Clinical Comparison of a Small-Aperture Intraocular Lens Versus a Monofocal Control

John Vukich, MD; Satish Modi, MD, FRCS(C), CPI; Bret L. Fisher, MD; Karl Stonecipher, MD; Ling Lin, PhD; Magda Michna, PhD

ABSTRACT

PURPOSE: To evaluate range of visual acuity, visual quality, and safety of the IC-8 small-aperture (SA) intraocular lens (IOL) (Apthera; Bausch & Lomb, Inc) in patients with cataract.

METHODS: This was a prospective, multicenter, open-label, parallel-group, non-randomized, examiner-masked, 12-month clinical study conducted at 21 sites in the United States. Included patients (N = 453) received either the SA IOL (targeted to -0.75 diopters) in one eye and a monofocal or monofocal toric IOL (targeted to plano) in the fellow eye (SA IOL group, n = 343) or bilateral monofocal/monofocal toric IOLs (control group, n = 110).

RESULTS: At 6 months, the SA IOL group achieved superior binocular uncorrected intermediate and near visual acuity (*P* < .0001) and equivalent binocular uncorrected distance visual acuity versus the control group. In SA IOL eyes, 99.1% achieved monocular corrected distance visual acuity of 0.3 logarithm of the minimum angle of resolution or better. The SA IOL and control groups had comparable binocular photopic and mesopic contrast sensitivities at 6 months both with and without glare. The SA IOL group reported few visual symptoms overall, although at higher rates than in the control group.

CONCLUSIONS: The SA IOL group exhibited improved intermediate and near vision, comparable distance vision and binocular contrast sensitivities, and few visual symptoms or adverse events versus the bilateral monofocal/monofocal toric IOL group, suggesting that the SA IOL is an effective option for presbyopia correction at the time of cataract surgery.

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Cataract surgery increasingly provides patients with an array of options in terms of techniques, technology, and types of intraocular lenses (IOLs) tailored to their lifestyle and needs.[1] Despite these advances, monofocal IOLs are associated with inferior near and intermediate vision and depth of focus.[2-5] Although multifocal IOLs provide an extended range of vision, patients often experience decreased contrast sensitivity and increased visual phenomena, including glare, halos, and starbursts.[6,7]

The small-aperture (SA) IOL capitalizes on the concept of a pinhole, in which decreased pupil size leads to a smaller blur circle diameter on the retinal surface.[8,9] The IC-8 IOL (Apthera; Bausch & Lomb, Inc) is a small-aperture (1.36 mm), one-piece, hydrophobic, acrylic, posterior chamber IOL with a circular opaque mask, the FilterRing (Bausch & Lomb, Inc), that blocks unfocused peripheral light while allowing through more focused central light, extending the depth of fo-

From Summit Eye Care of Wisconsin, Wauwatosa, Wisconsin (JV); Seeta Eye, Poughkeepsie, New York (SM); Eye Center of North Florida, Panama City, Florida (BLF); Laser Defined Vision, Greensboro, North Carolina (KS); and AcuFocus, Inc, Irvine, California (LL, MM).

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Disclosure: JV is a consultant for AcuFocus, Inc and Bausch & Lomb, Inc; BLF is a consultant for Alcon Laboratories, Inc, Bausch & Lomb, Inc, and Imprimis Pharmaceuticals and has participated in a safety monitoring board or advisory board for Stroma Medical and Ziemer. KS has received grants or contracts from AcuFocus, Inc (payment to institution) and Bausch Health (payment to institution), is a consultant for Bausch & Lomb, Inc, receives honoraria from Bausch & Lomb, Inc, and has received equipment, materials, drugs, medical writing, gifts, or other services from AcuFocus, Inc (delivered to institution) and Bausch & Lomb, Inc (delivered to institution). LL is a current employee of and MM is a former employee of AcuFocus, Inc. SM has disclosed no potential conflicts of interest, financial or otherwise.

Address correspondence to John Vukich, MD, 10425 West North Avenue, Suite 140, Wauwatosa, WI 53226; email: javukich@gmail.com.

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cus.[10] It is the first SA IOL approved by the U.S. Food and Drug Administration (FDA) and the first extended depth of focus IOL approved for monovision. The SA IOL is also approved in the United States for eyes with up to 1.50 diopters (D) of corneal astigmatism and is the only extended depth of focus IOL to provide monofocal IOL–like binocular contrast sensitivity.[11] The SA IOL is intended for primary implantation in the capsular bag of the nondominant eye after successful fellow-eye implantation of a monofocal or monofocal toric IOL (ie, an uncorrected distance visual acuity [UDVA] of 20/32 or better and corrected distance visual acuity [CDVA] of 20/25 or better).[11] Early data on the SA IOL are promising, with comparable visual acuity, a broad range of vision, high patient satisfaction, and favorable safety outcomes.[8,12-15] The SA IOL has also shown effectiveness outside the United States in patients with cataracts and presbyopia.[8,16]

This prospective, open-label, parallel-group, examiner-masked, 12-month clinical study was designed to evaluate the SA IOL for long-term safety and clinical effectiveness in patients with cataracts. Data presented here compare the SA IOL to monofocal control IOL performance across binocular and/or monocular assessments, including distance, intermediate, and near visual acuities (uncorrected and distance-corrected), photopic and mesopic contrast sensitivities, subjective visual quality, and rates of adverse events.

PATIENTS AND METHODS

This was a prospective, multicenter, open-label, parallel-group, non-randomized, examiner-masked, 12-month clinical study (NCT03633695) conducted at 21 investigational sites in the United States. Of these, 19 sites used institutional review board (IRB) approval from Alpha, IRB (San Clemente, CA), one site used IRB approvals from Advarra IRB (Columbia, MD), and Baylor College of Medicine and Affiliated Hospitals IRB (Houston, TX), and one site used IRB approvals from Alpha IRB (San Clemente, CA), SSM Health Wisconsin IRB (Madison, WI), and Dean IRB (Madison, WI). The study was performed in accordance with the Health Insurance Portability and Accountability Act (HIPAA), the tenets of the Declaration of Helsinki, and the IRB of each participating center. Written informed consent was obtained from all patients.

