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A Randomized Trial of Soft Multifocal Contact Lenses for Myopia Control: Baseline Data and Methods

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Abstract

Significance—The Bifocal LensesIn Nearsighted Kids (BLINK) study is the first soft multifocal contact lens myopia control study to compare add powers and measure peripheral refractive error in the vertical meridian, so it will provide important information about the potential mechanism of myopia control.

Purpose—The BLINK study is a National Eye Institute-sponsored, double-masked, randomized clinical trial to investigate the effects of soft multifocal contact lenses on myopia progression. This article describes the subjects' baseline characteristics and study methods.

Methods—Subjects were 7 to 11 years old, had −0.75 to −5.00 spherical component and less than 1.00 diopter (D) astigmatism, and had 20/25 or better logMAR distance visual acuity with manifest refraction in each eye and with +2.50-D add soft bifocal contact lenses on both eyes.

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Children were randomly assigned to wear Biofinity single-vision, Biofinity Multifocal “D” with a +1.50-D add power, or Biofinity Multifocal “D” with a +2.50-D add power contact lenses.

Results—We examined 443 subjects at the baseline visits, and 294 (66.4%) subjects were enrolled. Of the enrolled subjects, 177 (60.2%) were female, and 200 (68%) were white. The mean (± SD) age was 10.3 ±1.2 years, and 117 (39.8%) of the eligible subjects were younger than 10 years. The mean spherical equivalent refractive error, measured by cycloplegic autorefraction was −2.39 ± 1.00 D. The best-corrected binocular logMAR visual acuity with glasses was +0.01 ± 0.06 (20/21) at distance and −0.03 ± 0.08 (20/18) at near.

Conclusions—The BLINK study subjects are similar to patients who would routinely be eligible for myopia control in practice, so the results will provide clinical information about soft bifocal contact lens myopia control as well as information about the mechanism of the treatment effect, if one occurs.

Peripheral retina, as well as central retina, plays a role in regulating eye growth. Primates with form deprivation[1] or hyperopic blur[2] imposed outside the macula experience excessive axial elongation and myopia progression. After removing the stimulus to increase eye growth, axial elongation slows, and the amount of imposed myopia reduces, even if the macula is ablated.[1,2] Myopic humans exhibit more relative peripheral hyperopia than emmetropic or hyperopic humans.[3–5] This relative peripheral hyperopia exists prior to the onset of myopia,[6,7] suggesting that relative hyperopic defocus may lead to myopia development,[6] although controversy exists.[8,9] Furthermore, less relative peripheral refractive error was associated with slower myopic progression in a previous multifocal contact lens myopia control study.[10] Because extrafoveal retina also controls eye growth, optical signals that slow eye growth without significantly degrading vision may be applied to the eye.

Corneal reshaping contact lenses provide clear vision simultaneously with peripheral myopic blur,[11–14] which may act as a cue to slow myopic eye growth compared with single-vision glasses or contact lenses.[15–23] The peripheral portion of center-distance soft multifocal contact lenses also presents myopic blur to the retina, and they have also been shown to slow myopia progression by a weighted average percent slowing of 36.4% and axial elongation by a weighted average percent slowing of 37.9% (Table 1)[10,24,26–31]

To determine the weighted average percent slowing of eye growth for each study, we subtracted the mean eye growth of the experimental group from the control group and divided by the eye growth of the control group. We then calculated the total person-years for each study by multiplying the number of subjects who completed the study by the length of the study in years. To determine the weighted percent slowing, we multiplied the percent slowing of eye growth by the total person-years of the study.

For example, the eyes grew 0.25 mm for the experimental group (n = 65) and 0.37 mm for the control group (n = 63).

Percent slowing = (0.37 – 0.25)/0.37 = 32.4%.

Total person-years = (65 × 2) + (63 × 2) = 256 person-years.

Weighted percent slowing = 256 × 32.4 = 8294.4.

Finally, we divided the sum of the weighted percent slowing for each study by the sum of the total person-years for each study to determine the weighted average percent slowing.

Although there is strong evidence that soft multifocal contact lenses slow myopia progression and axial elongation, little is known about the mechanism of the myopia control effect. In more than half of the soft multifocal contact lens myopia control studies, subjects wore multifocal contact lenses for 1 year or less, and none of the subjects wore treatment for more than 2 years. Myopia control modalities frequently exhibit initial meaningful myopia control that does not persist beyond the first year,[32,33] so studies should last a minimum of 2 years in order to understand the efficacy of myopia control throughout the age children are expected to progress.[34] The Bifocal Lenses In Nearsighted Kids (BLINK) study will measure myopia progression annually over 3 years.

In general, orthokeratology contact lens wearers exhibit slower axial elongation if they have higher baseline myopia, whereas subjects wearing single-vision correction exhibit the opposite or no relationship.[18,20,22] Because uncorrected refractive error extends across the retina,[14,35,36] greater baseline myopia may have led to greater peripheral myopic blur for orthokeratology contact lens wearers but not for single-vision spectacle or contact lens wearers whose peripheral refractive error was corrected. It is believed that higher add power contact lenses produce more myopic blur and lead to slower myopia progression. However, this hypothesis has not been evaluated to date. The BLINK study will randomly assign subjects to single vision, +1.50-D add, or +2.50-D add to determine whether higher add powers provide better myopia control.

Only two[29,37] of the eight soft multifocal contact lens studies used a commercially available contact lens, so eye care practitioners have very little information about contact lenses that they can potentially use for myopia control. The BLINK study uses Biofinity Multifocal “D” contact lenses (Comfilcon A; CooperVision, Victor, NY), so practitioners will be able to apply the results of the BLINK study immediately.

Only three of the eight soft multifocal contact lens studies examined the role of peripheral refractive error in the horizontal meridian on myopia progression,[10,26,28] and none examined the vertical meridian. The BLINK study will examine the role of refractive error measured at 20, 30, and 40 degrees in the nasal and temporal retina, as well as at 20 and 30 degrees in the superior and inferior retina. Peripheral defocus with the contact lens on the eye will be measured while subjects look at both distance and near targets, and peripheral refractive error without the contact lens will be measured while looking at a distant target. Overall, the BLINK study will provide a much more thorough investigation of the optical ramifications of the soft multifocal contact lens on myopia progression than any study reported to date.

