ARTICLE

Clinical and patient-reported outcomes of bilateral implantation of a +2.5 diopter multifocal intraocular lens

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Purpose: To assess the effectiveness and safety of a multifocal intraocular lens (IOL) with +2.5 diopter (D) additional power compared with a monofocal IOL.

Setting: Fifteen sites in the United States.

Design: Prospective randomized patient- and observer-masked clinical trial.

Methods: Randomized patients received multifocal or monofocal IOLs bilaterally. Visual acuity (33 cm, 40 cm, 53 cm, 60 cm, 4 m) was measured; safety was assessed through adverse event rates. Patient-reported visual outcomes were evaluated using the Visual Tasks questionnaire. The frequency and severity of visual disturbances were evaluated using the Assessment of Photic Phenomena and Lens EffectS questionnaire.

Results: The multifocal IOL (n = 155) provided better corrected distance visual acuity at 53 cm than the monofocal IOL (n = 165) (0.322 versus 0.512 logMAR; between-group difference, −0.190 logMAR; $P < .0001$) and 40 cm but not at 4 m. Ocular adverse event rates were less than 3.84% in both groups. Serious adverse event rates were comparable between the 2 IOL types. Patients with multifocal IOLs reported less difficulty with near tasks (with and without correction) and intermediate tasks (without correction). Difficulty with extended-intermediate and distance tasks was similar between groups. The most frequently reported self-rated severe phenomena were halos, starbursts, and glare. Most patients (monofocal ≥72%; multifocal ≥73%) reported never experiencing blurred, distorted, or double vision.

Conclusions: The +2.5 D multifocal IOL provided better vision at 40 cm and 53 cm and similar vision at 4 m compared with the monofocal IOL. Safety profiles and visual phenomena were comparable between groups.

J Cataract Refract Surg 2017; 43:29–41 © 2017 ASCRS and ESCRS

Supplemental material available at www.jcrsjournal.org.

Cataract is a leading cause of visual impairment worldwide. In most developed countries, the standard approach to cataract treatment is surgical removal of the natural lens and implantation of an intraocular lens (IOL).[1,2] Based on United States Census data, an estimated 20.5 million individuals older than 40 years had cataracts in 2000.[3] That number is expected to rise to 30.1 million in 2020.[3] Monofocal IOLs provide distance vision but do not provide the ability to accommodate for near and intermediate distances. Because of this limited range of vision, patients receiving monofocal IOLs frequently require spectacles to complete near and intermediate vision tasks.[4]

Multifocal IOLs (ie, IOLs with more than 1 focal point) are designed with refractive and/or diffractive optical properties that provide vision over a range of distances[5] and decreased spectacle dependence compared with conventional monofocal IOLs.[6–9] Multifocal IOLs have been

Submitted: May 10, 2016 | Final revision submitted: September 14, 2016 | Accepted: October 26, 2016

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Supported by Alcon Research, Ltd., Fort Worth, Texas, USA.

Magda Michna, PhD, Aldo M. Martinez, PhD, and Val Injev, MBA, PE, Alcon Research, Ltd., assisted with manuscript preparation. Medical writing assistance was provided by Heather D. Starkey, PhD, and Natalia Zhukovskaya, PhD, Complete Healthcare Communications, LLC, Chadds Ford, Pennsylvania, and was funded by Alcon. Melissa Cable, MD, Jason Jones, MD, David Nethery, MD, and John Wood, MD, were additional study investigators.

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0886-3350/$ - see frontmatter
http://dx.doi.org/10.1016/j.jcrs.2016.10.026

associated with compromised distance vision quality, reduced contrast sensitivity, and increased photic phenomena compared with standard monofocal IOLs.[4] Photic phenomena such as halos and glare can be bothersome to patients and make tasks such as nighttime driving or reading in low light difficult, contributing to patient dissatisfaction with their IOLs.[8,10,11] Recent reports of the incidence of halo have been inconsistent. A review of 16 completed and 2 ongoing trials[4] found that patients with monofocal IOLs reported fewer problems with halos than those with multifocal IOLs. However, results in another metaanalysis[12] suggest that more recent multifocal IOL designs are associated with levels of halo and postsurgical patient satisfaction similar to monofocal IOLs.

The Acrysof IQ Restor +2.5 diopter (D) (Alcon Laboratories, Inc.) is a posterior chamber ultraviolet and blue light–filtering multifocal IOL with an apodized diffractive aspheric design. This multifocal IOL was designed with +2.5 D additional (add) power at the IOL plane, which results in approximately +1.9 D add power at the corneal plane and provides a range of functional vision from distance to near,[13] with greater distance dominance in the energy distribution between near images and distant images. The IOL provides a near focal point to enhance vision for tasks at near and intermediate distances (approximately 40 to 50 cm),[14] and its optical design was chosen to reduce visual disturbances that have been reported with some multifocal IOLs. Laboratory testing suggests that the +2.5 D multifocal IOL provides good optical quality at 53 cm.[15] This is supported by the results in a small clinical trial of 21 patients receiving the +2.5 D multifocal IOL[13]; patients achieved good uncorrected near and intermediate acuity (approximately 20/45 and 20/33, respectively) and excellent uncorrected distance visual acuity (UDVA) (20/23). Furthermore, halos associated with simulated headlight targets might be less severe with the +2.5 D multifocal IOL than with trifocal IOLs, which have near, intermediate, and distance focal points.[15]

The goal of this clinical study was to assess the effectiveness and safety of the +2.5 D multifocal IOL, to assess whether it provided better near and intermediate vision simultaneously with distance vision than a standard monofocal IOL, and to evaluate patient-reported visual outcomes.

PATIENTS AND METHODS

Study Design

This prospective randomized patient- and observer-masked parallel-group clinical trial was performed at 15 clinical sites in the U.S. between February and December 2012 (ClinicalTrials.gov identifier, NCT01510717[A]). Patients provided written informed consent before enrollment. The study was approved by RCRC Institutional Review Board (IRB) (now Salus IRB, Austin, Texas), Saint Elizabeth Medical Center IRB (Edgewood, Kentucky), and Saint Agnes Medical Center (Fresno, California). The study was performed in compliance with the ethical principles of the Declaration of Helsinki, International Organization for Standardization (ISO) 14155:2011[16] (Good Clinical Practice), and the U.S. Code of Federal Regulations.

The study consisted of 10 visits as follows: a preoperative screening, 2 operative visits (first-eye and second-eye surgeries), after implantation visits 1 to 2 days, 7 to 14 days, and 30 to 60 days after first-eye and second-eye surgeries, and a postimplantation visit 120 to 180 days after the second-eye surgery. Electronic system randomization assignment of treatment occurred 2 days before the first operative visit, with patient and evaluator masking maintained.