Included patients (N = 453) were 22 years or older, had cataractous lens changes as observed by a 20/40 or worse CDVA with or without a glare source, and planned bilateral crystalline lens removal by phacoemulsification—with or without femtosecond laser–assisted extraction—and posterior chamber IOL implantation. Included patients also had the potential for a postoperative CDVA of 20/25 or better in each eye as estimated by an instrument such as a potential acuity meter or investigator estimation, and clear intraocular media other than cataract. Patients were excluded if they required an SA IOL outside the available spherical power range of +15.50 to +27.50 D, had preoperative corneal astigmatism of greater than 1.50 D in either eye, had irregular astigmatism in either eye, had a pharmacologically dilated pupil size less than 6 mm in either eye, were unable to achieve stable keratometric readings following discontinuation of contact lens wear, had active or recurrent anterior segment pathology, or had ocular abnormalities other than cataract. Patients were also excluded if they had previous corneal or intraocular surgery (except pterygium surgery), a history of ocular trauma or ocular conditions expected to require retinal laser treatment or other surgical intervention, dry eye with inadequate maintenance of eye comfort or vision with dry eye treatment, congenital cataracts, use of systemic or ocular medications that may affect vision or were likely to impact pupil dilation or iris structure, had acute, chronic, or uncontrolled systemic disease with the potential to increase operative risk or confound study outcomes, or had recently participated in other clinical trials.

As part of the screening process, preoperative pupil size was assessed under photopic, mesopic, and dilated conditions. Pupil size was also assessed under these three conditions at months 3, 6, and 12, but analyses in which the data were stratified by pupil size are beyond the scope of the data reported here.

Treatment group assignments were based on patient preference or investigator determination. The investigator determined the monofocal eye and the SA IOL eye based on patient preference and their assessment of the best predictive outcome based on preoperative assessments of the degree of cataract in each eye, the patient's occupational and/or recreational needs, history of monovision contact lens wear, habitual spectacle prescription, or if the eye required a lens outside the available power range of the SA IOL. There was no specific instruction on whether to place the SA IOL in the dominant or nondominant eye, but almost all patients in the SA IOL group (92.1% [316 of 343]) received the SA IOL in the non-dominant eye. Sighting dominance was established via three consistent trials of the "hole-in-the-card" test, in which the patient holds a rectangular card with a circular hole in the middle and, through the aperture, reads a single letter on the 4-m distance logarithm of the minimum angle of resolution (logMAR) Early Treatment Diabetic Retinopathy Study (ETDRS) with one eye closed. After alternating which eye is closed, the dominant eye is recorded as the one that continued to see the letter when its companion was covered.

All patients underwent crystalline lens removal by phacoemulsification, either with or without femtosecond laser–assisted extraction, followed by posterior chamber implantation of the corresponding IOL according to the patient's treatment group assignment. For the first IOL implantation, patients in both treatment groups received a monofocal/monofocal toric IOL, targeted to plano: AcrySof IQ (SA60WF; Alcon Laboratories, Inc) or TECNIS aspheric monofocal IOLs (ZCB00; Johnson & Johnson) or monofocal toric IOLs (AcrySof SA6AT3 or SA6AT4 IOLs; TECNIS ZCT150 or ZCT225 IOLs).

Successful implantation of the first eye was defined as achievement of uncorrected distance visual acuity (UDVA) of 20/32 or better and CDVA 20/25 or better at postoperative week 1; meeting success criteria was required before proceeding to the second eye surgery. For the second IOL implantation, patients received either the SA IOL (SA IOL group) targeted to -0.75 D (per the FDA-approved indication for the SA IOL) or a monofocal/monofocal toric IOL (control group) targeted to plano. The SA IOL is designed to extend depth of focus, so the targeted refraction was set to be slightly myopic to further enhance range of vision.

For SA IOL eyes, the appropriate IOL power was calculated following biometric assessment using the Barrett Universal II formula.[17] Power calculations for monofocal/monofocal toric IOLs were left to the surgeon's discretion. Patients completed up to 12 study visits over 12 months, including preoperative, operative, and postoperative day 1, week 1, and month 1, 3, 6, and 12 visits.

This report includes the following effectiveness endpoints: refractive outcomes, mean photopic binocular and monocular UDVA, uncorrected intermediate visual acuity (UIVA), and uncorrected near visual acuity (UNVA), mean photopic monocular distance-corrected intermediate (DCIVA), and near visual acuity (DCNVA), all at 6 months.

Safety endpoints assessed at 12 months included CDVA in the SA IOL eye, patient-reported visual symptoms, rates of concurrent or persistent ocular adverse events compared with International Organization for Standardization (ISO) Safety and Performance Endpoint rates for posterior chamber IOLs (ISO 11979-7:2014),[11,18] and incidence of SA IOL removals. The safety endpoint of photopic and mesopic contrast sensitivity was assessed at 6 months.

Visual Acuity

At each time point, visual acuities were measured under photopic conditions using the ETDRS chart at 4 m for distance visual acuity, 66 cm for intermediate visual acuity, and 40 cm for near visual acuity. Distance-corrected visual acuities were measured in photopic conditions with manifest refraction in place. The ETDRS chart was presented on a self-calibrating monitor in the M&S Technologies Clinical Trial Suite (CTS; M&S Technologies) and recorded in logMAR, with a 0.02 logMAR increment corresponding to a single letter on the ETDRS chart. ETDRS data were converted to Snellen format for further analysis. Additionally, for all visual acuity testing, the examiner was masked to each patient's treatment group. To avoid letter memorization by the patients, the CTS automatically randomized the letters.

Refractive accuracy was assessed at several timepoints postoperatively using the CTS at 4 m, with the middle point of the emmetropic range determined via the duochrome technique. To avoid between-group bias, manifest refraction was assessed using the same technique for all eyes.[17]

Contrast Sensitivity

Contrast sensitivity under photopic and mesopic conditions was measured at the 6-month postoperative visit in a contract sensitivity subgroup (n = 260 patients in the SA IOL group and 68 patients in the control group) using the sine wave grating in the M&S CTS. All patients evaluated at sites with the ability to measure contrast sensitivity were included in the contrast sensitivity analysis.

Visual Symptoms

Visual symptoms were assessed at the 12-month postoperative visit, prior to any ocular testing, using the Quality of Vision instrument, a 30-item linear scale based on 10 visual symptoms: glares, halos, starbursts, hazy vision, blurred vision, distortion, double or multiple images, fluctuations in vision, focusing difficulties, and judging distance or depth perception.[19] Patients reported on the frequency, severity, and bothersomeness of these symptoms.

Adverse Events

Adverse events were defined per ISO 14155:2011, including events related to the comparator device and/or the procedures involved.