Soft multifocal contact lenses slow axial elongation of the eye, but no myopia control studies have examined the peripheral growth of the eye to determine the extent of spatial integration of optical cues to globally slow eye growth or whether the eye experiences only local changes in eye growth that result in slower myopia progression. The BLINK study will measure eye length centrally and at 20 and 30 degrees in the superior, inferior, nasal, and

temporal retina to provide information about growth patterns over time with soft multifocal contact lens wear.

In summary, the BLINK study is a 3-year randomized clinical trial to investigate the effect of commercially available soft multifocal contact lenses on myopia progression in children. In addition, this will be the first longitudinal myopia control study with control subjects to determine whether higher add powers provide better myopia control, to examine peripheral refractive error in both the horizontal and vertical meridians, and to measure peripheral eye growth. This article provides the baseline characteristics of the subjects enrolled in the BLINK study and details the methods used in the investigation.

Methods

Study Aims

With a 3-year, double-masked, equal-allocation randomized clinical trial of 294 myopic children between the ages of 7 and 11 years at baseline, we will accomplish the following specific aims:

Specific aim 1: to compare the change in myopia between single-vision contact lens wearers and soft bifocal contact lens wearers to test the hypothesis that soft bifocal contact lenses slow myopia progression in a dose-dependent manner in children,

Specific aim 2: to determine whether peripheral defocus created by soft bifocal contact lenses is associated with myopia progression to test the hypothesis that peripheral myopic defocus slows myopia progression in children, and.

Specific aim 3: to determine whether changes in ocular shape differ between children wearing single-vision and soft bifocal contact lenses to test the hypothesis that peripheral myopic defocus globally slows eye growth.

Human Subjects Protection

The protocols were approved by The Ohio State University Bio-medical Institutional Review Board and the University of Houston Committee for the Protection of Human Subjects. Parental permission was provided by a parent or guardian, and assent was provided by the subject. The trial is registered with ClinicalTrials.gov (NCT02255474).

Subjects

Consecutive subjects meeting the entry criteria (Table 2) were enrolled in the study. The minimum age of 7 years was chosen because younger children may be less able to care for contact lenses; the maximum age of 11 years ensures that subjects will be younger than the expected age of cessation of myopia progression at the conclusion of the study.[34] The minimum amount of myopia (−0.75 diopter [D]) was used because children with less myopia may not be as motivated to wear contact lenses.[25] The upper limit (−5.00 D) eliminates pathological myopia that may have a different mechanism and protects against refractive error imbalance between the two treatment groups because of extreme outliers. Astigmatism was limited to less than 1.00 DC to improve the likelihood of acceptable vision

with spherical contact lens correction. The visual acuity had to be 20/25 or better with spectacle correction to reduce the likelihood of enrolling an amblyopic child and 20/25 or better with a +2.50-D add to reduce the likelihood of poor subjective vision with the highest add power used in the study. Subjects could not report more than 1 month of gas-permeable, soft bifocal, or orthokeratology contact lens wear or more than 1 month of myopia control (including atropine or bifocal spectacles). Previous single-vision soft contact lens wear was permitted because single-vision soft contact lenses do not alter the progression of myopia.[38,39] Subjects also needed to be free of systemic issues that may have affected myopia or myopia progression, could not be chronically using oral or ophthalmic steroids, and had to be willing to participate in the study for 3 years to reduce the likelihood of dropout.

Visits

During the baseline visit, eligibility was evaluated, and baseline measures were conducted. The date of all subsequent visits was determined based on completion of the baseline examination. Contact lens care, insertion, and removal were taught, and contact lenses were dispensed at the 1-week visit. At 3 weeks, the contact lens fit assessed, and the Pediatric Refractive Error Profile 2 and Convergence Insufficiency Symptom Survey were administered. During the 6-, 18-, and 30-month visits, the contact lens fit and compliance were assessed, and surveys were administered. During the annual visits, all outcome measurements were made, contact lens fit and compliance were assessed, and surveys were administered (Table 3).

Randomization

REDCap, a Web-based electronic data capture system,[40] verified eligibility of all subjects, then randomly assigned them to wear single-vision, soft multifocal with +1.50-D add, or soft multifocal with +2.50-D add contact lenses. The randomization assignment was stratified by clinical site and age group (7 to 9 vs 10 to 11 years old) using a random permuted block design to ensure sequential balance of the distribution of the three treatments among the age groups and clinic sites and prevent knowledge of the subsequent treatment assignment. A varying block size was used, and the allocations were made with equal probability. The randomization schedule was created by the director of the coordinating center using a random-number generator in Excel and imported into REDCap. Treatment assignments were concealed until the eligibility form was verified, at which time REDCap produced the next allocation in the sequence.

Masking

All study personnel were unmasked except the masked examiners, who performed cycloplegic autorefraction, axial length, peripheral refractive error without contact lenses, and peripheral eye length. Masked examiners were not allowed in the clinical area, other than to perform their masked examination duties. They never examined subjects while they were wearing contact lenses, and all contact lens cases and packages were hidden during the masked portion of the examinations. If masked examiners became unmasked, they never examined that subject again.

Subjects and parents were also masked, and they were told not to discuss their contact lens wear, vision, or care with the masked examiner. All contact lens boxes were eliminated, and all labels on contact lens blister packs were removed prior to dispensing so that subjects and parents were unaware of the treatment they received. If subjects or parents believed they were unmasked, we never confirmed whether they were correct or not, so they were never certain of whether they were unmasked.

Adverse Events

Adverse events were determined by three different methods:

1. if the subject experienced ocular signs or symptoms worse than those encountered during routine contact lens wear (e.g., a slit-lamp sign of grade 3 or worse)
2. if the parent responds positively to the question, “Has your child experienced any changes in his/her eyes, vision, or health since the last visit?” and the examiner determines the condition is chronic, was not previously documented, and requires a change in medications or change in daily activities over an extended period; or if the examiner feels the condition is acute and warranted, such as a broken bone or head trauma
3. if the examiner determines a symptom from the symptom checklist (burning or stinging, itching, dryness, poor comfort at the end of the day, excessive tearing or discharge, blurry vision, headache) may be related to the study treatment after asking the subject and parent, “Have you or your child noticed any of the following symptoms related to his/her eyes since the last visit?”