Patients

Eligible patients were aged 21 years or older and diagnosed with bilateral cataract with planned cataract removal by phacoemulsification. Additional inclusion criteria were preoperative astigmatism less than 1.0 D, preoperative corrected distance visual acuity (CDVA) worse than 0.2 logMAR, potential postoperative visual acuity of 0.2 logMAR or better in both eyes, clear intraocular media other than cataract in study eyes, and completion of the second-eye surgery within 7 to 30 days after the first-eye surgery. Eyes were categorized by pupil size ($\leq$2.5 mm, $>$2.5 to 4.0 mm, or $\geq$4.0 mm).

Key exclusion criteria were significant irregular corneal aberration; corneal inflammation or edema; diagnosis of degenerative visual disorder predicted to cause future acuity losses to worse than 0.2 logMAR; previous refractive surgery; amblyopia; severe corneal dystrophy; keratitis, keratoconjunctivitis, keratouveitis, keratopathy, or kerectasia; diabetic retinopathy; extremely shallow anterior chamber; microphthalmos; previous retinal detachment (RD) or corneal transplantation; recurrent severe anterior or posterior segment inflammation of unknown etiology; rubella or traumatic cataract; iris neovascularization; glaucoma; aniridia; or optic nerve atrophy.

Intraocular Lenses

Patients were randomized 1:1 to have bilateral implantation of Acrysof IQ monofocal IOLs (SN60WF, Alcon Laboratories, Inc.) or Acrysof IQ Restor +2.5 D multifocal IOLs (SN6AD2 [SV25T0]) (Supplemental Table S1, available at http://jcrsjournal.org). Randomization was stratified by center to ensure balanced treatment assignments. Sodium hyaluronate 3.0%–chondroitin sulfate 4.0% (Viscoat) or other ophthalmic viscosurgical devices were allowed during surgery. The first eye to have IOL implantation was the one with the more advanced cataract at the preoperative visit.

Intraocular lenses were not implanted if patients had other ocular surgical procedures planned during the study; needed mechanical or surgical manipulation to enlarge the pupil or had dilated pupil size of less than 4.5 mm; had excessive iris mobility; experienced significant vitreous loss, significant anterior chamber hyphema, uncontrollable intraocular pressure (IOP), or zonular or capsular rupture; or had bag–sulcus, sulcus–sulcus, or unknown placement of the haptics.

Clinical Outcomes and Assessments

The primary effectiveness endpoint was the mean photopic monocular CDVA at 53 cm (selected based on the design of the +2.5 D multifocal IOL), evaluated at 120 to 180 days after implantation in the second eye. Secondary effectiveness endpoints included mean photopic monocular CDVA at 4 m and mean photopic monocular distance-corrected near visual acuity (DCNVA) at 40 cm; both were evaluated 120 to 180 days after implantation in the second eye. Binocular defocus response was also assessed.

Visual acuity testing was performed using 100% contrast Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts, and results were recorded in logMAR. Photopic lighting conditions used chart luminance of approximately 85 candelas (cd)/m^2. The distance-corrected intermediate visual acuity at 53 cm and DCNVA at 40 cm were tested using patients' manifest refraction adjusted for optical infinity. The CDVA at 4 m was tested using correction from patients' manifest refractions. Binocular defocus

testing was also performed using a 100% contrast ETDRS chart at 4 m under photopic lighting conditions. Patients were defocused with −5.00 D spherical correction from their distance correction determined by manifest refraction. Minus power was decreased in 0.5 D increments, and visual acuity was recorded until only the best distance correction remained. Patients were then defocused using +2.00 D spherical correction from their distance correction. Plus power was decreased in 0.5 D increments, and logMAR acuity was recorded until only the distance correction remained.

Patient-Reported Outcomes

Patient-reported outcomes included the Visual Tasks (VISTAS) self-rated questionnaire and the Assessment of Photic Phenomena and Lens EffectS (APPLES) 21-item self-rated questionnaire. The VISTAS questionnaire assessed distance-specific task function for near (<2 feet), intermediate (2 to 3 feet), extended-intermediate (3 to 15 feet), and distance (>15 feet) vision. Scores were calculated as the mean of items with a valid response on a scale of 1 (no difficulty) to 5 (cannot accomplish), with lower mean scores indicative of less difficulty in performing tasks. The APPLES questions addressed the frequency and severity of phenomena, including glare, halos, starbursts, hazy vision, blurred vision, distortion in which straight lines look tilted, distortion in which flat surfaces look curved, double vision, color distortion, and feeling sick to one's stomach due to visual distortions. Responses were reported on a 4-point categorical scale ranging from "never" to "always" for frequency items and from "none" to "severe" for severity items. Both questionnaires were completed at the preoperative visit and 120 to 180 days after IOL implantation in the second eye. Intraocular lens observations of glistenings were assessed during postoperative visits by the surgeons who implanted the IOLs and were graded as clinically significant or not clinically significant.

Safety

Safety was assessed by monitoring adverse events and binocular distance contrast sensitivity (with and without glare and under photopic and mesopic conditions). All adverse events observed during clinical assessments at each visit throughout the study were reported by the investigators; adverse events were also spontaneously reported by patients. Adverse event rates were compared with safety performance endpoint rates defined by ISO guidelines for IOLs.[17] Binocular distance contrast sensitivity was measured using the CSV-1000 chart (Vectorvision, Inc.) at a distance of 8 feet using the patient's spectacle corrections. Photopic contrast sensitivity was tested at spatial frequencies of 3, 6, 12, and 18 cycles per degree (cpd) at a chart luminance level of approximately 85 cd/m^2; mesopic contrast sensitivity was tested at spatial frequencies of 1.5, 3.0, 6.0, and 12.0 cpd with a neutral density filter that reduced chart luminance to approximately 3 cd/m^2. Patients were dark adapted for 10 minutes before mesopic testing. The last correct response at each frequency was recorded as the contrast sensitivity. Raw scores were transformed to log units. Treatment differences of 0.3 log units were considered to be clinically significant when they occurred at 2 or more spatial frequencies based on ANSI Z80.12-2007[18] and IS EN ISO 11979-9:2006.[19]

Statistical Analysis

The implanted data set (ie, all eyes with successful IOL implantation) was the primary data set used for analysis of effectiveness endpoints. Data were analyzed on the observed case basis; there was no imputation for missing data. The primary safety and effectiveness analyses were performed 120 to 180 days after the second-eye surgery for the 155 multifocal and 165 monofocal patients (all-implanted data set).