Statistical Analyses

Study sample sizes were based on Annex B of ISO 11979-7:2014, with 300 evaluable total test patients needed at 1 year for evaluation of safety endpoints versus Safety and Performance Endpoint rates. Allowing for an approximate 10% attrition rate over the 1-year study and an additional 5% disqualification rate for

TABLE 1

Endpoints and Success Criteria

Endpoint	Statistical Success Criteria	Clinical Success Criteria
Effectiveness		
Mean photopic binocular UDVA (4 m) at 6 months	Statistical non-inferiority of the SA IOL group over the control group	At least 50% of patients in the SA IOL group achieve 0.10 logMAR or better
Mean photopic binocular UIVA (66 cm) at 6 months	Statistical superiority of the SA IOL group over the control group	At least 50% of patients in the SA IOL group achieve 0.10 logMAR or better and at least 25% higher than patients in the control group
Mean photopic binocular UNVA (40 cm) at 6 months	Statistical superiority of the SA IOL group over the control group	At least 50% of patients in the SA IOL group achieve 0.30 logMAR or better and at least 25% higher than patients in the control group
Mean photopic monocular DCIVA (66 cm) at 6 months	Statistical superiority of SA IOL eyes versus fellow eyes	At least 50% of SA IOL eyes achieve DCIVA of 0.2 logMAR or better
Safety		
Mean monocular CDVA at 12 months	Statistical non-inferiority of the SA IOL eyes over fellow eyes	The proportion of SA IOL eyes achieving a CDVA of 0.30 logMAR or better exceeds the SPE rate listed in ISO 11979-7:2014
Binocular CS	Descriptive statistics of the SA IOL group versus the control group under photopic and mesopic conditions with and without glare	N/A
AE monitoring	For each type of AE listed in the ISO 11979-7:2014 Table B.2, the rate for SA IOL eyes is not statistically greater than the SPE rate for that event	N/A
Rate of SA IOL removal	The one-sided 95% UCL of the SA IOL removal rate (using exact binomial distribution) is < 3.1%	N/A

AE = adverse event; CDVA = corrected distance visual acuity; CS = contrast sensitivity; DCIVA = distance-corrected intermediate visual acuity; EDOF = extended depth of focus; IOL = intraocular lens; logMAR = logarithm of the minimum angle of resolution; N/A = not applicable; SA = small aperture; SPE = Seriousness, Predictability and Expectedness; UCL = upper confidence limit; UDVA = uncorrected distance visual acuity; UIVA = uncorrected intermediate visual acuity; UNVA = uncorrected near visual acuity

[a]Key AEs include but are not limited to AEs per ISO 11979-7:2014, AEs potentially related to the EDOF IOL design (eg, related to the optical characteristics of the IOL), and any other significant ocular AEs.

the first eye, a total of 355 were planned for the SA IOL group and 120 for the control group to ensure that 300 and 100, respectively, would complete 1-year follow-up and be available for analysis. The sample size calculation for the contrast sensitivity analysis subgroup was based on the method outlined in ISO 11979-7 C.3.2. The analysis assumed a non-inferiority margin of 0.15 log units with a true mean between-group difference of zero and a 0.4 log-unit standard deviation. With a 3:1 planned enrollment ratio, the sample size analysis determined that the treatment groups should be at least 177 for the SA IOL group and 59 for the control group.

The statistical analysis for each endpoint is detailed in figure footnotes. Each study endpoint was assessed against its respective statistical and clinical success criteria.[11] Statistical and clinical success criteria for each applicable endpoint are detailed in **Table 1**. Adverse event rates were defined per Safety and Performance Endpoint ISO 14155:2011, including events related to the comparator device and/or the procedures involved.

RESULTS

Patient Disposition and Demographics

Study patients (N = 453) were enrolled in the SA IOL group (n = 343) or control group (n = 110). The demographics of study patients in the SA IOL group were described previously.[11] Treatment groups were comparable across all demographic assessments, with the exception of more patients aged 80 years or older in the control group. Both groups were comparable in terms of overall mean pupil size. Compared to the control group, a greater percentage of eyes in the SA IOL group had a photopic pupil size of 4 mm or greater and dilated pupil size of 9 mm or greater.

All eyes were assessed for preoperative pupil size under photopic, mesopic, and dilated conditions (**Table 2**).

TABLE 2

Preoperative Pupil Sizes by Eye in Photopic, Mesopic, and Dilated Conditions

	SA IOL Group		Control Group	
Parameter	**SA IOL Eyes (n = 343)**	**Fellow Eyes (n = 343)**	**Second Eyes (n = 110)**	**First Eyes (n = 110)**
Photopic conditions				
No. of eyes available for analysis	343	434	110	110
Mean ± pupil size (mm)	3.702 ± 0.8322	3.720 ± 0.8305	3.271 ± 0.8837	3.245 ± 0.9454
Range	2.00 to 6.50	2.00 to 6.20	1.50 to 5.70	1.00 to 5.80
Mesopic conditions				
No. eyes available for analysis	343	343	110	110
Mean ± SD pupil size (mm)	4.853 ± 1.0299	4.856 ± 1.0180	4.501 ± 1.0963	4.439 ± 1.1449
Range	2.00 to 8.00	2.00 to 8.00	2.00 to 6.50	2.00 to 6.80
Dilated conditions				
No. eyes available for analysis	342[a]	342[a]	110	110
Mean ± SD pupil size (mm)	7.757 ± 0.9691	7.754 ± 0.9455	7.333 ± 0.9103	7.365 ± 0.9119
Range	6.00 to 10.00	6.00 to 10.00	6.00 to 10.00	6.00 to 10.00

IOL = intraocular lens; SA = small aperture; SD = standard deviation
[a]The dilated pupil size data for one patient in the SA IOL group were not reported.

Overall, there were no meaningful differences preoperatively either between eyes or treatment between groups.

Postoperative Refractive Outcomes

Per protocol, SA IOL eyes were targeted to -0.75 D and monofocal/monofocal toric lenses were targeted to emmetropia. At 6 months, less than 85% of eyes in both the SA IOL and control groups had actual refractive outcomes 1.00 D or less from their target. Overall, manifest refractive spherical equivalents remained relatively stable postoperatively in all groups, with a mean change of -0.035 D in SA IOL eyes and 0.108 D or less for fellow and control group eyes across 12 months. The mean postoperative residual refractive cylinder was similar between the SA IOL and control groups across all postoperative visits, ranging from 0.284 to 0.316 D in SA IOL eyes and from 0.238 and 0.370 D for monofocal/monofocal toric eyes in both the SA IOL and control groups (**Table 3**).