The final decision of whether each event is an adverse event was decided by the executive committee during weekly conference calls. All adverse events were categorized as ocular or nonocular; serious or nonserious; mild, moderate, or severe; contact lens was not discontinued, temporarily discontinued, or permanently discontinued; and expected or unexpected.

Sample Size

All sample size calculations were performed using PASS 2005 software using $\alpha = 0.05$ and $\beta = 0.20$ (power = 80%). Estimates of sample size were computed for each specific aim.

Aim 1 compares the spherical equivalent myopia progression between the three equalsized treatment groups at 1, 2, and 3 years. Refractive error measurements for the primary outcome are conducted annually because myopia progresses slowly, and more frequent measurements add to subjects' burden without a significant gain in information. A repeated-measures analysis of covariance, with the baseline spherical equivalent used as a covariate, is used to compare myopia progression. In another contact lens myopia control study, the mean (±SD) myopia progression of single-vision contact lens wearers was −1.29 D ± 0.71 over 3 years.[38] To detect a 50% treatment effect for the progression of spherical equivalent refractive error and a treatment effect for the +1.50-D add group that is halfway between the single-vision contact lenses and the +2.50-D add group, the sample size required for 80%

power is 24 per treatment group or a total sample size of 72 subjects. Only two add powers were used because of financial concerns with additional treatment groups, and it would be difficult to determine differences between greater numbers of add powers because of significant variability in eye shape between subjects, which ultimately leads to large variability in peripheral defocus. Change in refractive error was used as the primary outcome because a clinically meaningful effect based on change in refractive error is much easier for clinicians to understand than axial elongation; change in refractive error is a more variable measure than change in axial length, so it allows for adequate power to determine statistically significant differences for change in both refractive error and axial length; and because change in refractive error is the primary outcome in many myopia control studies. We will also analyze and report the difference in axial elongation between treatment groups at the end of the study.

Specific aim 2 determines whether higher levels of peripheral myopic defocus are associated with a decreased rate of myopia progression. Peripheral defocus is measured 20, 30, and 40 degrees nasal and temporal to the fovea and 20 and 30 degrees superior and inferior to the fovea. The association between peripheral defocus and myopia progression will be assessed using a correlation analysis and linear regression. Based on recent work by Sankaridurg et al.,[10] a clinically meaningful magnitude of correlation between peripheral defocus and myopia progression is 0.25. A total of 123 subjects are required to detect a correlation of that magnitude.

Specific aim 3 is designed to evaluate differences in the change in ocular shape between the soft bifocal and single-vision contact lens wearers. Although there are no longitudinal data assessing the amount of change in the periphery that can be considered clinically meaningful, it is reasonable to assume that a clinically meaningful change in the central retina would be considered a clinically meaningful change in the periphery as well. The minimal difference in central refractive error change detected in a previous study was 0.13 D over 1 year.[27] If this difference was expanded linearly for 3 years, the minimal meaningful difference would be 0.39 D. The SD of the change was set at 0.85, based on the most conservative SD in the change in relative peripheral refraction seen across peripheral measures in the STAMP (Study of Theories about Myopia Progression) study.[41] Using this information, the sample size required to detect this magnitude of difference in the change in ocular shape between treatment groups was 89 subjects per group, for a total sample size of 267 subjects.

Using the maximum sample size from the three aims and adjusting for 10% loss to follow-up give a total sample of 294. Ten percent loss to follow-up was conservatively determined based on previous retention rates of 96.5%[42] and 100%[43] in previous 3-year longitudinal contact lens studies conducted on children of similar ages by members of the study team.

Contact Lens Options

All subjects were randomly assigned to wear Biofinity, Biofinity Multifocal “D” with a +1.50-D add power, or Biofinity Multifocal “D” with a +2.50-D add power contact lenses. Biofinity Multifocal contact lenses were chosen because they provide myopic defocus at 20, 30, and 40 degrees nasally and temporally while looking at distance, although no myopic

blur while looking at near was detected.[44] If a subject exhibited an unacceptable fit (limbal exposure, excessive movement, or no movement) at the baseline visit with Biofinity contact lenses, then he/she was ineligible for the study. If a poor fit was exhibited during any other study visit, the subject was fitted with Proclear or Proclear Multifocal "D" contact lenses as the primary backup because they have a similar optical profile to the Biofinity Multifocal "D" contact lens. Other contact lenses were used as deemed clinically necessary because all subjects who were randomly assigned to a treatment group were analyzed according to the intention-to-treat principle.[45] Parameters of the primary and secondary contact lenses are listed in Table 4. All subjects received free contact lenses, solutions, and contact lens cases throughout the study. A new contact lens power was provided if the overrefraction exhibited myopia progression of more than 0.50 D, or if the examiner deemed it to be necessary. All subjects initially received Biotrue (Bausch + Lomb, Rochester, NY) contact lens solution. Subjects were encouraged to wear their contact lenses during the day as often as they could comfortably do so (no extended wear), but they were also reminded that they could wear their glasses any time they wished. Wearing time was monitored every 6 months by asking parents and subjects the number of weekdays and weekend days that they usually wear contact lenses and the time they usually insert and remove contact lenses during those periods. From that information, the number of hours per week that contact lenses were typically worn was calculated.