Binocular defocus and contrast sensitivity were evaluated using the best-case data set (all eyes with successful implantation that had at least 1 postoperative visit, no preoperative pathology or macular degeneration, and no major protocol deviations at any time) and summarized descriptively. All eyes with attempted IOL implantation were included in the safety analysis set.

Assuming a 5% dropout rate for a 6-month follow-up, approximately 320 patients were planned for enrollment on a 1:1 randomization ratio. A group size of 150 patients per IOL type was determined to provide more than 99% power to detect a 1-line difference (equal to 0.1 logMAR) for tests of superiority assuming a standard deviation (SD) of 0.17 logMAR and based on a 1-sided 2-sample t test with type 1 error rates of 5%. For testing the noninferiority of visual acuity endpoints, 150 patients per implantation group provided more than 99% probability that the lower 1-sided 95% confidence interval (CI) for the between-group difference would be more than −1 logMAR, assuming an SD of 0.17 logMAR.

Primary and secondary outcomes were analyzed using repeated-measures analysis of variance with study site as a covariate; unless otherwise noted, data are presented as the least squares mean ± the standard error. For mean photopic monocular CDVA at 53 cm, the superiority of the multifocal IOL in the primary eye was to be concluded if the mean visual acuity was better than that for the monofocal IOL. For mean monocular CDVA at 4 m, noninferiority of the multifocal IOL compared with the monofocal IOL was to be concluded if the upper bound of the 2-sided 90% CI of the between-group difference was less than 0.1 logMAR. For mean photopic monocular DCNVA at 40 cm, superiority of the multifocal IOL was to be concluded if the mean acuity was better than that for the monofocal IOL. Superiority and noninferiority analyses were performed using data from the first eye to have IOL implantation.

Data from patient-reported outcomes (APPLES and VISTAS questionnaires) were summarized descriptively by implantation group. The VISTAS questionnaire data were evaluated in the all-implanted data set (all eyes with successful IOL implantation); the mean, SD, and 2-sided 90% CIs were calculated for the 4 distance-specific function scales. Patients who responded "not applicable" to all 50 tasks covered by the "with corrective aids" questions were considered to not require spectacles to perform the tasks. The percentage of patients considered to not require spectacles to perform tasks was compared between groups using a Mantel-Haenszel test with stratification by study site. The APPLES data, IOL observations, and adverse events were evaluated in the safety data set (all eyes with attempted IOL implantation). The APPLES data from patients with bilateral IOL implantation were used to calculate the percentage of patients with a "severe" response to any of the reported phenomena addressed in the questionnaire.

Safety data were summarized using descriptive statistics. The primary statistical objective of the safety analysis was to show that the adverse event rates with the multifocal IOL at 120 to 180 days after implantation were not worse than ISO safety performance endpoint rates. For serious adverse events and categories of cystoid macular edema (CME), hypopyon, endophthalmitis, IOL dislocation, pupillary block, RD, and secondary surgical intervention, rates were compared with the cumulative adverse event safety performance endpoint rates. Persistent serious adverse event rates for corneal stromal edema, CME, iritis, and increased IOP requiring treatment were compared with persistent adverse event safety performance endpoint rates using 1-sided exact binomial testing performed separately for first surgical eye and second surgical eye.

RESULTS

Patients

Of the 409 patients enrolled, 329 were randomized to monofocal or multifocal IOLs; on average, 22 patients (range 1 to 35 patients) were randomized per study site. Eighty patients were excluded before randomization

because of screening failure. The most common causes of screening failure were a preoperative CDVA better than 0.2 logMAR and preoperative astigmatism more than 1.0 D. Sixteen randomized patients were terminated early from the study, 9 of whom discontinued before IOL implantation because the patient no longer wished to participate (monofocal, n = 2; multifocal, n = 2), because of financial reasons (multifocal, n = 2), and because the required IOL power was not available (multifocal, n = 3). Seven patients discontinued after IOL implantation because of adverse events (monofocal, n = 3; multifocal, n = 1), capsulorhexis tear (multifocal, n = 1), loss to follow-up (monofocal, n = 1), and death (multifocal, n = 1). The remaining 313 patients (153 in the multifocal group; 160 in the monofocal group) completed the study. The all-implanted population comprised 320 patients. The mean age was 69 years ± 9 (SD); 193 patients (60%) were women, and 292 (91%) were white. Patient demographics and baseline characteristics were similar between the monofocal group and the multifocal group (Table 1). In general, outcomes were similar regardless of pupil size.

Effectiveness

The multifocal IOL group had significantly better monocular CDVA at 53 cm than the monofocal IOL group (Figure 1) ($P < .0001$). The differences between the multifocal IOL group and monofocal IOL group were equivalent to approximately 2 lines on an ETDRS visual acuity chart. The difference in monocular CDVA at 4 m was not significant between the 2 groups (Figure 2, *A*). The between-group difference was 0.022 logMAR (90% CI, 0.002 to 0.043 logMAR) in the first eye and 0.006 logMAR (90% CI, −0.014 to 0.025 logMAR) in the second eye. The monocular DCNVA at 40 cm was significantly better in the multifocal IOL group than in the monofocal IOL group (Figure 2, *B*). The between-group difference was −0.206 logMAR (90% CI, −0.238 to −0.175 logMAR; $P < .0001$) in the first eye and −0.180 logMAR (90% CI, −0.212 to −0.149) in the second eye.

At near distance (33 cm), patients with multifocal IOLs had at least 0.1 logMAR better uncorrected near visual acuity (UNVA) and DCNVA than patients with monofocal IOLs. Patients with multifocal IOLs achieved mean UNVA at 33 cm of 0.55 ± 0.196 logMAR and 0.55 ± 0.193 logMAR in the first eye and second eye, respectively. The mean UNVA at 33 cm was 0.66 ± 0.183 logMAR and 0.65 ± 0.189 logMAR in the first eye and second eye of patients with monofocal IOLs. Patients with multifocal IOLs achieved a mean DCNVA at 33 cm of 0.56 ± 0.175 logMAR and 0.55 ± 0.175 logMAR in the first eye and second eye, respectively. The mean DCNVA at 33 cm was 0.70 ± 0.189 logMAR and 0.70 ± 0.178 logMAR in the first eye and second eye of patients with monofocal IOLs.

At intermediate distance (60 cm), patients with multifocal IOLs had no clinically relevant differences in monocular and binocular uncorrected visual acuity and at least 0.1 logMAR better CDVA compared with patients with monofocal IOLs. The mean uncorrected visual acuity at 60 cm was 0.34 ± 0.159 logMAR and 0.33 ± 0.165 logMAR in the first eye and second eye of patients with multifocal IOLs. The mean uncorrected visual acuity at 60 cm was 0.39 ± 0.182 logMAR and 0.36 ± 0.180 logMAR in the

Table 1. Patient demographics and baseline characteristics (all-implanted data set).

