: 199 myopic (-0.75D to -4.50D) children aged 7 to 12 years.

Methods: Participants were randomized with stratification into myopia control (EE, EV or DF) or SV arms at 9 clinical sites in 3 countries. Post-cycloplegia axial length (AL) and spherical equivalent autorefraction (SECAR) were measured at baseline and 26 weeks. AL was also measured without cycloplegia at baseline, 1, 4, 13, and 26 weeks. Progression was analyzed using linear mixed models by intention-to-treat population. Visual acuity (VA) and vision quality were monitored.

Main Outcome Measures: Axial elongation, change in SECAR.

Results: A total of 185 subjects completed the study (n = 44, 49, 45, and 47, for EE, EV, DF, and SV, respectively). There were no serious/significant ocular adverse events. After 26 weeks, EE, EV, and DF all had statistically significantly less axial elongation compared to SV (unadjusted mean [SD]: EE, 0.079 [0.125]; EV, 0.119 [0.101]; DF, 0.135 [0.117]; SV; 0.189 [0.121] mm). The estimated least-square mean (LSM) difference (adjusted 95% CI) compared to SV were -0.105 (-0.149, -0.062), -0.063 (-0.106, -0.020), and -0.056 (-0.100, -0.013) mm for EE, EV, and DF, respectively. EE alone had statistically significantly less progression of SECAR than SV (EE: -0.12 [0.27] D vs. SV: -0.35 [0.33] D; LSM difference: 0.22 D [0.09, 0.35]). EE also had statistically
significantly less axial elongation compared to DF (-0.049 mm [-0.093, -0.004]). Changes in AL and SECAR of EV and DF were not statistically different. All three myopia control lenses had mean VA close to 0.00 logMAR with estimated 95% CIs less than 0.10 logMAR. EE and DF produced similar reports of haloes, but more than EV and SV.

**Conclusions:** The prototype contact lenses met the design intent; EE was more efficacious in slowing axial elongation than DF with comparable vision performance, while EV produced comparable efficacy to DF with similar vision performance to SV.

**Introduction**

With increased prevalence of myopia worldwide, a recent focus of clinical and scientific research has been to find safe, effective methods for controlling myopia progression.\(^1\)\(^2\) Eye care practitioners have a long history of introducing relative plus power (“ADD” power) to myopia correcting lenses to slow myopia progression, albeit originally in relation to a perceived link between binocular and accommodative problems and myopia progression.\(^3\)\(^4\) Also, research in young animals shows that hyperopic defocus at the retina leads to development of myopia.\(^5\) As such, various modern optical interventions that introduce myopic defocus in the visual field have been applied for myopia control.\(^1\)\(^6\) These include a variety of ‘simultaneous vision’ soft contact lenses, such as aspheric progressive, dual-focus, traditional multifocal, and extended depth of focus designs.\(^6\)\(^7\) These optical designs inevitably introduce aberrations to the eye, affecting vision.
Despite advances in methodologies, there appear to be limitations to the extent to which myopic progression may be slowed. Increasing the ADD power in the treatment zone of myopia control soft lenses has been shown to result in increased treatment efficacy. However, increasing ADD power in simultaneous vision lenses ostensibly increases the impact on vision. Thus, it is generally held that there is a trade-off between vision quality and myopia control efficacy when manipulating the magnitude of ADD power or the size and location of the treatment zone.

In striving to limit the compromise involved in this efficacy-vision trade-off, we have developed a new concept that differs from earlier designs. Most previous soft contact lens designs generally rely on presbyopic principles to achieve myopia control effect; that is, the ADD power in the treatment zone serves to focus rays from a near point source more or less to a focal point at the retina in an unaccommodated eye. Thus, rays originating from a distant object passing through this zone will be focused in front of the retina and degrade vision. This practice sets a constraint in the ADD power, size, and location of the treatment zone before vision quality is significantly compromised and, as it turns out, is unnecessary. An essential design objective of the concept tested here was to break this interdependence between efficacy and vision quality.

Here, we investigate this new design concept by comparing the myopia control efficacy and vision performance of two prototype contact lenses (EE and EV, designed to enhance efficacy and vision, respectively) with concentric annulus, dual-focus (DF) and single-vision (SV) lenses. We hypothesized that both prototype lenses would show significant reduction in axial...
elongation compared to the SV lens. We also hypothesized that EE would outperform the DF lens in myopia control efficacy but with similar vision performance and EV would outperform the DF lens in vision performance with similar myopia control efficacy.