Central Refractive Error

The primary outcome of the BLINK study is the 3-year change in spherical equivalent, cycloplegic autorefraction. Central refractive error was measured by cycloplegic autorefraction using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL). Cycloplegia was achieved using one drop of 0.5% proparacaine or tetracaine followed by two drops of 1.0% tropicamide, separated by 5 minutes. Measurements were taken 25 minutes after the second drop of tropicamide was instilled. Ten spherocylindrical autorefraction measurements were taken while the subject fixated 6/9 (20/30) size letters on a near point test card viewed through a +4.00 D Badal lens. The letters were presented at optical infinity, then moved to a slightly blurred position to ensure relaxation of residual accommodation.[46] The 10 spherocylindrical autorefractions were averaged using the power vector analysis described by Thibos et al.[47]

Visual Acuity

All visual acuity charts were calibrated to 75 to 120 cd/m^2 using a Sekonic L-508 Zoom Master (Sekonic, Tokyo, Japan) light meter. Bailey-Lovie logMAR high-contrast charts 4 and 5 and low-contrast visual acuity chart 6 were used at a test distance of 4 m. Subjects read the first letter of every line until one was incorrectly read. The subject then read all five letters of the line, beginning two lines above the first letter missed. If a subject missed a letter on the first complete line read, then the subject read one line above until correctly reading all five letters on the line. The subject continued reading all five letters on every line, moving down the chart, until three or more letters were missed on the same line. If the subject read three or more letters correctlyonthe bottom line, then the subject moved to 6 m and started the process again. If the subject missed any letters of the top line on the chart, the subject moved to 2 m and started the process again. The number of letters read correctly and

the test distance were recorded. The same protocol was used at near using the Logarithmic Visual Acuity Chart 2000 “New ETDRS” near visual acuity chart (Precision Vision, LaSalle, IL) held 40 cm from the eye by holding a bead at the lateral canthus and extending the string attached to the chart.

During the baseline visit, best-corrected high-contrast distance visual acuity was measured with each eye through the manifest refraction. Best-corrected low-contrast distance visual acuity, high-contrast near visual acuity, and high-contrast distance visual acuity were also measured binocularly while wearing the manifest refraction in a trial frame during the baseline visit. All subjects also performed binocular high-contrast distance visual acuity while wearing +2.50-D add multifocal contact lenses with the spherical overrefraction in a trial frame. During visits 3 through 9, high-contrast distance, low-contrast distance, and high-contrast near visual acuities were measured binocularly with the subject's habitual correction and the spherical overrefraction in a trial frame.

Pupillometry

Measurement of pupil diameter of the right eye was performed with the NeurOptics VIP-200 Pupillometer (NeurOptics, Inc., Irvine, CA). For the photopic condition, the subject stood facing the examiner with his/her back toward the wall-mounted visual acuity chart calibrated to 75 to 120cd/m^2. For the mesopic condition (<1 cd/m^2), the subject stood in the same location with all room lights off except an incandescent lamp pointed straight down at the opposite end of the room.

The eye cup of the pupillometer was held against the right eye while pressing the “OD” button. When the pupil was marked with a green circle, the button was released, and the measurement was performed. If the green circle was not centered over the pupil, the measure was deleted, and the procedure was performed until the green measurement circle was centered over the pupil. The pupil size was recorded to the nearest 0.1 mm.

Axial and Peripheral Eye Length

The Lenstar LS 900 (Haag-Streit USA, Mason, OH) was used to measure axial (right and left eye) and peripheral (right eye only) eye length. Lenstar was chosen over IOLMaster because it provides similar axial[48] and peripheral[49] eye length repeatability as IOLMaster, and it provides biometry of the entire eye (corneal thickness, anterior chamber depth, lens thickness, and axial length) in a single measure. Axial length was measured by covering the subject's contralateral eye with a patch while the subject fixated the internal red fixation light. Once good focus of two rings of light reflecting off of the cornea was obtained, the button on the joystick was pressed to obtain a more magnified view. The instrument was moved slightly in or out according to the Lenstar software's dynamic alignment prompts. When the crosshairs were in the middle of the small green focusing circle, the subject blinked and held his/her eyes open. The joystick button was pressed, and the measurement was captured. Axial measurements were repeated until five readings without a poor-quality warning indicator or red highlight indicating implausible measurements were obtained. Peripheral measurements were performed while subjects turned their eye to view small targets placed on the instrument head at 20 and 30 degrees nasal, temporal, superior, and

inferior to primary gaze, in the right eye only. The peripheral measurements were also repeated until five reliable readings without red highlights that indicate invalid readings were obtained.

Peripheral Refractive Error

Peripheral refractive error (without the contact lens) was measured in the right eye, with the left eye patched, while looking at distance using the Grand Seiko WAM-5500 Binocular Autorefractor/ Keratometer (AIT Industries). Subjects viewed spots on the wall created by a laser pointer at 20, 30, and 40 degrees nasal and temporal and at physical targets at 20 and 30 degrees superior and inferior. All vertical targets were placed on the wall in the appropriate location except the 30-degree inferior target, which was located within the housing of the autorefractor. For horizontal readings, the forehead rest was removed, the subject's chin was placed on the chinrest, and the subject turned the head (as opposed to the eyes) to the target while maintaining primary gaze. The pink reticule was centered in the entrance pupil (not in the white keratometry circle reflecting off of the cornea), and the iris was focused. At least five readings in which neither the sphere nor cylinder differed from the median by more than 1.00 D were recorded. For vertical readings, the forehead rest was used, and the subject's chin was placed on the chinrest. The subject turned the eyes to each target, and at least five readings in which neither the sphere nor cylinder differed from the median by more than 1.00 D were recorded.

Peripheral Defocus

Peripheral defocus (with the contact lens) was measured on the right eye while the left was patched. The subject was measured while looking at distance and near using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries). Subjects viewed targets at 20, 30, and 40 degrees nasal and temporal for both distance and near readings. All distance targets were created by a laser pointer on the wall. Near targets were placed at 33 cm 2.06 M size letters (20/125 Snellen equivalent). For these measurements, the forehead rest was removed, the subject's chin was placed on the chinrest, and the subject turned the head to the target while maintaining primary gaze. The pink reticule was centered in the entrance pupil (not in the white keratometry circle reflecting off of the cornea), and the iris was focused. At least five readings in which neither the sphere nor cylinder differed from the median by more than 1.00 D were recorded, and the average M, J_0, and J_{45} were calculated from the last five valid, remaining readings.