Parameter	Multifocal (n = 155)	Monofocal (n = 165)
Age (y)		
Mean ± SD	68.7 ± 9.6	69.4 ± 8.3
Min, max	26, 88	40, 90
Sex, n (%)		
Female	96 (62)	97 (59)
Male	59 (38)	68 (41)
Race, n (%)		
White	138 (89)	154 (93)
Black or African American	12 (8)	9 (6)
Asian	2 (1)	1 (1)
American Indian or Alaska native	2 (1)	0
Multiracial	1 (1)	0
Other	0	1 (1)
Preop photopic pupil size (mm)		
Mean ± SD	3.6 ± 0.8	3.7 ± 0.8
Min, max	2.0, 6.0	2.0, 6.5

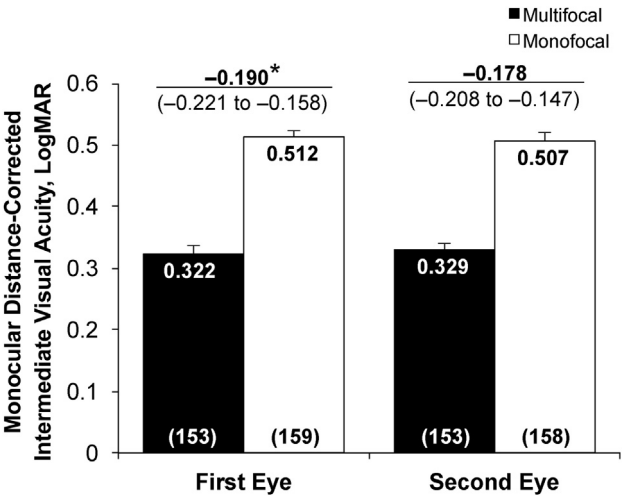

Figure 1. Monocular distance-corrected visual acuity at 53 cm. Data reflect least squares means and standard error. Superiority analysis was performed using data from the first eye to have surgery. The numbers centered over the bars at the top represent the between-group differences (logMAR), and the numbers underneath the line represent the 90% CI). Group sizes are indicated within the bars in parentheses (* = $P < .0001$).

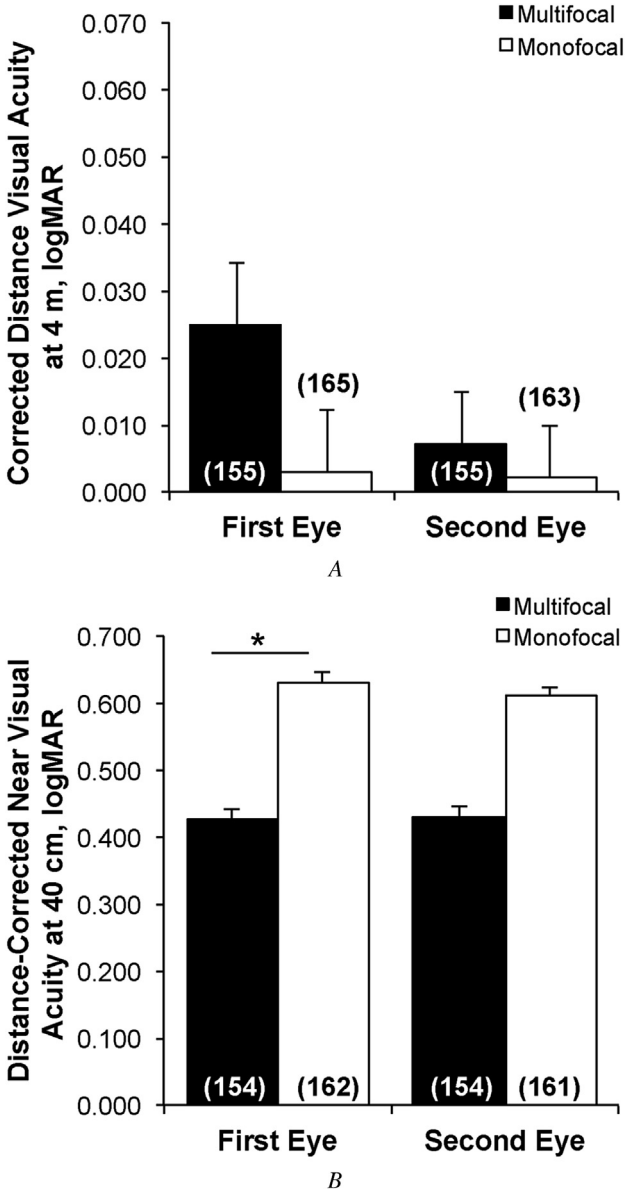

Figure 2. Monocular CDVA at 4 m (*A*) and DCNVA at 40 cm (*B*). Data reflect least squares means and standard error. Noninferiority and superiority analyses were performed using data from the first eye to have surgery. Group sizes are indicated within the bars in parentheses (* = $P < .0001$).

first and second eyes of patients with monofocal IOLs. Patients with multifocal IOLs achieved a mean distance-corrected visual acuity at 60 cm of 0.33 ± 0.174 logMAR and 0.32 ± 0.157 logMAR in the first eye and second eye, respectively. The mean distance-corrected visual acuity at 60 cm was 0.43 ± 0.169 logMAR and 0.44 ± 0.165 logMAR in the first eye and second eye of patients who received monofocal IOLs.

The multifocal IOL provided a range of functional vision from near to distance; both the multifocal IOL and the monofocal IOL provided good distance vision (Figure 3). Patients achieved 20/40 or better binocular vision from +2.00 to −2.75 D with the multifocal IOL and from +1.50 to −2.00 D with the monofocal IOL. The multifocal

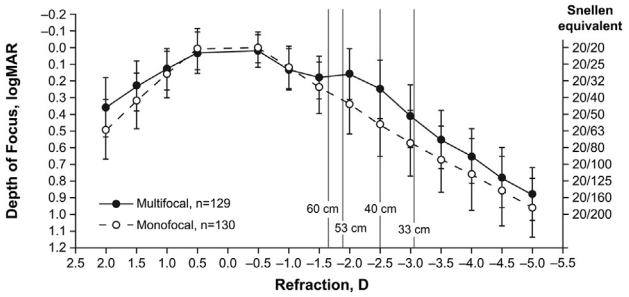

Figure 3. Depth of focus. Data reflect the mean and SD.