**Methods**

The clinical trial was performed in accordance with the ethical principles of the Declaration of Helsinki and standards for Good Clinical Practice. Prior to participation, informed assent and informed consent were obtained from each pediatric subject and their parent(s) or legal guardian(s), respectively. The research was approved by appropriate Institutional Review Boards or Independent Ethic Committees and Regulatory Authorities. This clinical trial was registered on ClinicalTrials.gov with the identifier NCT03408444 and conformed with the 2017 Final Rule for Clinical Trials Registration and Results Information Submission in accordance with Section 801 of the United States Food and Drug Administration Amendments Act of 2007.

**Study Design**

This was a multi-site, prospective, randomized, controlled, double-masked clinical trial of four study soft contact lenses with a four-arm-parallel group design conducted between December 2017 and May 2019 at nine international clinical sites (one in Canada, four in China, and four in the United States). Detailed site information can be found in Acknowledgment section of this paper.
Healthy male and female children between 7 and 12 years of age (inclusive) with myopia between -0.75D and -4.50D (inclusive) and 1.00D or less astigmatism were invited to participate in the study. Eligible subjects had best sphero-cylindrical corrected visual acuity of 20/25 (i.e., 0.10 logMAR) or better in each eye and were free of ocular and systemic pathologies.

The subjects were randomly assigned in a 1:1:1:1 ratio to wear one of four lens types in a daily disposable modality for a minimum of six months. Randomization was first stratified by site. At each site, subjects were further stratified based on age (7 to 9 and 10 to 12 years) and baseline refraction (-0.75 to -2.00 D and -2.25 D to -4.50 D). Each clinical site followed a computer-generated randomization scheme for study lens assignment. The randomization scheme was generated using randomly-permuted block randomization in the SAS software (Version 9.4, SAS Institute, Cary, NC), with each block containing four different lens codes that were the only identifiers of the study lenses.

After initial lens fitting and dispensing, subjects were examined at 1 week (7 ± 3 days), 4 weeks (28 ± 7 days), 13 weeks (91 ± 7 days), and 26 weeks (182 ± 14 days) for measurement of study related parameters and general contact lens wear evaluation. Contact lens power was adjusted if visual acuity was less than 20/25 during the study. The study was terminated after all subjects had completed the 26-week follow-up visit. A study duration of six months was selected because efficacy in a myopia control contact lens should become apparent within this timeframe. In other words, if a meaningful effect was not evident within six months, we considered that this would be indicative of failure of the lens design concept.
Sample size was based on treatment efficacy of $> 0.08$ mm (SD: 0.10) in axial elongation from baseline and $> 0.20$ D (SD: 0.32) in change of spherical equivalent cycloplegic autorefraction (SECAR) from baseline at six months. At a 2-sided Type I error level of 0.05, a sample size of 40 subjects per group would yield more than 80% power for detecting differences in axial length and SECAR between two lens groups.

Development of EE and EV lenses

Extensive pre-clinical work was performed on an optical table to establish design concepts that would mitigate the compromise between efficacy and vision. Change in axial length of eyes of human subjects was measured by optical biometry to track choroidal thickness change, a biomarker for myopigenic or myopia protective optical signals. A spatial light modulator was used to present various optical designs to the eye, obviating the need to manufacture prototype lenses and allowing high throughput of designs for proof-of-concept testing. A pupil tracking device maintained the position of the design relative to the eye. Vision performance testing, including visual acuity and contrast sensitivity were incorporated into the apparatus. A purpose-built halometer was also added to the optical table to allow width and brightness of haloes to be measured.

With the above-described apparatus, dozens of different optical stimuli were tested to arrive at an understanding of design features that drive short-term changes of choroidal thickness and impact vision, which led to the development and optimization of two prototype lens designs.
Like other soft lenses used for controlling myopia progression, these designs have zones with relative plus optical power compared to that required to correct myopic error. As such, the vision correction zone neutralizes refractive error to provide clear vision while rays of light passing through these “plus” zones create positive retinal blur (myopic defocus) for myopia control. Unlike conventional multifocal or dual-focus designs, the “plus” power in the prototype lenses is created without generating a coaxial point focus. Rays passing through concentric annular zones of the prototype lenses form a ring focus in front of the retina. The dispersal of these rays is such that the impact on vision can be modulated compared to existing coaxial multifocal designs, while still allowing control of myopia progression. These two prototype lenses were constructed to achieve either of two specific objectives. EE was designed to increase myopia control efficacy via introduction of a greater amount of plus power than conventional multifocal or dual-focus lens designs, while maintaining comparable visual performance. EV was designed to optimize vision while maintaining similar myopia control efficacy to a standard dual-focus lens. Both lenses included two concentric, annular zones with +7 D non-coaxial plus power for myopia control treatment, but these annular treatment zones in the EE lens were positioned closer to the center of the lens than for EV. EE also includes a +10 D co-axial treatment zone that was designed to further “boost” myopia control efficacy while limiting its impact on vision. These lens prototypes were granted “Breakthrough Device” designation by the United States Food and Drug Administration.
Study Contact Lenses