Uncorrected Visual Acuities

At 6 months, the SA IOL group was statistically non-inferior in binocular UDVA and statistically superior in binocular UIVA and UNVA versus the control group ($P < .0001$; **Figure 1A**). For binocular UDVA, the SA IOL group achieved a mean -0.010 logMAR (0.1063) versus 0.002 logMAR (0.0992) in the control group, a mean between-group difference of 0.012 logMAR (95% upper confident limit, 0.007 logMAR), which is below the 0.10 logMAR non-inferiority margin. Further, 89.6% (300 of 335) of patients achieved UDVA of 0.10 logMAR or better, exceeding the 50% success criteria.

The mean ± standard deviation binocular UIVA was 0.051 ± 0.1629 logMAR for the SA IOL group and 0.228 ± 0.1646 logMAR for the control group, a between-group difference of -0.177 logMAR ($P < .0001$; 95% upper confident limit, -0.140 logMAR; **Figure 1A**). Of patients in the SA IOL group, 79.1% (265 of 335) achieved binocular UIVA of 0.10 logMAR or better, a 57.1% difference in favor of the SA IOL group, exceeding the clinical success criterion of 50% in the SA IOL group and 25% higher than the control group.

For binocular UNVA, the mean ± standard deviation was 0.186 ± 0.1425 logMAR for the SA IOL group and 0.377 ± 0.1576 logMAR for the control group; the between-group difference was -0.191 logMAR ($P < .0001$; 95% upper confident limit, -0.158 logMAR). Further, 83.6% (280 of 335) of patients in the SA IOL group achieved a binocular UNVA of 0.30 logMAR or better, yielding a 50.6% difference in favor of the SA IOL group, thereby exceeding the clinical success criteria of 50%.

Comparing uncorrected monocular visual acuities in the SA IOL versus fellow (monofocal/monofocal toric) eyes at 6 months, SA IOL eyes achieved comparable mean (Snellen equivalent) UDVA (SA IOL eyes: 0.128 ± 0.1420 logMAR [20/27]; fellow eyes: 0.034 ± 0.1259 logMAR [20/22]) and numerically higher UIVA

TABLE 3

MRSE vs Target Refraction at 6 Months for SA IOL and Fellow Eyes and Control Group First and Second Eyes (D)

	SA IOL Group		Control Group	
Parameter	**SA IOL Eyes (n = 344)**	**Fellow Eyes (n = 344)**	**Second Eyes (n = 100)**	**First Eyes (n = 100)**
Mean ± SD	0.538 ± 0.4695	0.187 ± 0.3804	0.131 ± 0.3678	0.144 ± 0.3805
Median	0.620	0.210	0.093	0.175
Range	-1.52 to 1.72	-0.81 to 1.63	-0.65 to 1.37	-0.64 to 1.14
Distribution, n (%)				
< -1.50	1 (0.3)	0	0	0
-1.50 to -1.01	1 (0.3)	0	0	0
-1.00 to -0.51	6 (1.8)	14 (4.2)	5 (5.0)	2 (2.0)
-0.50 to -0.26	12 (3.6)	21 (6.3)	10 (10.0)	15 (15.0)
-0.25 to +0.25	62 (18.6)	162 (48.5)	47 (47.0)	46 (46.0)
+0.26 to +0.50	65 (19.5)	74 (22.2)	25 (25.0)	16 (16.0)
+0.51 to +1.00	142 (42.5)	56 (16.8)	12 (12.0)	20 (20.0)
+1.01 to +1.50	42 (12.6)	6 (1.8)	1 (1.0)	1 (1.0)
> +1.50	3 (0.9)	1 (0.3)	0	0

D = diopters; IOL = intraocular lens; MRSE = manifest refraction spherical equivalent; SA = small aperture; SD = standard deviation
[a]Although these assessments were collected across multiple timepoints, data are presented at 6 months to coincide with the 6-month visual acuity data presented elsewhere in this report.

(SA IOL eyes: 0.081 ± 0.1881 logMAR [20/24]; fellow eyes: 0.292 ± 0.1801 logMAR [20/39]) and UNVA (SA IOL eyes: 0.206 ± 0.1569 logMAR [20/32]; fellow eyes: 0.483 ± 0.1689 logMAR [20/61]; $P > .05$; **Figure 1B**).

Monocular Distance-Corrected Visual Acuity

Monocular distance-corrected visual acuities were assessed in SA IOL eyes. At 6 months, mean (Snellen equivalent) monocular DCIVA was significantly superior in SA IOL eyes (0.144 ± 0.1709 logMAR [20/28]) versus fellow eyes (0.325 ± 0.1687 logMAR [20/42]), with a mean difference of -0.180 logMAR ($P < .0001$; **Figure 2**). Additionally, 73.4% (246 of 335) of SA IOL eyes achieved DCIVA of 0.20 logMAR (Snellen equivalent: 20/32) or better, exceeding the clinical success criterion of 50%. At 6 months, the mean (Snellen equivalent) monocular DCNVA was significantly superior in SA IOL eyes (0.302 ± 0.1441 logMAR [20/40]) versus fellow eyes (0.519 ± 0.1621 logMAR [20/66]), with a mean difference of -0.217 logMAR ($P < .0001$; **Figure 2**). At 12 months, SA IOL eyes had a non-inferior mean (Snellen equivalent) monocular CDVA of 0.009 ± 0.1131 logMAR (20/20) versus fellow eyes (-0.059 ± 0.928 logMAR [$P < .0001$).

Contrast Sensitivity

At 6 months, the SA IOL group had comparable binocular contrast sensitivities to the control group in both photopic and mesopic conditions, with and without glare (**Figure 3**). For the patients included in the contrast sensitivity testing, the mean pupil size for the SA IOL group was 3.775 ± 0.8428 mm (range: 2.00 to 6.50 mm) in photopic conditions and 4.945 ± 1.0136 mm (range: 2.50 to 8.00 mm) in mesopic conditions; in the control group, mean pupil size was 3.454 ± 0.8574 mm (range: 2.00 to 5.70 mm) in photopic conditions and 4.550 ± 1.1583 mm (range: 2.00 to 6.50 mm) in photopic conditions. In both groups and in both mesopic and photopic conditions, mean contrast sensitivity values fell within normal ranges.