IOL defocus curve showed the expected bimodal peak pattern, with a distance visual acuity peak at 0.00 D with acuity at 20/20 or better and an intermediate visual acuity peak at approximately −2.00 D (corresponding to a distance of approximately 53 cm). Visual acuity was approximately 2 lines better in the multifocal IOL group than in the monofocal IOL group at −2.50 D (40 cm) and −2.00 D (53 cm) and was more than 1 line better at −3.00 D (33 cm) of defocus.

Patient-Reported Outcomes

At the preoperative visit, VISTAS distance-specific task scores with and without corrective aids were slightly higher in the multifocal group than in the monofocal group (Supplemental Table S2, available at http://jcrsjournal.org). Patients who received multifocal IOLs reported lower mean VISTAS scores 120 to 180 days after implantation, where lower scores reflected less difficulty in performing tasks without corrective aids for near and intermediate function scales (Figure 4, *A*). The mean scores for near tasks were 3.0 ± 1.2 in the multifocal group (90% CI, 2.83-3.14) and 3.3 ± 1.2 in the monofocal group (90% CI, 3.18-3.51). The mean scores for intermediate tasks were 1.8 ± 1.0 in the multifocal group (90% CI, 1.68-1.96) and 2.1 ± 1.2 in the monofocal group (90% CI, 1.95-2.27). Extended-intermediate and distance function scale outcomes were similar between implantation groups (Figure 4, *A*). Among patients using corrective aids, the mean scores for near function were lower (less difficulty) in the monofocal group compared with the multifocal group (monofocal: 1.3 ± 0.5, 90% CI, 1.25-1.39; multifocal: 1.5 ± 0.7, 90% CI, 1.37-1.57) (Figure 4, *B*). Scores for intermediate, extended-intermediate, and distance function scales completed while patients were using corrective aids were similar between the IOL groups (Figure 4, *B*). At the postoperative visit, significantly more patients with multifocal IOLs were considered to not require spectacles to perform tasks compared with patients with monofocal IOLs (19 of 155 patients [12%] versus 8 of 165 patients [5%]; $P = .0157$).

The frequency of patient-reported photic phenomena decreased in both groups after bilateral implantation; considerably more patients in both groups reported never experiencing glare, halos, starbursts, hazy vision, blurred vision, visual distortion, double vision, or color distortion at the postoperative visit compared with the preoperative visit (Table 2). At the postoperative visit, the most

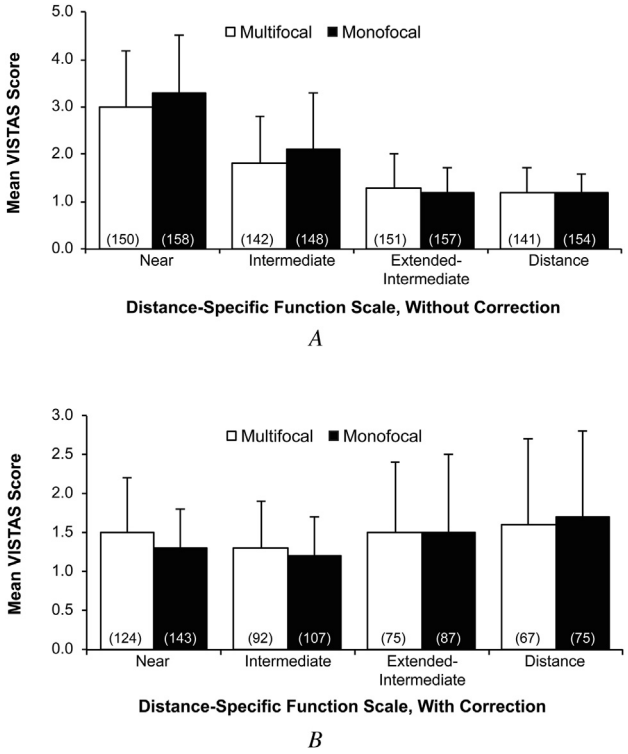

Figure 4. VISTAS questionnaire scores 120 to 180 days after implantation (*A*) without corrective aids and (*B*) with corrective aids. Group sizes are indicated at bottom of bars (Distance = over 15 feet; Extended-Intermediate = 3 to 15 feet; Intermediate = 2 to 3 feet; Near = less than 2 feet; VISTAS = Visual Tasks self-rated questionnaire).

frequently reported severe visual disturbances in both groups were halos, starbursts, and glare (Table 2). The incidence of severe halos, starbursts, and glare was decreased from preoperative levels in both IOL groups.

At the final postoperative visit 120 to 180 days after the implantation of the second IOL, observations showed no glistenings in the IOL in approximately 95% of eyes (301/313 for first eyes; 295/311 for second eyes). In the multifocal group, 96% (147/153) of first eyes and 94% (144/153) of second eyes had no reported glistenings; in the monofocal group, no glistenings were reported in 96% of first eyes (154/160) and second eyes (151/158). None of the reported glistenings was considered clinically significant by the investigators.

Safety

The incidence of cumulative or persistent serious adverse events in the multifocal IOL group was not significantly different from the safety performance endpoint rates (ISO 11979-7:2006) for posterior chamber IOLs (PC IOLs) ($P \geq .540$), and no adverse events in the prespecified categories exceeded the minimum threshold rate (Table 3). Results were the same for first eyes and second eyes. Serious adverse event rates for first- and second-implanted eyes were approximately 1% in each implantation group (multifocal, n $\leq$ 2; monofocal, n $\leq$ 1). Cystoid macular edema was reported in 4 eyes in the multifocal IOL group. In the monofocal IOL group, increased IOP and open-angle glaucoma were each reported in 2 eyes; cataract operation complication, traumatic device dislocation, eye operation, intraocular injection, iritis, retinal vein occlusion, repeated surgical procedure, and wound complication were each reported for 1 eye. No unanticipated serious adverse device effects were reported. Overall, the most frequently reported ocular adverse events were increased IOP, dry eye, and vitreous detachment. Ocular adverse events reported for 2% or more of eyes in either group are summarized in Table 4. Adverse device effects of glare and halo vision (1 event each) were reported for first and second eyes in the multifocal IOL group. Three device deficiencies were observed during surgery and replacement IOLs were implanted; 2 multifocal IOLs and 1 monofocal IOL showed visible damage to the optics or haptics from manufacturing or handling of the IOL. There were no reports of IOL explantation after the surgery.

There were no clinically relevant differences in binocular contrast sensitivity under photopic or mesopic conditions, with or without glare, between the multifocal group and the monofocal group (Table 5).