Four soft contact lenses were included in the study, comprising the two prototype lenses with multi-zone, concentric annulus, non-coaxial ring-focus designs (EE and EV), one lens with standard dual-focus design (DF) as a positive control, and one single-vision (SV) negative control lens.

All four study lenses were manufactured in silicone hydrogel material (senofilcon A) and were identical in major design aspects and manufacturing process, with the front surface optical design being the only differentiating factor. Lens dimensional parameters were determined in previous studies to provide optimal fit in pediatric patients, with a diameter of 13.8 mm and an aspheric back surface with a central curvature of 7.9 mm. There were no visible features either on visual inspection (naked eye) or under slit lamp examination to differentiate the four study lenses. Further, all four lenses were manufactured with the same packaging. Pre-assigned lens codes were printed on the primary label of the lens blister packs and cartons of the secondary packaging as the only information identifying the four study lenses. Both study personnel and subjects were masked to the identity of the study lenses. There was no breaking of double-masking during the study.

Lenses were worn in daily disposable mode with minimum compliant wear time of 8 hours per day, 5 days per week and recommended wear time of 10 hours or more per day, 7 days per week. Lens wear compliance was evaluated at each follow-up visit based on the subject/parent-reported typical time of lens insertion and removal (during both weekdays and weekends).
From this, average number of hours of lens wear per day and weighted average daily wear time per week were computed for each follow-up period.

**Endpoints and Procedure**

The two co-primary efficacy endpoints were axial elongation and change in spherical equivalent cycloplegic autorefraction (SECAR) from baseline to 26 weeks. Axial length was measured with Lenstar LS 900 (Haag-Streit, Bern, Switzerland) at 8 clinical sites and IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany) at 1 clinical site in China both before and after cycloplegia at baseline and 26 weeks. Additionally, axial length was measured at 1, 4, and 13 weeks without cycloplegia to provide information on the time course of axial elongation within the first six months of treatment. Five repeated measurements of axial length were obtained at each visit.

Cycloplegic autorefraction was measured at baseline and 26 weeks using an open-field autorefractor (WAM-5500, Grand Seiko, Shigiya Machinery Works Ltd., Hiroshima, Japan). Five repeated measures of sphero-cylindrical refraction, each of which was the mean of three consecutive readings, were obtained at each visit. Spherical equivalent power was computed from each of the five repeated measures. The averages of the five repeated measures of axial length and SECAR were used for statistical analysis. Cycloplegia was achieved by 2 drops of 1% cyclopentolate 5 minutes apart. A third drop of 1% cyclopentolate was used if residual accommodation was 2.00 D or more 30 minutes after the second drop. Post-cycloplegia axial length and SECAR were measured at least 30 minutes after the last drop.
Monocular and binocular visual acuities were measured with a high-contrast Landolt C logMAR visual acuity chart (Precision Vision, Woodstock, Illinois) under high luminance (190 cd/m²) conditions. Measurements were taken at baseline with subjects corrected with spherical lenses in a trial frame and at each subsequent visit with subjects wearing the study lenses. Patient-reported outcomes regarding vision, comfort, and handling of study lenses were collected through a pediatric Contact Lens User Experience questionnaire (pCLUE). This was internally developed specifically for use by pediatric contact lens wearers based on the existing CLUE™ questionnaire for the adult population. pCLUE included 9 questions on vision, 7 questions on comfort, and 6 questions on handling, all of which were graded on a 5-point frequency scale (Always to Never), except selected questions on ease of handling which were rated on a severity scale (Extremely easy to Not easy). Only results for 1 week, 4 weeks, and 26 weeks are presented in this report.