Visual Symptoms

At 12 months, patients in the SA IOL group on average reported relatively low frequency, severity, and bothersomeness of glare, halos, starbursts, and surroundings seeming dimmer, with the majority of patients in both the SA IOL and control groups reporting low scores for both frequency and bothersomeness for all visual symptoms (**Figure 4**). Compared with the control group, the SA IOL group reported higher frequency, severity, and bothersomeness of visual symptoms. However, in both the SA IOL and control groups, an overall summary of visual symptoms showed that more than 80% of patients reported that they "never experienced" symptoms, "experienced but not bothered at all" by symptoms, or "were a little bothered"

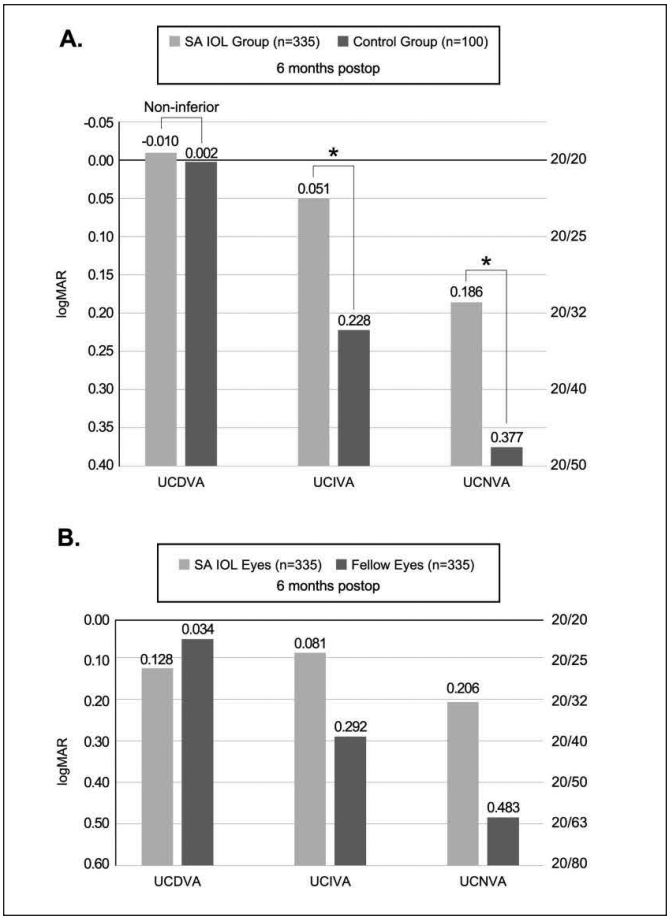

Figure 1. Mean photopic uncorrected distance, intermediate, and near visual acuities (UDVA, UIVA, and UNVA) at 6 months. (A) Binocular visual acuities in the IC-8 small-aperture intraocular lens (SA IOL) (Bausch & Lomb, Inc) and control groups. (B) Monocular visual acuities in SA IOL eyes versus fellow eyes. *P < .0001. For binocular visual acuities, mean values between the SA IOL and control groups were compared using two-sided t-tests for UIVA and UNVA and a one-sided two-sample t-test with a non-inferiority margin of 0.1 logarithm of the minimum angle of resolution (logMAR) (Snellen equivalent 20/25) for UDVA. For monocular visual acuities, mean values between the SA IOL eye and the fellow eye were compared using two-sample t-tests.

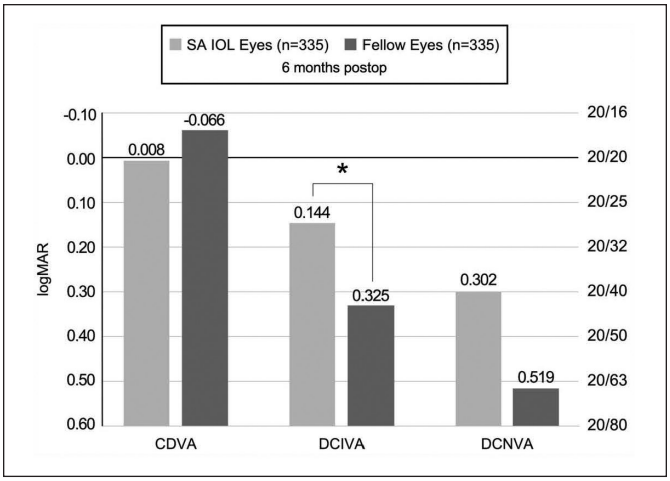

Figure 2. Mean monocular photopic corrected distance, distance-corrected intermediate, and distance-corrected near visual acuities (CDVA, DCIVA, and DCNVA) at 6 months for the IC-8 small-aperture intraocular lens (SA IOL) (Bausch & Lomb, Inc) versus fellow eyes. *P < .0001. Mean DCIVA values between SA IOL and fellow eyes in the SA IOL group were compared using a two-sided one-sample t-test for within-subject differences. No P value was available for DCNVA. Twenty patients had their monocular DCIVA scores eroneously recorded as worse than 0.30 logarithm of the minimum angle of resolution (logMAR) (Snellen equivalent 20/40) for SA IOL eyes and fellow eyes due to incorrect viewing distance used during testing.

for all visual symptoms. In the SA IOL group, only 3.0% (10 of 331) of patients reported severe glare, and both severe halos and starbursts were reported by 3.6% (12 of 331) of patients; less than 1% of patients reported that surroundings seemed dimmer. Stratification of visual symptoms experience/bothersomeness rating by preoperative mesopic pupil size (≤ 4 mm, > 4 to < 6 mm and ≥ 6 mm) in the SA IOL group indicated minimal worsening of visual symptoms with increasing pupil size.

Adverse Events

At 12 months, the 95% LCLs for rates of all observed cumulative and persistent ocular adverse events for SA IOL eyes were statistically below the Safety and Performance Endpoint ISO 11979-7:2014 rates, except for secondary surgical interventions (**Table 4**).[18] Additionally, the 95% LCL rates for all persistent adverse events in SA IOL eyes were statistically below the Safety and Performance Endpoint rates persistent serious adverse events. There were no removals of the SA IOL during the study. Ten SA IOL eyes received secondary surgical interventions, only one of which was related to the IOL, which was reported as a repositioning of the IOL due to vaulting. The remaining SA IOL eyes had non-IOL interventions. Among eyes with vitrectomies, 2 had pars plana vitrectomy procedures to remove capsular remnants affecting vision; 1 had a modified vitrectomy procedure concurrent with an intravitreal injection for endophthalmitis; and 1 patient underwent vitrectomy in both eyes, 1 with the SA IOL and the other with the monofocal/monofocal toric IOL to treat significant preoperative floaters.