DISCUSSION

In this 6-month study, patients having bilateral cataract surgery received multifocal IOLs with a +2.5 D add power designed to provide an intermediate focal point in addition to distance vision or standard monofocal IOLs designed to provide distance vision only. The multifocal IOL performed better than the monofocal IOL in terms of photopic monocular distance-corrected intermediate visual acuity at 53 cm and DCNVA at 40 cm and was noninferior to the monofocal IOL for CDVA at 4 m. Distance-corrected visual acuity at 53 cm was approximately 2 lines better in patients with multifocal IOLs than in those with monofocal IOLs, and patients with multifocal IOLs reported less difficulty completing intermediate tasks without corrective aids. Postoperatively (120 to 180 days after IOL implantation), the incidence of severe visual disturbances was considerably lower than preoperatively in both groups. Halos and starbursts were the most frequently reported severe photic phenomena in both groups, and 4% or less of patients in both groups reported severe glare. A low incidence of adverse events was observed in both groups, and the incidence of serious adverse events in the multifocal IOL group met safety criteria for PC IOLs.

A benefit of multifocal IOLs is that they provide good near and distance vision, whereas monofocal IOLs provide good distance vision but poorer near vision.[4] A metaanalysis of 20 studies evaluating bilateral implantation of multifocal or monofocal IOLs[12] found that multifocal IOLs provided significantly better UDVA and near visual acuity than monofocal IOLs. For patients desiring increased spectacle independence for tasks at a range of distances, a multifocal IOL that provides good intermediate vision in addition to near and distance vision might be beneficial. In a laboratory study comparing an apodized diffractive

Table 2. Responses to APPLES questionnaire.

Symptom	Number (%)			
	Preoperative		Postoperative (Day 120–180)	
	Multifocal	Monofocal	Multifocal	Monofocal
Glare*	155	165	153	160
Frequency				
Never	21 (14)	21 (13)	60 (39)	75 (47)
Sometimes	60 (39)	71 (43)	65 (42)	69 (43)
Often	39 (25)	49 (30)	21 (14)	13 (8)
Always	35 (23)	24 (15)	7 (5)	3 (2)
Severity				
None	23 (15)	26 (16)	61 (40)	79 (49)
Mild	44 (28)	42 (25)	55 (36)	54 (34)
Moderate	50 (32)	68 (41)	32 (21)	21 (13)
Severe	38 (25)	29 (18)	5 (3)	6 (4)
Halos*	155	164	153	160
Frequency				
Never	25 (16)	39 (24)	52 (34)	98 (61)
Sometimes	37 (24)	41 (25)	45 (29)	45 (28)
Often	41 (26)	31 (19)	18 (12)	9 (6)
Always	52 (34)	53 (32)	38 (25)	8 (5)
Severity				
None	25 (16)	41 (25)	57 (37)	99 (62)
Mild	26 (17)	29 (18)	46 (30)	43 (27)
Moderate	59 (38)	51 (31)	34 (22)	12 (8)
Severe	45 (29)	43 (26)	16 (10)	6 (4)
Starbursts*	154	164	153	160
Frequency				
Never	27 (18)	34 (21)	81 (53)	98 (61)
Sometimes	49 (32)	54 (33)	43 (28)	45 (28)
Often	40 (26)	34 (21)	12 (8)	10 (6)
Always	38 (25)	42 (26)	17 (11)	7 (4)
Severity				
None	29 (19)	36 (22)	85 (56)	99 (62)
Mild	36 (23)	43 (26)	38 (25)	43 (27)
Moderate	46 (30)	45 (27)	18 (12)	12 (8)
Severe	43 (28)	40 (24)	12 (8)	6 (4)
Hazy vision*	155	165	153	160
Frequency				
Never	16 (10)	18 (11)	97 (63)	106 (66)
Sometimes	34 (22)	52 (32)	50 (33)	45 (28)
Often	50 (32)	52 (32)	4 (3)	8 (5)
Always	55 (35)	43 (26)	2 (1)	1 (1)

(*continued on next page*)

Table 2. (Cont.)

Symptom	Number (%)			
	Preoperative		Postoperative (Day 120–180)	
	Multifocal	Monofocal	Multifocal	Monofocal
Severity				
None	14 (9)	18 (11)	101 (66)	107 (67)
Mild	37 (24)	44 (27)	41 (27)	39 (24)
Moderate	64 (41)	68 (41)	10 (7)	12 (8)
Severe	40 (26)	35 (21)	1 (1)	2 (1)
Blurred vision*	155	165	153	160
Frequency				
Never	24 (15)	31 (19)	112 (73)	115 (72)
Sometimes	41 (26)	56 (34)	34 (22)	39 (24)
Often	55 (35)	42 (25)	7 (5)	6 (4)
Always	35 (23)	36 (22)	0	0
Severity				
None	23 (15)	31 (19)	113 (74)	115 (72)
Mild	36 (23)	36 (22)	30 (20)	37 (23)
Moderate	63 (41)	70 (42)	10 (7)	8 (5)
Severe	33 (21)	28 (17)	0	0
Distortion: straight lines look tilted*	155	165	153	160
Frequency				
Never	101 (65)	111 (67)	140 (92)	152 (95)
Sometimes	38 (25)	33 (20)	11 (7)	7 (4)
Often	13 (8)	13 (8)	2 (1)	1 (1)
Always	3 (2)	8 (5)	0	0
Severity				
None	100 (65)	112 (68)	139 (91)	149 (93)
Mild	34 (22)	29 (18)	11 (7)	9 (6)
Moderate	16 (10)	15 (9)	3 (2)	0
Severe	5 (3)	9 (5)	0	2 (1)
Distortion: flat surfaces look curved*	155	165	153	160
Frequency				
Never	111 (72)	124 (75)	146 (95)	154 (96)
Sometimes	31 (20)	29 (18)	4 (3)	5 (3)
Often	10 (6)	9 (5)	2 (1)	0
Always	3 (2)	3 (2)	1 (1)	1 (1)
Severity				
None	111 (72)	128 (78)	146 (95)	152 (95)
Mild	26 (17)	19 (12)	4 (3)	5 (3)
Moderate	17 (11)	12 (7)	3 (2)	1 (1)
Severe	1 (1)	6 (4)	0	2 (1)

(*continued on next page*)

Table 2. (Cont.)