Statistical Analysis
The primary efficacy endpoint analyses were comparisons of post-cycloplegic axial elongation and change in SECAR in the EE, EV, and DF groups with those of the SV group. Axial elongation and change in SECAR from baseline to 26 weeks were analyzed separately using linear mixed models with repeated measures (MMRM) on the intent-to-treat population. The MMRM model included treatment group as a fixed effect and site as a random effect (G-side). Other baseline characteristics such as age, gender, race, and the corresponding baseline measures (axial length or SECAR) were included as fixed covariates. The within-subject repeated measures collected from different eyes was considered as a random effect (R-side) with the covariance of residuals.
modeled using the unstructured (UN) covariance structure. Adjustment for multiple
comparisons to control the inflation of Type I error rate was conducted using Dunnett’s
method.²¹

The same MMRM models were used for post-hoc comparisons of axial elongation and change
in SECAR among EE, EV, and DF lenses. Simulation based method was used to adjust the
multiple comparisons among the three study lenses.²² Post-hoc analysis of proportion of eyes
with shrinkage effect (i.e., reduction of non-cycloplegic axial length from baseline) over time
was conducted using a similar MMRM model by controlling for key demographic and baseline
characteristics and appropriately modelling random and repeated effects. Multiplicity was
adjusted using Dunnett’s method. The effect of mesopic pupil size and lens wear time in
myopia progression and potential interactions with lens type were also examined in a post-hoc
fashion.

Contact lens visual acuity and change of visual acuity from baseline were analyzed separately
for the four study groups utilizing a similar statistical approach to those described above. Safety
was assessed qualitatively by summarizing the number and rate of ocular Adverse Events by
subjects and by eyes.
Results

Subject disposition

A total of 240 subjects were screened between December 2017 and October 2018, with 199 eligible subjects randomly assigned to the four study arms. Fourteen subjects discontinued; therefore, 185 subjects completed the study. Subject flow and reasons for discontinuation are presented in Figure 1. The study was concluded after the last subjects completed the 26-week follow-up.

Baseline characteristics

Most of the enrolled subjects were neophytes who were either single-vision spectacle lens wearers (69%) or with no correction (20%) at the time of enrollment; the remaining 11% of subjects were habitual, single-vision, soft contact lens wearers. Demographics and baseline characteristics of the 199 randomized subjects are presented in Table 1. Of the 185 completed subjects, mean (SD) age was 10.0 (1.5) years (range: 7-12), 53% were females, 52% were Asians (50% of all completed subjects were ethnic Chinese), and 43% were White. Homogeneity testing found no statistically significant differences among the four groups with respect to age, gender, race, and baseline axial length and SECAR in randomized (intent-to-treat) subjects.

Compliance with wear time

Average lens wear time (hours/day) was similar among all four lens groups. The mean (SD) weighted average daily wear time was 10.9 (2.4), 11.4 (1.8), 11.1 (2.1), and 11.2 (2.0) hours at
1-week and 12.6 (1.6), 12.2 (1.8), 12.7 (1.6), and 13.1 (1.4) hours at 26 weeks, for EE, EV, DF, and SV groups, respectively.

Safety

There were no serious or significant ocular adverse events reported throughout the study. A total of 17 non-significant ocular adverse events (all reported as mild in severity) affecting 14 subjects (7% of all randomized subjects) were recorded. The most reported adverse event diagnoses were dryness (4 events in 2 subjects), followed by Grade 2 or less slit lamp findings (3 events in 3 subjects) and conjunctival foreign bodies (3 events in 2 subjects). There was one asymptomatic, non-significant infiltrative event reported from one site in China at 26 weeks with no treatment required. Other adverse events included one case each of bacterial conjunctivitis, unspecified conjunctivitis, meibomian gland dysfunction, meibomianitis, stye, and chalazion. Four of the events were deemed possibly related, six unlikely to be related, and seven not related to the lenses under study. None of the reported ocular adverse events led to subjects being discontinued from the study. Throughout the study, there were no observations of any grade 3 or higher slit lamp findings. There were two non-serious, non-ocular adverse events (both “headaches”) reported from two subjects in the SV group that were deemed possibly related to the SV lens. One case was deemed severe in symptoms, which led to subject withdrawal from the study, the other case was deemed mild, and the subject completed the study with no action taken.
Efficacy