DISCUSSION

The SA IOL, across studies large and small, short term and long term, has consistently provided patients with improved visual acuity outcomes and low rates of visual symptoms or adverse effects. Additionally, the SA IOL extends patients' depth of focus relative to monofocal/monofocal toric IOLs and provides monofocal-like contrast sensitivity. The current clinical study sought to assess the long-term safety and ef-

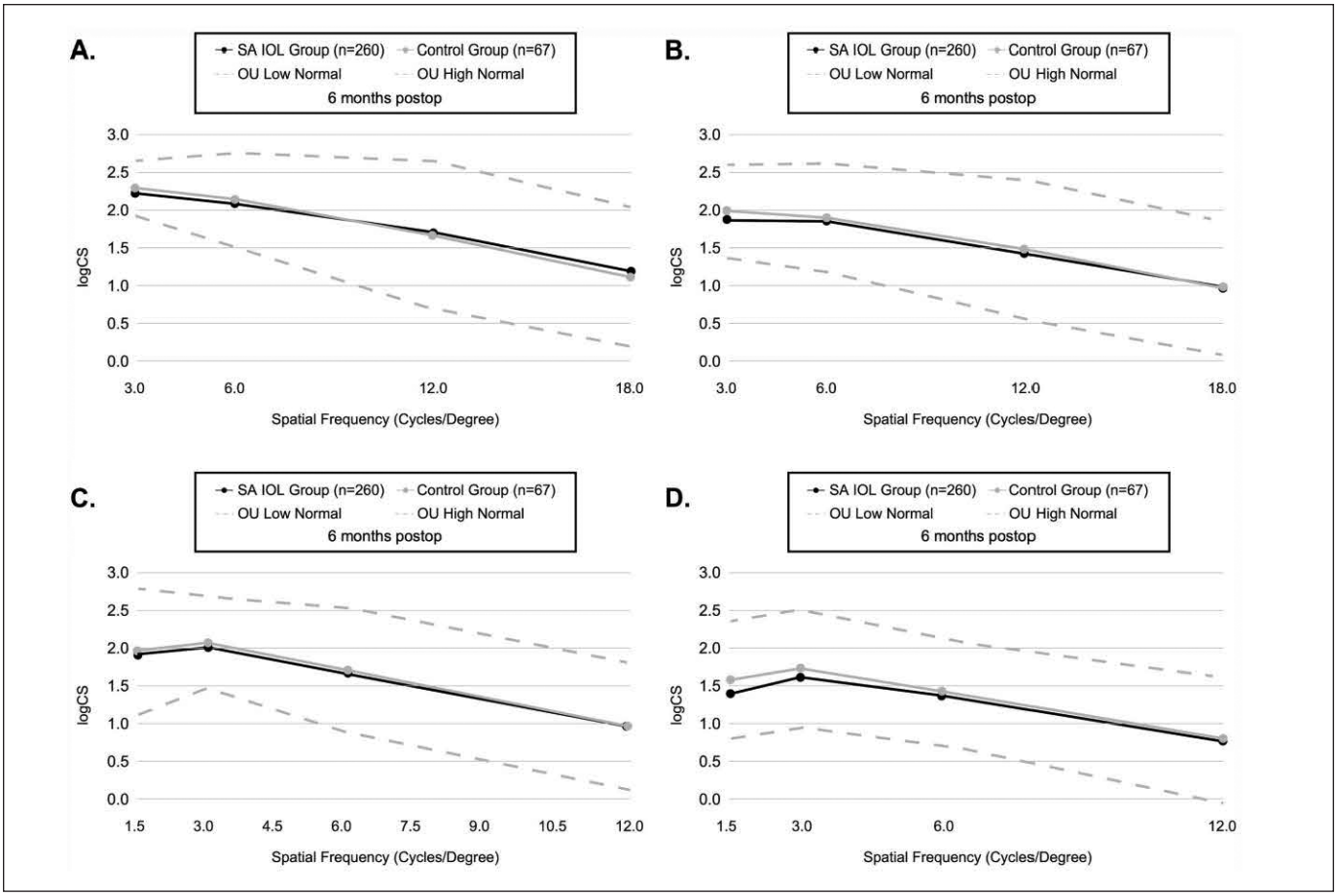

Figure 3. Binocular contrast sensitivity (CS) in the small-aperture intraocular lens (SA IOL) (Bausch & Lomb, Inc) and control groups at 6 months: (A) photopic CS without glare, (B) photopic CS with glare, (C) mesopic CS without glare, (D) mesopic CS with glare. For photopic CS, dotted lines on the graph represent one standard deviation of the monofocual CS. For mesopic CS, dotted lines on the graph represent 1.96 standard deviation of the control group's CS curve. logCS = logarithm of contrast sensitivity; OU = both eyes

fectiveness of the SA IOL versus a control group in a large study population, evaluating visual acuity, contrast sensitivity, and visual disturbance outcomes, as well as the incidence of adverse events.

In previous work, the SA IOL is associated with strong visual outcomes. A systematic review of 22 case studies or case series (N = 460 eyes from 442 patients followed up for up to 23.6 months) demonstrated significant improvements in UDVA, UIVA, and UNVA following the SA IOL.[20] Another large case series (N = 126) in Australia found that more than 90% of patients who received the SA IOL achieved uncorrected visual acuities of 20/40 at any distance.[14] Additionally, in a prospective, noncomparative trial, patients who received the SA IOL in one eye and a monofocal/monofocal toric IOL in the fellow eye (N = 105) found that, at 6 months, the mean monocular UDVA, UIVA, and UNVA in SA IOL eyes were 20/23, 20/24, and 20/30, respectively.[13] Furthermore, these data demonstrate that, at 6 months postoperatively, the SA IOL provides 20/32 or better uncorrected visual acuity in 99% of patients at distance, 95% of patients at intermediate, and 79% of patients at near.[13] In addition to visual acuity data, the SA IOL has, in previous research, demonstrated positive contrast sensitivity outcomes: in a small (N = 3) case study of patients who previously had laser in situ keratomileusis who received the SA IOL, contrast sensitivity remained at acceptable levels through 6 months postoperatively.[21]

These more discrete visual outcomes pair up well with subjective assessments of visual quality. Overall, previous work found that the SA IOL is associated with low rates of visual disturbances—such as halo or glare—out to nearly 24 months and that the visual disturbances that did arise were mild in severity.[12,13,20,22] Furthermore, the SA IOL can help achieve reduced spectacle use. In one study, 84.8% of patients reported reduced spectacle use at 6 months postoperatively,[13] and another found that, at an average follow-up time of just over 6.5 months, more than 50% of patients reported complete spectacle independence at distance,