Accommodative Lag

Baseline accommodative lag was measured prior to instillation of cycloplegic drops with the spherical equivalent of the manifest refraction in a trial frame using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries). Measurements were performed while the right eye was corrected with a trial lens equal to the spherical equivalent of the manifest refraction and the left eye was occluded. Subjects viewed a 4 × 4 grid of 20/125 size letters illuminated by ambient room light at a distance of 33 cm, and they were constantly told to keep the print clear. A minimum of five readings without the “retry” message were averaged.[50] All subsequent measures of accommodative lag were performed in a similar manner while the subject wore his/her assigned treatment.

Slit-Lamp Examination

Conjunctival redness, limbal redness, corneal neovascularization, corneal staining, papillary conjunctivitis, blepharitis, meibomian gland dysfunction, and corneal infiltrates were graded using the Efron Grading Scales.[51] For corneal staining, fluorescein was applied by touching a strip to the superior bulbar conjunctiva. Observations were made with cobalt blue and Wratten no. 12 filters. Contact lens movement was graded as extremely inadequate (no movement), slightly inadequate (<0.2 mm), optimum (0.2 to 0.4 mm), slightly excessive (0.4 to 1.0 mm), and extremely excessive (>1.0 mm). Contact lens centration was graded as optimum, slightly decentered (no limbal exposure), and extremely decentered (limbal exposure). Lens movement upon push-up was graded as excessive, unacceptable; moderate, acceptable; optimum; minimal, acceptable; and insufficient, unacceptable.

Convergence Insufficiency Symptom Survey and Pediatric Refractive Error Profile

The Convergence Insufficiency Symptom Survey, an established, validated survey,[52,53] was administered according to the protocol established for the Convergence Insufficiency Treatment Trial.[54] In short, an examiner read questions pertaining to symptoms associated with binocular vision issues, and children stated whether that symptom occurred “never,” “infrequently,” “sometimes,” “fairly often,” or “always.” “Always” elicited a score of 4, “fairlyoften” ascoreof 3, “sometimes” ascoreof 2, “infrequently” a score of 1, and “never” a score of 0. The sum of the scores provided the symptom score; for children, a score of 16 or more indicated symptomatic vision issues.

The new Pediatric Refractive Error Profile 2 elicited vision-specific quality-of-life scores sensitive enough to measure differences between children affected only by refractive error who wore different vision correction devices.[55,56] The Pediatric Refractive Error Profile 2 consisted of 56 items, half positively worded and half negatively worded in seven scales: overall, vision, symptoms, appearance, activities, handling, and peer perception. Subjects responded to each item with “strongly agree,” “agree,” “neutral,” “disagree,” and “strongly disagree.” For positively worded statements, “strongly agree” was scored as 5 and “strongly disagree” was scored as 1; the scoring was reversed for negatively worded questions. Higher scores represented greater vision-specific quality of life. The Pediatric Refractive Error Profile 2 was validated in subjects 8 to 14 years of age.[57]

Study Monitoring

Study outcomes are reviewed by a Data Safety Monitoring Committee appointed by the National Eye Institute, which is composed of members with expertise in study design and administration, bio-statistics, myopia, and clinical issues. The Data Safety Monitoring Committee holds annual in-person meetings and conference calls at the 6-month interval between in-person meetings. The Data Safety Monitoring Committee reviews planned interim reports to monitor recruitment, retention, protocol adherence, and data quality. The Data Safety Monitoring Committee also determines whether differences observed between treatment groups warrant discontinuation of the study due to a need to notify participants, as well as the clinical and scientific communities.

Statistical Analyses

The comparability of the treatment groups at baseline was evaluated by the χ^2 or Fisher exact test for categorical variables or an analysis of variance for continuous variables to verify a reasonable distribution of covariates as a result of randomization. Site and age, as well as imbalances identified among the three groups at baseline, will be controlled for in the final multivariate analyses.

Specific aim 1 is to compare spherical equivalent myopia progression from baseline among the two add powers of soft bifocal contact lens wearers and single-vision contact lens wearers using data from the 1-, 2-, and 3-year visits. Data are collected from both eyes over repeated, masked annual visits (a total of six observations after baseline—two eyes × three visits). Using these repeated measurements gives us the greatest power to detect differences between the treatment groups by maximizing the degrees of freedom associated with the estimated mean square error, giving the best estimate of variability. It also allows for comparison of results at each masked visit to determine whether the slowing of progression is an accumulating phenomenon, or whether it occurs predominantly between baseline and 1 year, as other myopia treatment studies have shown.[32,33] To compare results at year 3 while using all available data, a three-group × three-time-period × two-eye repeated-measures analysis of covariance will be performed.

The second specific aim is to determine whether peripheral defocus created by soft bifocal contact lenses is associated with myopia progression to test the hypothesis that peripheral myopic defocus slows myopia progression in children. Although the peripheral defocus will be likely related to treatment group, this analysis will be performed on the entire sample, not by treatment group because the peripheral myopic defocus depends on the optical profile of the lens worn and the shape of the eye. The benefits of peripheral myopic defocus may be exhibited by all treatment groups, especially the multifocal groups, so we will examine peripheral myopic defocus across the entire sample. Pearson correlations and linear regression models will be used to examine the relationship between the amount of peripheral defocus and the resulting myopia progression. Myopia progression will be measured by the change in cycloplegic spherical equivalent refractive error from baseline to 3 years. Peripheral myopic defocus is quantified (right eye only) by peripheral refractive error in the nasal and temporal locations in gaze directions at 20, 30, and 40 degrees and in the superior and inferior locations at 20 and 30 degrees while the subject is wearing the treatment contact lens. Both the horizontal and vertical meridians will be measured because differences in peripheral refractive error have been demonstrated in humans.[4,35,36,58] Correlations and scatterplots of gaze direction and location with myopia progression will be useful in examining the relationship and determining if there is a common functional form to be used in the linear model (e.g., linear, quadratic, step function) for assessing the relationship between the amount of peripheral defocus and progression.