Figure 2 presents the unadjusted mean (SD) axial elongation (A) and change in SECAR (B) by lens type across time. At 26 weeks, mean (SD) axial elongation from baseline was 0.079 (0.125), 0.119 (0.101), and 0.135 (0.117) mm for EE, EV, and DF, respectively, and 0.189 (0.121) mm for SV. Unadjusted mean SECAR change from baseline was EE, -0.12 (0.27); EV, -0.26 (0.32); DF, -0.25 (0.35) D; and SV, -0.35 (0.33) D. Table 2 show differences in statistically adjusted means (least-square mean, LSM) for the three myopia control lenses compared to SV with the corresponding adjusted 95% confidence intervals (95% CIs) at 26 weeks. All three myopia control lenses had statistically significantly less axial elongation than the SV lens, while EE was the only lens that also had statistically significantly less refractive progression (adjusted p < 0.05) than the SV lens. From the pairwise comparisons among the three myopia control lenses, EE also demonstrated statistically significantly less axial elongation compared to DF (LSM difference, adjusted 95%CI: -0.049, -0.093 to -0.004 mm, adjusted p < 0.05).

Reduction of axial length from baseline (defined as a negative change in non-cycloplegic axial length) was observed at 1 week in some subjects of all four lens groups. The proportion of subjects showing reduced axial length varied by time and lens group. The odds of showing reduced axial length were significantly higher among subjects wearing EE and DF compared to SV at 4 weeks (47% and 34% vs 15%; odds ratio [adjusted 95%CI] of 4.9 [1.8, 13.2] and 2.9 [1.1, 7.9], respectively; adjusted p < 0.05). At 13 and 26 weeks, EE was the only group that showed statistically significant odds of reduction of axial length compared to SV (24% vs. 7% and 23%
vs. 4%, respectively; odds ratio [adjusted 95% CI] of 4.0 [1.3, 12.2] and 7.4 [2.1, 26.5], respectively; adjusted p < 0.05).

At 4 weeks, significantly less mean axial elongation from baseline (LSM difference [adjusted 95% CI]) was observed for EE (-0.022 [-0.039, -0.004]) and DF (-0.022 [-0.037, -0.007]) compared to SV (adjusted p < 0.05). By 12 weeks, all three myopia control lens groups demonstrated statistically significantly less axial elongation than SV (-0.066 [-0.096, -0.035], -0.045 [-0.075, -0.015], and -0.044 [-0.074, -0.015], for EE, EV, and DF, respectively; adjusted p < 0.05), an effect which increased in magnitude by 26 weeks.

Post-hoc analyses were conducted to examine the role of age, gender, baseline refraction, mesopic pupil size, and lens wear time in myopia progression (axial elongation and change in SECAR) as well as their interactions with lens type by including these variables as covariates in statistical models. In both axial elongation and SECAR models, race was a significant factor (p<0.0001 and p=0.005, respectively) with Asians associated with more axial elongation and myopia progression, while race-by-lens type interaction was not statistically significant (p=0.85 and p=0.68, respectively). Age at baseline was only a significant factor for the axial elongation model (p=0.002) with younger age associated with more axial elongation, while age-by-lens type interaction was not significant (p=0.26). Baseline axial length and refraction, as well as mesopic pupil size were all found to be statistically insignificant in the axial elongation and SECAR models. Lens wear time was found to be significant (p=0.006 and 0.037, respectively),
and wear time-by-lens type interaction was significant in the axial elongation model at 0.15 significance level \((p=0.098)\), with longer wear time associated with less axial elongation.

**Vision performance**

Figure 3 plots unadjusted mean (\(\pm\) SD) monocular distance logMAR visual acuity at baseline with best-sphere spectacle correction and with study lenses at each visit (A), as well as changes of visual acuity from baseline (B). There was no significant difference in visual acuity among the four lens groups at baseline. At initial lens fitting, mean (\(\pm\) SD) best contact lens corrected visual acuity was -0.00 \(\pm\) 0.09, -0.04 \(\pm\) 0.09, -0.04 \(\pm\) 0.09, and -0.06 \(\pm\) 0.09 logMAR, for EE, EV, DF, and SV, respectively. None of the three groups wearing myopia control lenses had mean visual acuity that was statistically different from 0.00 logMAR, and none were statistically worse than baseline best-sphere spectacle correction (\(p > 0.05\)). Similar results were found in follow-up visits for EE and DF except that, at 13 weeks, EE showed statistically significant improvement in visual acuity by 0.03 (0.00, 0.05) logMAR compared to baseline (\(p < 0.05\)). Visual acuity with both EV and SV were found at several follow-up visits to be statistically better than 0.00 logMAR (e.g., -0.06 to -0.08 logMAR) and better than baseline by 0.03 to 0.06 logMAR (\(p < 0.05\)).