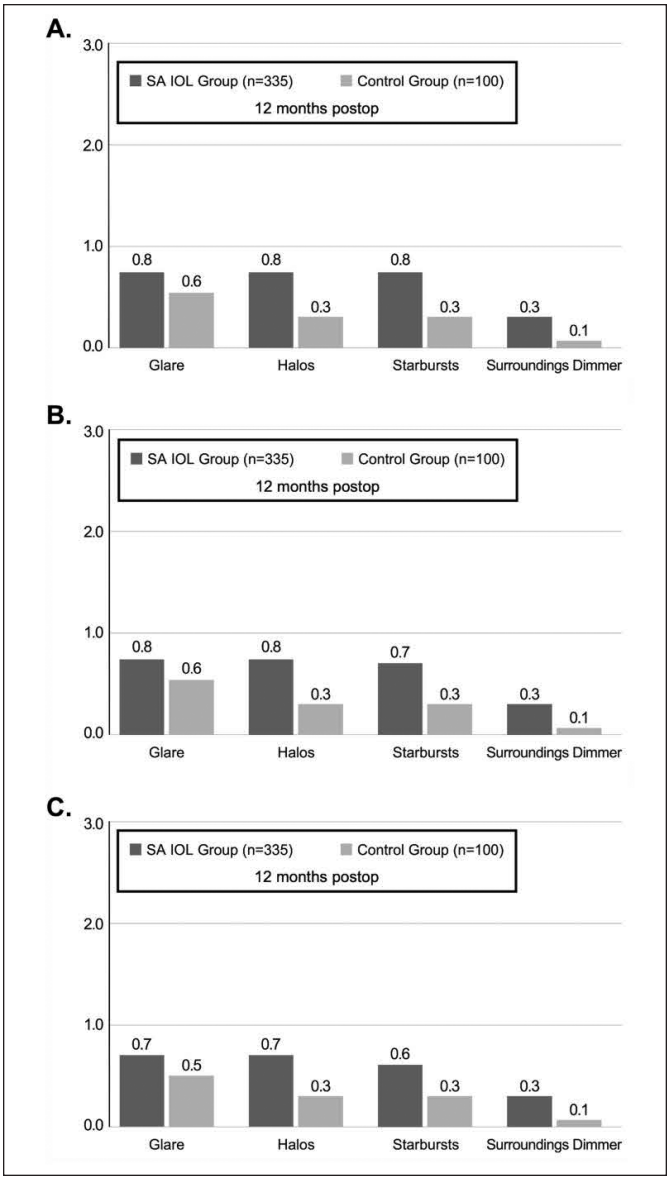

Figure 4. Patient-reported visual symptoms at 12 month in the small-aperture intraocular lens (SA IOL) (Bausch & Lomb, Inc) and control groups: (A) frequency, (B) severity, (C) bothersomeness. Mean visual symptoms experience/bothersomeness rating on a scale of 0 to 3, with 0 = never experience/not at all bothered, 1 = a little bothered, 2 = quite bothered, and 3 = very bothered.

intermediate, and near.[14] In line with these visual quality and spectacle independence data, patients overall report high satisfaction with the SA IOL.[20]

Building on previous evidence, this clinical study aimed to evaluate the safety and effectiveness of the SA IOL compared with traditional monofocal/monofocal toric IOLs. Binocular and monocular assessments were performed across a variety of conditions to simulate SA IOL performance and safety in the real world, including uncorrected and corrected vision at various distances, photopic and mesopic contrast sensitivities, patient-reported visual symptoms, and adverse events.

The SA IOL group was superior to the control group at 6 months in binocular uncorrected visual acuity, both at near and intermediate, while non-inferior at distance (**Figure 1**). Monocular CDVA, a safety endpoint, showed non-inferiority in SA IOL versus fellow eyes and exceeded the ISO Safety and Performance Endpoint threshold at 12 months (**Figure 2**).[11,18] Additionally, among SA IOL eyes, 99.1% achieved a monocular corrected distance visual acuity of 0.3 logMAR (Snellen equivalent: 20/40) or better.

Contrast sensitivity assessments used for lighting and glare conditions were meant to approximate what a patient might encounter on a daily basis[23]: photopic and mesopic, with and without glare. In photopic conditions with and without glare, binocular contrast sensitivity in the SA IOL and control groups were equivalent in contrast thresholds at each spatial frequency, with the exception of a -0.164 logCS mean between-group difference at 1.5 cycles per degree in the binocular/mesopic/with-glare condition (**Figure 3**).[18] These data indicate that, when the SA IOL is implanted contralaterally with a monofocal/monofocal toric IOL, binocular contrast sensitivity is comparable to that for monofocal/monofocal toric IOLs across a variety of natural viewing conditions.

In addition to monitoring adverse events, safety measures included patient-reported visual symptom rates. Overall, patients indicated that the SA IOL did not introduce visual symptoms of meaningful frequency, severity, or bothersomeness (**Figure 4**). Further, no visual symptom was reported as severe at a rate higher than 3.6% (for halos and starbursts) at 12 months, except dry eye, which 4.8% of patients rated as severe.[11]

Regarding adverse events, this study replicates prior work demonstrating that the SA IOL is not associated with significant safety risks, with a low rate of ocular adverse events (**Table 4**). The SSI rate in SA IOL eyes was significantly higher than the ISO Safety and Performance Endpoint rate[18] However, there were no SA IOL removals during the study, and of the 10 secondary surgical infections reported, only one was for an IOL intervention (repositioning).