Symptom	Number (%)			
	Preoperative		Postoperative (Day 120–180)	
	Multifocal	Monofocal	Multifocal	Monofocal
Double vision*	155	165	153	160
Frequency				
Never	82 (53)	98 (59)	142 (93)	154 (96)
Sometimes	46 (30)	50 (30)	10 (7)	4 (3)
Often	23 (15)	12 (7)	1 (1)	2 (1)
Always	4 (3)	5 (3)	0	0
Severity				
None	82 (53)	99 (60)	142 (93)	153 (96)
Mild	41 (26)	37 (22)	7 (5)	4 (3)
Moderate	25 (16)	21 (13)	3 (2)	1 (1)
Severe	7 (5)	8 (5)	1 (1)	2 (1)
Color distortion*	155	165	153	160
Frequency				
Never	99 (64)	111 (67)	143 (93)	150 (94)
Sometimes	37 (24)	36 (22)	10 (7)	8 (5)
Often	17 (11)	15 (9)	0	2 (1)
Always	2 (1)	3 (2)	0	0
Severity				
None	98 (63)	114 (69)	144 (94)	150 (94)
Mild	29 (19)	26 (16)	8 (5)	9 (6)
Moderate	21 (14)	20 (12)	1 (1)	1 (1)
Severe	7 (5)	5 (3)	0	0
Feeling sick to one's stomach due to visual distortion*	155	164	153	160
Frequency				
Never	123 (79)	123 (79)	144 (94)	147 (92)
Sometimes	23 (15)	25 (15)	9 (6)	13 (8)
Often	8 (5)	8 (5)	0	0
Always	1 (1)	1 (1)	0	0
Severity				
None	123 (79)	135 (82)	146 (95)	147 (92)
Mild	22 (14)	16 (10)	6 (4)	10 (6)
Moderate	9 (6)	10 (6)	1 (1)	3 (2)
Severe	1 (1)	3 (2)	0	0
Questionnaire completed based on experiences with or without glasses*	155	165	153	160
Without glasses	60 (39)	61 (37)	121 (79)	111 (69)
With glasses	95 (61)	104 (63)	32 (21)	49 (31)

*Number only.

Table 3. Multifocal IOL comparison with safety performance endpoints (safety data set)*

Parameter	n (%)	UCL† (%)	SPE (%)	Threshold‡ (%)	*P* Value
Cumulative SAEs					
Cystoid macular edema	1 (0.6)	3.0	3.0	7.2	.948
Endophthalmitis	0	1.9	0.1	1.9	1.000
Hypopyon	0	1.9	0.3	2.7	1.000
Lens dislocated from posterior chamber	0	1.9	0.1	1.9	1.000
Pupillary block	0	1.9	0.1	1.9	1.000
Retinal detachment	0	1.9	0.3	2.7	1.000
Secondary surgical intervention	0	1.9	0.8	3.5	1.000
Persistent SAEs					
Corneal stroma edema	0	1.9	0.3	2.7	1.000
Cystoid macular edema	1 (0.6)	3.0	0.5	2.7	.540
Iritis	0	1.9	0.3	2.7	1.000
Raised IOP requiring treatment	0	1.9	0.4	2.7	1.000

IOP = intraocular pressure; SAE = serious adverse event; SPE = safety performance endpoint; UCL = upper confidence limit
*Multifocal IOL group, first implanted eye (n = 155).
†Exact (Clopper-Pearson) 1-sided 95% upper confidence interval.
‡Minimum rate detectable as significantly different from the safety performance endpoint rate with a group size of 155.

+3.0 D multifocal IOL and a trifocal IOL,[20] the multifocal IOL provided good optical quality across a greater range of distances whereas the trifocal IOL provided better quality at an intermediate focal point of −1.5 D.

In the current study, patients with the +2.5 D multifocal IOL achieved significantly better visual acuity at 53 cm than patients with monofocal IOLs; acuity at 53 cm was approximately 0.32 logMAR (20/40 Snellen) in the multifocal group and 0.51 (20/64) in the monofocal group. The distance of 53 cm for the primary effectiveness endpoint was specific to the design of the +2.5 D multifocal IOL and was within the recommended range for computer work.[21]

Binocular defocus produced the bimodal curve expected for the +2.5 D multifocal IOL, with a peak at approximately 53 cm that was absent from the monofocal IOL curve. Furthermore, binocular defocus results showed that multifocal IOLs provided 20/40 acuity across a greater range than monofocal IOLs. These findings indicate that the +2.5 D multifocal IOL provides good near, intermediate, and distance vision.

Patient-reported VISTAS scores support the visual acuity data. Compared with patients with the monofocal IOLs, the percentage of patients with multifocal IOLs who did not use spectacles to perform tasks was higher and they had less

Table 4. Adverse events with an incidence of 2% or more in either eye.

Event	Number (%)			
	Multifocal		Monofocal	
	First Eye (n = 155)	Second Eye (n = 155)	First Eye (n = 165)	Second Eye (n = 163)
Allergic conjunctivitis	3 (2)	3 (2)	2 (1)	1 (1)
Blepharitis	2 (1)	2 (1)	3 (2)	1 (1)
Dry eye	4 (3)	5 (3)	4 (2)	3 (2)
Glare	4 (3)	4 (3)	1 (1)	1 (1)
Halos	4 (3)	4 (3)	0	0
Increased intraocular pressure	4 (3)	3 (2)	5 (3)	6 (4)
Iritis	3 (2)	4 (3)	1 (1)	2 (1)
Vitreous detachment	3 (2)	3 (2)	5 (3)	4 (3)

Table 5. Binocular contrast sensitivity (best-case data set).

Contrast Sensitivity	Mean ± SD	
	Multifocal*	Monofocal†
Photopic, with glare		
3 cpd	1.61 ± 0.31	1.70 ± 0.28
6 cpd	1.69 ± 0.32	1.85 ± 0.31
12 cpd	1.34 ± 0.32	1.48 ± 0.34
18 cpd	0.92 ± 0.33	1.04 ± 0.36
Photopic, without glare		
3 cpd	1.68 ± 0.26	1.74 ± 0.20
6 cpd	1.82 ± 0.26	1.94 ± 0.25
12 cpd	1.46 ± 0.31	1.56 ± 0.31
18 cpd	0.97 ± 0.35	1.11 ± 0.33
Mesopic, with glare		
1.5 cpd	1.54 ± 0.24	1.59 ± 0.25
3 cpd	1.54 ± 0.30	1.59 ± 0.31
6 cpd	1.54 ± 0.33	1.61 ± 0.29
12 cpd	1.04 ± 0.38	1.12 ± 0.38
Mesopic, without glare		
1.5 cpd	1.58 ± 0.24	1.62 ± 0.20
3 cpd	1.56 ± 0.27	1.62 ± 0.23
6 cpd	1.57 ± 0.30	1.67 ± 0.28
12 cpd	1.06 ± 0.37	1.19 ± 0.36

cpd = cycles per degree
*n = 103–131.
†n = 116–133.

difficulty with near and intermediate visual tasks without the use of corrective aids and less difficulty with near visual tasks with the use of corrective aids. Difficulty with extended-intermediate and distance tasks was similar between the multifocal IOLs and monofocal IOLs with and without use of corrective aids.