Throughout the study, there were no clinically or statistically significant differences between EV and SV groups in vision. Visual acuity with EE and DF was statistically worse than SV at some follow-up visits. The largest difference compared to SV was 0.07 (95%CI: 0.04, 0.10) logMAR for EE at 1 week and 0.05 (95%CI: 0.02, 0.07) logMAR for DF at 4 weeks. Despite this, the statistical
estimated mean visual acuity with EE and DF was not significantly different from 0.00 logMAR at all visits.

Subjective vision responses indicated that, for all four lens groups, more than 90% of subjects reported they were “very happy” with how well they could see. Only one subject (in the EE group) discontinued from the study due to unsatisfactory vision. Because of the nature of their optical designs, EE and DF were potentially expected to cause some reporting of visual symptoms such as halos or ghost images. Figure 4 plots the rates of positive and negative responses to vision questions. Shown are the proportions of responses indicating the two positive (top-2-boxes, T2B) and two negative (bottom-2-boxes, B2B) grades on a 5-point scale for each question in the questionnaire, respectively; for example, “always” or “usually” happy with clarity of vision throughout the day (T2B), “rarely” or “never” happy with how well they could see (B2B).

Consistent with findings of visual acuity measures, both EE and DF groups had more subjects with negative responses than EV and SV groups. The rate of reporting appeared to decrease over time, potentially due to subjects adapting to the lenses. At 1 week, the main visual symptom reported by subjects in the EE and DF groups was halos (B2B: 12% for both). By 26 weeks, this rate decreased to 5% and 7% for subjects of the EE and DF groups, respectively, while there were 14% of subjects in the DF group reporting ghost images at 26 weeks compared to 2% in the EE group.
Lens fit, handling and comfort performance

No instances of unacceptable lens fit were observed in any lens group throughout the study. Since all four study lenses had the identical lens geometry, as expected, all four study lenses had similar fitting characteristics. At all timepoints, all four groups had >90% eyes with centered lens fit. There were no reports of substantial lens decenteration. Optimal movement was reported in >86% of eyes (four groups combined) with no report of insufficient or excessive lens movement.

Study lenses were successfully dispensed in 96% of subjects after one training session for contact lens insertion and removal. pCLUE questionnaire indicated that among the 191 subjects completing 4 weeks of wear, 93% and 95% agreed that it was easy to insert and remove lenses, respectively.

There were no major issues identified in the pCLUE regarding subjective comfort. All four lenses performed similarly with regard to comfort. For example, rates of positive responses (top two grades on the 5-point scale) to the question “were the contact lenses comfortable” was above 85% at all follow-up visits.

Discussion

All three myopia control designs were effective at slowing axial elongation after six months of lens wear while providing good visual quality. Since EE produced greater myopia control efficacy while maintaining comparable visual performance to DF, and EV provided essentially
unaffected vision while maintaining similar myopia control efficacy to DF, the clinical performance of EV and EE was consistent with the design intent. The non-coaxial ring-focus technology of the prototype lenses used in this study offers potential performance advantages over traditional coaxial focus lenses and may mitigate the trade-off between efficacy and visual quality with such designs.

Axial length, as measured by optical biometry, is emerging as the preferred metric for assessing efficacy of myopia control products, as it is more repeatable than refractive error measurement, may be more closely related to the risk of complications later in life, and can be measured accurately without the need for cycloplegia. Indeed, efficacy with respect to axial elongation was evident at 4 weeks for EE and at 13 weeks for all of the myopia control lenses, where refractive error differences to SV remained not statistically significant for EV and DF at 26 weeks. Being able to discern a statistically significant treatment effect by optical biometry within a 4-week period may have implications for lessening the burden of screening myopia control prototype products.