As with any clinical trial, the current study comes with limitations. For example, the study was non-randomized, which could lead to selection bias when assigning patients to their treatment group; a non-randomized design was selected, but based on the ISO standard for multifocal lens studies, which does not recommend randomization. Also, because IOLs are permanent implants that directly affect patients' visual acuity and quality, true randomization,

TABLE 4

Cumulative SAEs at 12 Months in SA IOL and Fellow Eyes[a]

		SA IOL Eyes (n = 343)			Fellow Eyes (n = 343)		
Parameter	**SPE Rate**	**n (%)**	**95% LCL**	***P***	**n (%)**	**95% LCL**	***P***
Cystoid macular edema	3.0%	5 (1.5)	0.6%	.977	4 (1.2)	0.4%	.992
Hypopyon	0.3%	0 (0)	0.0%	> .999	0 (0)	0.0%	> .999
Endophthalmitis	0.1%	1 (0.3)	0.0%	.290	0 (0)	0.0%	> .999
Lens dislocated from posterior chamber	0.1%	0 (0)	0.0%	> .999	0 (0)	0.0%	> .999
Pupillary block	0.1%	0 (0)	0.0%	> .999	0 (0)	0.0%	> .999
Retinal detachment	0.3%	0 (0)	0.0%	> .999	0 (0)	0.0%	> .999
Secondary surgical intervention[b]	0.8%	10 (2.9)	1.6%	.001	6 (1.7)	0.8%	.060
IOL repositioning	N/A	1 (0.3)	0.0%	—	1 (0.3)	0.0%	—
Removal of retained cortex	N/A	2 (0.6)	0.1%	—	0 (0)	0.0%	—
Vitrectomy	N/A	4 (1.2)	0.4%		1 (0.3)	0.0%	—
Modified paracentesic[c]	N/A	4 (1.2)	0.4%	—	3 (0.9)	0.2%	—
Intravitreal injection[d]	N/A	1 (0.3)	0.0%	—	1 (0.3)	0.0%	—
Laser retinopexy[e]	N/A	0 (0)	0.0%	—	1 (0.3)	0.0%	—
Other: retinal vein occlusion	N/A	1 (0.3)	0.0%	—	0 (0)	0.0%	—

IDE = Investigational Device Exemption; IOL = intraocular lens; ISO = International Organization for Standardization; LCL = lower confidence limit; N/A = not applicable; SA = small aperture; SAE = serious adverse event; SPE = Safety and Performance Endpoint

[a]Adverse event (AE) rates are based on the proportion of eyes with events, %=(n/N)˙100. ISO 11979-7:2014 SPE rates were calculated for posterior-chamber IOLs.[18] The one-sided 95% LCL was based on exact binomial distribution. The SPE rate is considered not exceeded if the one-sided 95% LCL for an AE is less than the SPE rate, equivalent to P > .05. Only 1 of the 10 secondary surgical interventions was related to the IOL and reported as a repositioning of the IOL due to vaulting.

[b]No SA IOL removals were reported during the study. In the control group, 1 patient had with bilateral IOL removal during the study and replacement of both of their monofocal IOLs with different monofocal lenses due to visual complaints of dysphotopsia. Following exit from the IDE study but prior to completion of the 12-month postoperative period, 1 patient previously enrolled in the control group had their monofocal IOL removed in one eye due to visual complaints of double vision and a "yellow tint," and 2 patients previously enrolled in the SA IOL group had their SA IOLs removed. One patient had their SA IOL removed due to visual complaints of a "hinged blob." The other patient had their SA IOL removed due to subjective complaints of starburst, glare, and halo.

[c]Modified paracentesis procedures were performed as an outpatient procedure via the slit lamp through the original incision site.

[d]Intravitreal injection as treatment for cystoid macular edema.

[e]Laser retinopexy as treatment for operculated tear.

in which patients do not necessarily receive the IOL that is most appropriate for them or that they desire, would not be ethical. Patient demographics have been published previously,[11] and, aside from a greater number of patients older than 80 years in the control group, the SA IOL and control group demographics were similar. Additionally, baseline biometric assessments found no meaningful differences between the SA IOL and control groups.[11]

Another possible limitation in this clinical study is the different refractive targets set for the two treatment groups: the SA IOL group targeted -0.75 D as stipulated by the FDA and in accordance with the approved indication of the SA IOL, whereas the control group targeted plano as per standard practice.[11] Those in the SA IOL group, then, could experience a mini-monovision effect not present in the control group. Although it would be interesting to compare the SA IOL against monofocal IOLs corrected to the same refractive targets, the purpose of this study was to compare use of the SA IOL according to its FDA-approved indication to a "sham"-treated group; creating mini-monovision in the control group would constitute a non-standard use of monofocal/monofocal toric IOLs and would be more similar to a second treatment group rather than a "sham"-treated group.

Additionally, the SA IOL's Summary of Safety and Effectiveness Data, which includes data from this study, presents simulated monovision assessments performed at 6 months, where distance-corrected visual acuity was adjusted by adding a +0.75-D lens in front of the SA IOL in the SA IOL group and in front of the second eyes in the control group.[11] The intention of this comparison was to simulate the intended target of -0.75 D for the SA IOL eye in the SA IOL group and to compare visual acuity results if the control group had the same refractive mini-monovision target. In these assessments, 47.6% more SA IOL eyes achieved monocular +0.75 D DCIVA 20/25 or better versus control group second eyes. For monocular +0.75 D DCNVA, this number was 53.6%. In binocular assessments, 27.0% more SA IOL group patients had 20/25 or better DCIVA versus patients in

the control group; for +0.75 D DCNVA, 31.6% more SA IOL group patients achieved 20/25 vision or better than in the control group. Thus, at all distances tested, the SA IOL group still had better corrected visual acuities than the control group, indicating that improved vision with the SA IOL versus bilateral monofocal/monofocal toric IOLs is not solely due to a mini-monovision effect.

Correction for presbyopia following cataract surgery represents a significant challenge for cataract surgeons, and an increasingly diverse array of multifocal IOLs is now available that can provide varying levels of near and/or intermediate vision to compensate for presbyopia. Despite these advantages, multifocal IOLs often compromise the quality of distance vision, decrease contrast sensitivity, and increase patient-reported visual disturbances such as halos and glare.[5,24] Additionally, although some patients opt to have their presbyopia corrected with an extended depth of focus IOL, some use similar optical designs to traditional multifocal IOLs[25] and thus pose the same risks of decreased bilateral contrast sensitivity and increased visual symptoms as multifocal IOLs.

As the first small-aperture IOL, the SA IOL has demonstrated improved visual performance over monofocal IOLs—when implanted contralaterally with a monofocal/monofocal toric IOL—by increasing patients' range of vision, providing excellent visual acuity at multiple distances, and without loss of binocular contrast sensitivity or significant safety concerns. For patients interested in presbyopia-correcting IOLs, the SA IOL may represent a compelling option versus the current standard of care.

AUTHOR CONTRIBUTIONS

Study concept and design (MM); data collection (JV, SM, BLF, KC, LL, MM); analysis and interpretation of data (JV, SM, BLF, KC, LL, MM); writing the manuscript (MM); critical revision of the manuscript (JV, SM, BLF, KC, LL, MM); administrative, technical, or material support (MM); supervision (MM)

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