Multifocal IOLs provide simultaneous vision at more than 1 distance, and this can reduce contrast sensitivity compared with monofocal IOLs.[4,22] Contrast sensitivity can vary with IOL design, lighting conditions, and the presence of corneal aberrations.[22–24] In a prospective nonrandomized trial of patients with binocular monofocal or apodized diffractive multifocal IOLs,[25] monocular photopic contrast sensitivity was significantly reduced in the multifocal group compared with the monofocal group; however, no significant between-group difference was reported in binocular photopic contrast sensitivity. A small prospective study of 64 eyes of 32 patients with monofocal IOLs or diffractive multifocal IOLs with a +3.0 D add power[26] found no significant differences in contrast acuity under photopic or mesopic conditions. We observed no clinically relevant between-group differences in binocular contrast sensitivity between the multifocal IOL group and monofocal IOL group under photopic or mesopic conditions, with or without glare, at any tested spatial frequency.

Visual disturbances with several multifocal IOL designs have been reported, and the impact of phenomena such as glare and halos is often greater with multifocal IOLs than with monofocal IOLs.[8,12,27] However, a metaanalysis comparing multiple multifocal IOL designs with monofocal IOLs[12] suggested that more recent multifocal IOL designs might be associated with rates of halo and postoperative patient satisfaction comparable to those with monofocal IOLs. In our study, the frequency of patients reporting halos (sometimes to always) was 66% for multifocal IOLs and 39% for monofocal IOLs. The frequency of patient-reported starbursts (sometimes to always) was 47% and 39%, respectively. For 6 of the 9 APPLES questionnaire items, the incidence of severe ratings in either group was 0% or 1% (multifocal, 0.65%; monofocal, 1.25%) and most patients with multifocal IOLs (73% to 95%) or monofocal IOLs (72% to 96%) reported never experiencing events such as blurred vision, visual distortion, or double vision. Severe halos, starbursts, and glare were reported by 10%, 8%, and 3%, respectively, of patients in the multifocal group and by 4% each in the monofocal group; the frequency of severe visual disturbances was considerably reduced after IOL implantation in both groups compared with the preoperative visit. Other studies reported a similar frequency of severe photic phenomena. In a small randomized masked study,[6] the rates of glare were approximately 6% with both a diffractive multifocal IOL and a monofocal IOL. Of 119 patients who had bilateral implantation of an apodized diffractive +4.0 D multifocal IOL, severe glare and halos were reported by 9% of patients and 4% of patients, respectively.[5] Although a higher rate of severe halos was reported by patients in the multifocal group, there were no cases of IOL explantations over the course of this study.

We observed a low incidence of IOL glistenings compared with that in previous reports.[28] Glistenings are fluid-filled microvacuoles that can form over time in IOLs.[29] These artifacts have been reported at higher rates with hydrophobic acrylic IOLs than with other materials.[30,31] However, glistenings typically do not affect visual acuity or optical quality.[28,31,32] In this study, glistenings were observed at the final postoperative visit in approximately 5% of eyes with multifocal IOLs and 4% of eyes with monofocal IOLs. The duration of follow-up in the current study (120 to 180 days) might not have been sufficient to see a significant difference in the number of glistenings between the 2 IOL groups.[28]

Ocular adverse events, including those related to visual disturbances, were reported for less than 4% of eyes. Adverse device effects of glare and halo vision were each reported for 2 eyes (<1%) in the multifocal IOL group. This is a lower incidence than previously reported with other multifocal IOLs.[5,12,33] Serious adverse events, including adverse device effects, were reported at an incidence of approximately 1% in each group. All safety performance

endpoints for cumulative and persistent serious adverse events were met ($P > 0.5$). Cystoid macular edema was the only serious adverse event in the multifocal IOL group and was reported in 2 eyes.

In conclusion, compared with a monofocal IOL, the +2.5 D multifocal IOL provided better photopic monocular distance-corrected visual acuity at 53 cm, monocular CDVA that was not inferior at 4 m, and better monocular DCNVA at 40 cm. Depth-of-focus curves had a bimodal pattern with peaks for distance and intermediate (approximately 53 cm) vision for the multifocal IOL; patients with multifocal IOLs achieved 20/40 or better acuity from +2.00 D to −2.75 D. This represented an extended range compared with patients with monofocal IOLs (+1.50 to −2.00 D). The +2.5 D multifocal IOL provided reduced patient-reported difficulty with near and intermediate tasks and similar patient-reported difficulty with extended-intermediate and distance tasks compared with the standard monofocal IOL. The incidence and severity of most visual disturbances were relatively low in both groups. The +2.5 D multifocal IOL had a safety profile and contrast sensitivity similar to that of the monofocal IOL and might provide an effective multifocal IOL option for patients wishing to achieve functional distance, intermediate, and near vision.

WHAT WAS KNOWN

- Monofocal IOLs provide good distance vision; however, patients often require corrective aids for near and intermediate tasks.
- Multifocal IOLs provide good near to distance vision but can cause visual disturbances.
- A new multifocal IOL with +2.5 D add power was designed with a near vision focal point at a distance extended from currently approved multifocal IOLs to provide a range of functional vision from distance to near.

WHAT THIS PAPER ADDS

- The +2.5 D multifocal IOL was better than the standard monofocal IOL for intermediate (53 cm) and near (40 cm) visual acuity and not inferior for distance (4 m) visual acuity.
- The multifocal IOL met ISO 11979-7:2006 criteria for posterior chamber IOL safety, and there were no clinically relevant differences in serious adverse events or contrast sensitivity between the multifocal IOL group and the monofocal IOL group.
- Comparable low rates of postoperative photic phenomena and IOL effects were reported with both types of IOLs. There was a low incidence of patient-reported severe glare in both groups (multifocal, 3%; monofocal, 4%).

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DISCLOSURE: *Drs. Maxwell, Holland, and Cibik are consultants to Alcon Research, Ltd. Drs. Fakadej, Foster, and Toyos are researchers for, consultants to, and speakers for Alcon Research, Ltd. Dr. Weinstein has received research-related personal fees from Alcon. Dr. Grosinger has received research funding from Alcon Laboratories, Inc. Dr. Hartzell is a consultant to Abbott Medical Optics, Inc., Alcon Research, Ltd., Allergan, Inc., Glaukos Corp., IEC Technology, Inc., and Summit Technology, Inc. No other author has a financial or proprietary interest in any material or method mentioned.*