Table 3 shows control of axial elongation from other studies where contact lenses were used and 6-month myopia control data were reported. The efficacy of the EE lens in reducing axial elongation (0.105 mm compared to the SV control) observed in this study makes this lens a viable candidate for myopia control in young children.
Our results show consistency with previous studies. Subjects wearing the SV lens showed unadjusted axial elongation and myopia progression of 0.19 mm and 0.35 D, which are not unexpected values for a group of myopic children of around 10 years of age.\textsuperscript{23-25} In addition, while myopia progression was observed to be greater in younger children and Asians,\textsuperscript{26,27} there was no evidence that myopia control efficacy varies with age or race.\textsuperscript{23,28,29} Compliance was found to impact treatment efficacy, consistent with some previous work.\textsuperscript{25,30} Some subjects showed an initial reduction in axial length in response to myopia control treatment, a phenomenon which has been reported previously.\textsuperscript{8,31,32}

Strengths of this study included the application of the gold standard for intervention studies, that is, a controlled, randomized, double-masked design. This study was also multisite which is of higher value than single-center studies because the results are more generalizable.\textsuperscript{33} High completion rate, lens wearing time considerably surpassing the target, and good safety profile demonstrate that most children can successfully wear soft contact lenses made in senofilcon A material. Further, our efficacy analysis was based on intent-to-treat, so the results include those who were not compliant with minimum wearing times, reflecting what may be expected in “real-world” clinical practice.

The major limitation of this study was its relatively short duration. The 6-month results presented here currently do not allow confident prediction of longer-term treatment effect. The early rate of treatment efficacy in myopia control products has been shown to reduce over time,\textsuperscript{8,34,35} so linear (or percentage) projections are inappropriate.\textsuperscript{8} Models to project longer
term treatment efficacy from short-term trials are needed, as there are (i) ethical concerns
around assigning children to a control group in a myopia control clinical trial for a period of, say,
3 years, when known treatments are available, and (ii) logistical and resource challenges in
conducting long-term studies. At the time of study, there were no myopia control soft contact
lenses approved or available in the United States or China where 8 out of the 9 clinical sites
were located. In light of the above considerations, we chose to proceed with a 6-month,
placebo-controlled study for the purpose of validating the new design concepts. Our reasoning
was that a statistically distinguishable difference in the rate of eye growth between a treatment
and control group should emerge within this timeframe if the treatment is to provide a
meaningful performance difference over the longer term. Since subjects were randomized and
the enrollment period extended over 10 months, seasonal effects were more likely to
contribute random error than systematic bias. Nonetheless, due to the short study duration,
the magnitude of the observed myopia control efficacy for the EE lens, especially in comparison
to the DF lens, was limited and was statistically significant for the axial length endpoint alone.
Establishment of clinically meaningful superiority requires further evaluation over a longer
period of time.

In summary, the efficacy and vision performance of the EE and EV lens met the design intent,
demonstrating that non-coaxial ring-focus technology offers an alternative approach with
potential to mitigate some of the limitations of conventional presbyopic coaxial principles. We
consider EE a viable soft contact lens candidate for further investigation of myopia control in
children. Additional international, randomized, controlled clinical trials with longer study
duration are currently on-going to gather comprehensive clinical data on the lens safety and
efficacy.

Disclosure: The prototype lenses discussed in this paper are subject to US Patent No
10901237, assigned to Johnson & Johnson Inc. These lenses are commercially available in some
countries outside of the United States. The authors are employees of Johnson & Johnson Vision.

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Figure captions:

Figure 1: Flowchart illustrating the disposition of subjects from screening to completion, including reasons for subject discontinuation.

Figure 2: Unadjusted mean (standard error) change in (A) axial length and (B) spherical equivalent cycloplegic autorefraction (SECAR) by lens type across time. The two measures of axial length at 26 weeks represent non-cycloplegic (dark grey) and post-cycloplegic measures (black). (EE: for enhancing efficacy lens group, EV: for enhancing vision lens group, DF: dual-focus lens group, SV: single-vision lens group)

Figure 3: (A) Unadjusted mean (SD) monocular distance visual acuity with study lenses. (B) Change in visual acuity (SD) between baseline and different timepoints in the study. (EE: for enhancing efficacy lens group, EV: for enhancing vision lens group, DF: dual-focus lens group, SV: single-vision lens group)

Figure 4: Subject reported vision outcomes at 1-week (A) and 26-weeks (B) in frequencies (%) of top-2-box (T2B, two best grades) and bottom-2-box (B2B, two worst grades) on a 5-point scale for each question in the subjective vision questionnaire.
Table 1. Demographics and baseline characteristics of enrolled subjects