Specific aim 3 will determine whether changes in ocular shape differ between children wearing single vision and each add power of soft bifocal contact lenses to test the hypothesis that peripheral myopic defocus globally slows eye growth. The outcome of interest for this aim (ocular shape) is the change in peripheral refractive error of the right eye. To obtain peripheral refraction, autorefraction is measured (right eye) without the contact lens in the

superior and inferior retina at 20 and 30 degrees and temporal and nasal retina at 20, 30, and 40 degrees. The spherical equivalent is calculated at each measurement location, and relative peripheral refraction is calculated by subtracting the central value from each peripheral value. In order to provide the greatest power to detect differences by maximizing the degrees of freedom associated with the estimated mean square error, peripheral refraction at each gaze direction and location will be used in the analysis rather than obtaining an average peripheral refractive error across direction and location. The purpose of this analysis is to compare ocular shape change among the two add powers of soft bifocal lens wearers and single-vision contact lens wearers using data from the 1-, 2-, and 3-year visits. Indicators of gaze direction and location will be included along with treatment group and time in a repeated-measures analysis of covariance model.

Results

In order to avoid the potential for bias, results regarding outcome measures will not be presented by treatment group until the conclusion of the trial. Between October 17, 2014, and June 20, 2016, 443 subjects attended baseline visits to determine final eligibility, and 294 subjects were enrolled. The primary reasons for ineligibility were myopia out of range (n = 58), astigmatism too high (n = 44), monocular best-corrected visual acuity worse than +0.1 logMAR with manifest refraction (Snellen 20/25, n = 19), could not agree to participate for 3 years (n = 16), strabismus (n = 10), unaccepted contact lens fit (n = 3), anisometropia (n = 1), and previous bifocal spectacle wear for more than 1 month (n = 1). Only three subjects (0.7%) were ineligible because they could not achieve +0.1 logMAR binocular visual acuity while wearing +2.50-D add power contact lenses. Some subjects were ineligible for more than one reason. The proportion of female participants is the same as the median percentage (60%) of the other soft multifocal contact lens studies (range, 47% to 73%), and the average age is younger than all but one of the soft multifocal contact lens myopia control studies (Table 5). Spherical equivalent cycloplegic autorefraction ranged from −0.82 to −5.48 D. The range of astigmatism was +0.49 to −0.45 for J_0 and from +0.43 to −0.41 for J_{45}. Nearly 40% of the sample was younger than 10 years, and the ethnic diversity was very representative of the United States.

On average, the enrolled subjects had approximately −2.50 D myopia with 20/20 best-corrected visual acuity at distance and near (Table 6). There were no clinically meaningful differences between the clinical centers, but the ineligible subjects had slightly more with-the-rule astigmatism and read approximately two fewer letters during visual acuity testing compared with eligible subjects.

Discussion

The BLINK study will be the largest and longest contact lens myopia control study performed to date (Table 1). Subjects enrolled in the BLINK study were 7 to 11 years old at baseline, which is slightly younger than most other studies, but overlaps the range of all of them. The range of spherical equivalent myopia in the other studies was from −0.75 to −7.00 D, but the average in almost every case was in the −2.00 D range, as it was in the BLINK study.

The BLINK study will be the first 3-year soft multifocal contact lens myopia control investigation that uses a commercially available contact lens, measures peripheral eye growth, examines peripheral refractive error in both the horizontal and vertical meridians, and determines whether higher add powers provide better myopia control. This study will lead to information that will help optimize myopia control by understanding how optical signals may regulate eye growth and slow the progression of myopia.

The BLINK study utilizes a single contact lens designed for presbyopic patients, so it may not optimize myopia control. However, data resulting from the BLINK study may help determine the optimal way to control myopic progression with a contact lens. Center near or concentric ring multifocal contact lenses may also slow myopia progression, but they were not used in the BLINK study.

No study is free of limitations. The BLINK study used only one commercially available soft multifocal contact lens design, although other commercially available and proprietary designs are obtainable. The BLINK study will not objectively measure UV or visible light exposure or near work activities or visual environment during the study because those factors are expected to be equally distributed between the treatment groups. The BLINK study did not enhance the sample of Asian subjects because they should be evenly distributed between the treatment groups, there is no evidence that the mechanism of myopia progression is different in Asians (there is only evidence that the magnitude and prevalence differ), and because the study is not powered to examine ethnic differences. Myopia control may be strongest when it is initiated at earlier ages,[59] but the age of myopia onset varies widely. The sample was not limited to a younger age group in order to maximize generalizability of the results, which provides eye care practitioners with evidence for or against myopia control in the wide range of ages they treat.

In summary, the BLINK study provides the most comprehensive array of measures to determine whether soft multifocal contact lenses slow myopia progression, and if proven to be effective, this study will provide information on how soft multifocal contact lenses can be optimized for myopia control.

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Table 1

A summary of results from previous soft multifocal contact lens myopia control studies reported in the peer-reviewed literature and comparison of baseline variables to the BLINK study

Study	Country	Total sample size	Control treatment	Study design	Length (y)	Loss to follow-up (%)	Slowing myopia (%)	Slowing axial length (%)	Age range (y)	Baseline age (y)	Myopia (D)	Average myopia (D)
Anstice and Phillips[24] (2011)	New Zealand	70	Contact lens	Contralateral	0.8	12.5	36.2	50.0	11–14	Unknown	−1.25 to −4.50	−2.71 ± 1.10
Sankaridurg et al.[10] (2011)	China	82	Spectacle	Prospective	1	18.0	35.7	38.5	7–14	MF: 11.6 ± 1.5, spec: 10.8 ± 1.9	−0.75 to −3.50	MF: −2.24 ±0.79, spec: −1.99 ±0.62
Walline et al.[31] (2013)	United States	54	Contact lens	Historical control	2	19.4	50.5	29.3	8–11	MF: 10.8 ± 1.0, SV: 10.8 ± 0.7	−1.00 to −6.00	MF: −2.24 ± 1.02, SV: −2.35 ± 1.05
Fujikado et al.[26] (2014)	Japan	24	Contact lens	Randomized crossover	1	0	26.2	25.0	10–16	MF: 14.3 ± 1.3, SV: 13.1 ±1.9	−0.75 to −3.50	MF: −2.52 ± 1.69, SV: −3.61 ±0.98
Lam et al.[27] (2014)	Hong Kong	128	Contact lens	Randomized	2	42.1	25.3	32.4	8–13	MF: 11.1 ± 1.6, SV: 10.9 ± 1.7	−1.00 to −5.00	MF: −2.90 ± 1.05, SV: −2.08 ± 1.03
Paune et al.[28] (2015)	Spain	40	Spectacle	Prospective	2	43.7	42.9	20.0	9–16	MF: 13.3 ± 2.0, SV: 13.1 ± 2.8	−0.75 to −7.00	MF: −2.44 ±0.91, SV: −2.64 ± 1.1
Alleretal.[29] (2016)	United States	79	Contact lens	Randomized	1	8.1	77.2	79.2	8–18	MF: 13.0 ± 2.5, SV: 13.5 ± 2.2	−0.50 to −6.00	MF: −2.57 ± 1.34, SV: −2.81 ± 1.46
Cheng et al.[30] (2016)	United States	109	Contact lens	Randomized	1	14.2	20.6	38.9	8–11	MF: 9.7 ± 1.1, SV: 9.7 ± 1.1	−0.75 to −4.00	MF: −2.44 ±0.91, SV: −2.52 ± 1.46
BLINK study	United States	294	Contact lens	Randomized	3	N/A	N/A	N/A	7–11	10.3 ± 1.2	−0.75 to −5.00	−2.40 ± 0.99

MF = multifocal contact lens; spec = single-vision spectacle; SV = single-vision contact lens.

Table 2

Entry criteria for the BLINK study

Age	**7–11 y, inclusive, at baseline examination**
Myopia	−0.75 to −5.00 D, inclusive, spherical component, cycloplegic autorefraction in each eye
Astigmatism	≤1.00 DC, cycloplegic autorefraction in each eye
Anisometropia	≤2.00 D, spherical component, cycloplegic autorefraction in each eye
Visual acuity	+0.1 logMAR or better best-corrected distance visual acuity in each eye *AND* +0.1 logMAR or better best-corrected, binocular, high-contrast visual acuity at distance with +2.50-D add soft bifocal contact lenses on both eyes
Contact lens fit	The +2.50-D add soft bifocal contact lens must provide adequate movement and centration for continual wear
Ocular health	Free of eye disease or binocular vision problems (e.g., strabismus, amblyopia, corneal disease, etc.) that may affect vision or contact lens wear
Systemic health	Free of systemic disease that may affect vision, vision development, or contact lens wear (e.g., diabetes, Down syndrome, etc.)
Contact lens	By subject report, not >1 mo of gas-permeable, soft bifocal, or orthokeratology contact lens wear
Myopia control	By subject report, not >1 mo of participation in myopia control with treatments including, but not limited to, soft bifocal or orthokeratology contact lenses, atropine, bifocal spectacles
Medications	No chronic use of medications that may affect immunity, such as oral or ophthalmic corticosteroids
Participation	Agree to participate in the study for 3 y

Table 3

Schedule of measurements for the BLINK study

	Baseline	1 wk	3 wk	Semiannual	Annual
Manifest refraction (OU)	X				X
Spherical overrefraction (OU)		X	X	X	X
High-contrast visual acuity (OU) OD/OS at baseline	X (M)		X (CL)	X (CL)	X (CL)
Low-contrast visual acuity (OU)	X (M)		X (CL)	X (CL)	X (CL)
Near visual acuity (OU)	X (M)		X (CL)	X (CL)	X (CL)
Modified Thorington	X (M)		X (CL)		X (CL)
Accommodative lag and peripheral defocus with CL, near (OD)			X		X
Contact lens centration, movement (OU)	X	X	X	X	X
Choroidal thickness (OD)		X	X		X
Slit-lamp examination (OU, no contact lens)	X	X	X	X	X
Pupil size (OD)	X				X
Noncycloplegic autorefraction (OU)	X			X	X
Accommodative lag with manifest (OD)	X				
Cycloplegic autorefraction (1° outcome, OU) *	**X**				**X**
Peripheral refractive error without CL (OD) *	**X**				**X**
Axial length (OU) *	**X**				**X**
Peripheral eye length (OD) *	**X**				**X**
Aberrations with and without CL (OD) *					1 y only
Peripheral defocus with CL (OD) *	X				X
Intraocular pressure (OU) *	X				X
Dilated fundus examination (OU) *	X				X
Contact information form	X			X	X
History form	X			X	X
Myopia risk factor form	X				
PREP2 form			X	X	X

	Baseline	1 wk	3 wk	Semiannual	Annual
CISS form	X		X	6 mo only	X
Contact lens form			X	X	X
Parent compliance form			X	X	X
Insertion, removal, and care training		X			

Bold font indicates masked measures. The 1-week visit occurs within ±3 days of 1 week; the 3-week visit occurs within 1 week of the 3-week date; all subsequent visits occur at 6-month intervals ± 30 days.

*Cycloplegic measures; X (M), wearing manifest refraction in trial frame; X (CL), wearing habitual contact lens; OD, right eye; OS, left eye; OU, both eyes. CISS = Convergence Insufficiency Symptom Survey; PREP2 = Pediatric Refractive Error Profile 2.

Table 4

Parameters available for the primary and secondary contact lenses used in the BLINK study

	Primary		Backup	
	Biofinity	**Biofinity Multifocal "D"**	**Proclear**	**Proclear Multifocal "D"**
Material	Comfilcon A	Comfilcon A	Omafilcon A	Omafilcon A
Water content	48%	48%	60%	60%
Base curve	8.6	8.6	8.2, 8.6	8.7
Diameter	14.0	14.0	14.2	14.4
Add power	None	+1.50 or +2.50 D	None	+1.50 or +2.50 D
Powers	up to −12.00 (−0.50 steps >−6.00)	up to −10.00 (−0.50 steps >−6.00)	up to −20.00 in 8.6, up to −10.00 in 8.2 (−0.50 steps >−6.00)	up to −10.00 (−0.50 steps >−6.50)
dK	128.0	128.0	34.0	34.0

Table 5

Demographic information of subjects enrolled in the BLINK study by clinical site and total