<table>
<thead>
<tr>
<th></th>
<th>EE</th>
<th>EV</th>
<th>DF</th>
<th>SV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, Mean [SD])</td>
<td>10.0 (1.58)</td>
<td>10.1 (1.38)</td>
<td>10.2 (1.51)</td>
<td>9.9 (1.59)</td>
</tr>
<tr>
<td>% &lt;10 years</td>
<td>36</td>
<td>34</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>% female</td>
<td>48</td>
<td>56</td>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>% Asian</td>
<td>54</td>
<td>52</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>Axial Length (mm, Mean [SD])</td>
<td>24.65 (0.78)</td>
<td>24.42 (0.86)</td>
<td>24.31 (0.67)</td>
<td>24.43 (0.79)</td>
</tr>
<tr>
<td>SECAR (D, Mean [SD])</td>
<td>-2.50 (0.95)</td>
<td>-2.36 (0.99)</td>
<td>-2.34 (0.97)</td>
<td>-2.43 (1.00)</td>
</tr>
<tr>
<td>% &lt; -2.00D</td>
<td>36</td>
<td>45</td>
<td>45</td>
<td>46</td>
</tr>
</tbody>
</table>

EE: enhanced efficacy lens group, EV: enhanced vision lens group, DF: dual-focus lens group, SV: single-vision lens group, SD: standard deviation, SECAR: spherical equivalent cycloplegic autorefraction.

Table 2. Least-square mean differences with 95% confidence intervals in axial elongation (mm) and refractive change with EE, EV, and DF compared to SV at 26 weeks for the intent-to-treat population

<table>
<thead>
<tr>
<th>Lens</th>
<th>EE</th>
<th>EV</th>
<th>DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Elongation (mm)</td>
<td>-0.105&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.063&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.056&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(-0.149, -0.062)</td>
<td>(-0.106, -0.020)</td>
<td>(-0.100, -0.013)</td>
</tr>
<tr>
<td>SECAR Change (D)</td>
<td>0.219&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.084</td>
<td>0.118</td>
</tr>
<tr>
<td></td>
<td>(0.091, 0.348)</td>
<td>(-0.042, 0.210)</td>
<td>(-0.009, 0.246)</td>
</tr>
</tbody>
</table>

EE: enhanced efficacy lens group, EV: enhanced vision lens group, DF: dual-focus lens group, SV: single-vision lens group, SECAR: spherical equivalent cycloplegic autorefraction, <sup>a</sup>: adjusted p-value < 0.05.
Table 3. Previous 6-month results from studies using myopia control contact lenses

<table>
<thead>
<tr>
<th>Study (1st author, date)*</th>
<th>Treatment</th>
<th>Reduction in axial elongation (mm)</th>
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</thead>
<tbody>
<tr>
<td>This study</td>
<td>SMCL</td>
<td>0.11</td>
</tr>
<tr>
<td>Lam, 2014</td>
<td>SMCL</td>
<td>0.04</td>
</tr>
<tr>
<td>Aller, 2016</td>
<td>SMCL</td>
<td>0.11</td>
</tr>
<tr>
<td>Cheng, 2016</td>
<td>SMCL</td>
<td>0.11</td>
</tr>
<tr>
<td>Sankaridurg, 2019</td>
<td>SMCL</td>
<td>0.09</td>
</tr>
<tr>
<td>Sankaridurg, 2019</td>
<td>SMCL</td>
<td>0.07</td>
</tr>
<tr>
<td>Sankaridurg, 2019</td>
<td>SMCL</td>
<td>0.07</td>
</tr>
<tr>
<td>Sankaridurg, 2019</td>
<td>SMCL</td>
<td>0.08</td>
</tr>
<tr>
<td>Cho, 2012</td>
<td>OK</td>
<td>0.10</td>
</tr>
<tr>
<td>Santodomingo, 2012</td>
<td>OK</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Only studies reporting 6-month efficacy, using optical biometry and with data obtained over the last decade are included. Studies of spectacles lenses and orthokeratology studies with sub-populations of myopes (high myopia and significant astigmatism) are also not shown. SMCL: soft multifocal contact lens, OK: orthokeratology.
Screened 240

Ineligible 41

Randomized 199

EE 50
- Discontinued (6)
  - Unsatisfactory vision
  - Lens handling difficulty
  - Withdrew consent (3)
  - Lost to follow up
  - Completed 44

EV 50
- Discontinued (1)
  - No longer meet eligibility
  - Completed 49

DF 48
- Discontinued (3)
  - Lens discomfort
  - Withdrew consent (2)
  - Completed 45

SV 51
- Discontinued (4)
  - Adverse event
  - Not want to wear study lenses (3)
  - Completed 47
Precis:

Two prototype myopia control contact lenses (one with enhanced efficacy and the other with enhanced vision) were tested with a gold-standard clinical trial design over 6 months and were found to meet their design criteria.