	Ohio State (n = 144)	Houston (n = 150)	Total (n = 294)	Ineligible (n = 149)
Female	81 (56.3)	96 (64)	177 (60.2)	81 (54.7)
Age, y	10.2 ± 1.2	10.4 ± 1.2	10.3 ± 1.2	10.3 ± 1.3
7	8 (5.6)	6 (4)	14 (4.8)	10 (6.8)
8	14 (9.7)	17 (11.3)	31 (10.5)	18 (12.2)
9	38 (26.4)	34 (22.7)	72 (24.5)	30 (20.3)
10	43 (29.9)	35 (23.3)	78 (26.5)	39 (26.4)
11	41 (28.5)	58 (38.7)	99 (33.7)	51 (34.5)
Ethnicity *				
Hispanic or Latino	7 (4.9)	70 (46.7)	77 (26.3)	37 (25.2)
Not Hispanic or Latino	136 (95.1)	80 (53.3)	216 (73.7)	110 (74.8)
Race				
American Indian or Alaska Native	1 (0.7)	4 (2.7)	5 (1.7)	1 (0.7)
Asian	13 (9.0)	12 (8.0)	25 (8.5)	10 (6.7)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.7)	1 (0.3)	1 (0.7)
Black or African American	14 (9.7)	16 (10.7)	30 (10.2)	16 (10.7)
White	107 (74.3)	93 (62.0)	200 (68.0)	108 (72.5)
>1 Race	8 (5.6)	22 (14.7)	30 (10.2)	11 (7.4)
Unknown or not reported	1 (0.7)	2 (1.3)	3 (1.0)	2 (1.3)
Age of first glasses, y	7.58 ± 1.49	7.73 ± 1.69	7.65 ± 1.6	7.49 ± 1.88
Parental myopia				
Father *	86 (66.2)	56 (41.8)	142 (53.8)	78 (58.2)
Mother *	107 (76.4)	85 (57.8)	192 (66.9)	99 (71.7)
Near work, h/wk outside school				
Study or read for school assignments *	5.11 ± 4.23	6.68 ± 5.65	5.91 ± 5.06	5.46 ± 4.93
Read for fun (pleasure)	4.62 ± 3.99	4.14 ± 4.43	4.38 ±4.22	4.42 ± 4.16
Watch television *	6.9 ± 6.14	5.57 ± 4.62	6.22 ± 5.45	6.44 ± 6.79
Use a computer *	3.43 ± 3.38	2.61 ± 3.44	3.01 ±3.43	3.05 ± 3.29
Play video games (Xbox, PlayStation, Wii) *	2.36 ± 3.58	1.50 ± 2.73	1.92 ±3.20	1.97 ± 3.24
Uses handheld electronic devices (iPad, Nintendo DS, etc.)	6.19 ± 6.30	5.34 ± 5.76	5.75 ± 6.03	4.86 ± 4.94
Time spent outdoors *†	9.71 ± 7.38	6.54 ± 5.35	8.09 ± 6.61	6.82 ± 4.86
CISS score	13.4 ±8.4	15.1 ± 9.0	14.2 ±8.7	14.5 ±8.1

Mean ± SD are presented for continuous variables and number (proportion) for categorical data.

* Significant difference ($P < 0.05$) between Ohio State and Houston.

[†] Significant difference ($P < 0.05$) between total and ineligible.

CISS = Convergence Insufficiency Symptom Survey.

Table 6

Mean ± SD right eye, unless otherwise noted, ocular data of subjects enrolled in the BLINK study by clinical site and total

	Ohio State (n = 144)	Houston (n = 150)	Total (n = 294)	Ineligible (n = 149)
Refractive error				
Spherical equivalent, D	−2.38 ± 0.92	−2.40 ± 1.07	−2.39 ± 1.00	−2.31 ± 1.64
J_0, * D	+0.07 ± 0.19	+0.05 ± 0.19	+0.06 ± 0.19	+0.17 ± 0.33
J_{45}, * D	+0.06 ± 0.14	+0.04 ± 0.13	+0.05 ± 0.14	+0.09 ± 0.19
LogMAR visual acuity				
Best-corrected high-contrast distance OD *†	0.00 ± 0.07	+0.02 ± 0.05	+0.01 ± 0.06	+0.03 ± 0.08
Best-corrected high-contrast distance OS *	0.00 ± 0.06	+0.01 ± 0.06	0.00 ± 0.06	+0.02 ± 0.08
Best-corrected high-contrast distance OU †	−0.02 ± 0.07	0.00 ± 0.06	−0.01 ± 0.06	0.00 ± 0.08
Best-corrected low-contrast distance OU	+0.10 ± 0.07	+0.11 ± 0.06	+0.10 ± 0.07	+0.10 ± 0.08
Best-corrected high-contrast near OU	−0.03 ± 0.08	−0.03 ± 0.07	−0.03 ± 0.08	−0.02 ± 0.09
Pupil size, mm				
Photopic	5.4 ± 0.7	5.3 ± 0.7	5.4 ± 0.7	5.2 ± 0.8
Mesopic	6.4 ± 0.6	6.5 ± 0.7	6.5 ± 0.7	6.4 ± 0.7
Simulated keratometry, D				
Steep meridian	44.15 ± 1.41	44.09 ± 1.63	44.12 ± 1.52	Not measured
Flat meridian	43.38 ± 1.35	43.33 ± 1.57	43.36 ± 1.47	Not measured
Biometry, mm				
Anterior chamber depth	3.99 ± 0.23	3.97 ± 0.22	3.98 ± 0.22	Not measured
Lens thickness	3.32 ± 0.13	3.33 ± 0.14	3.33 ± 0.13	Not measured
Vitreous chamber depth	17.15 ± 0.84	17.21 ± 0.78	17.18 ± 0.81	Not measured
Axial length	24.46 ± 0.85	24.51 ± 0.77	24.48 ± 0.81	Not measured

*Significant difference ($P < 0.05$) between total and ineligible.

†Significant difference ($P < 0.05$) between Ohio State and Houston.

J_0 = with- and against-the-rule astigmatism components; J_{45} = oblique astigmatism components; OD = right eye; OS = left eye; OU = both eyes.