United States Food and Drug Administration Clinical Trial of the Implantable Collamer Lens (ICL) for Moderate to High Myopia

Three-Year Follow-up

*ICL in Treatment of Myopia (ITM) Study Group**

Purpose: To report on 3-year postoperative safety and efficacy outcomes with the Myopic Implantable Collamer Lens (ICL).

Design: Prospective nonrandomized clinical trial.

Participants: Five hundred twenty-six eyes of 294 patients with between 3.0 and 20.0 diopters (D) of myopia participating in the United States Food and Drug Administration clinical trial of the ICL for myopia.

Intervention: Implantation of the ICL.

Main Outcome Measures: Uncorrected visual acuity (VA), refraction, best spectacle-corrected VA (BSCVA), adverse events, operative and postoperative complications, lens opacity analysis, subjective satisfaction, and patient symptoms.

Results: At 3 years, 59.3% had 20/20 or better VA, and 94.7% had 20/40 or better uncorrected VA if BSCVA was 20/20 and patients were targeted for emmetropia; 67.5% of patients were within 0.5 D and 88.2% were within 1.0 D of predicted refraction. The mean improvement in BSCVA ranged between 0.5 and 0.6 lines. At 3 years postoperatively, 3 eyes (0.8%) decreased by $\geq$2 lines of BSCVA, in contrast to 40 eyes (10.8%) that improved by a similar amount. Contrast sensitivity improved postoperatively. Cumulative 3-year corneal endothelial cell loss was under 10%. Early largely asymptomatic, presumably surgically induced anterior subcapsular opacities (trace or greater) were seen in 14 eyes (2.7%), with only 2 being clinically significant. Five eyes (0.9%) of 3 patients developed nuclear opacities of grade $>$2 at 2 to 3 years postoperatively. Three (0.6%) ICL removals with cataract extraction and IOL implantation have been performed. Only 0.6% reported dissatisfaction; 97.1% of patients reported they would choose ICL implantation again. Incidences of patient symptoms, glare, halos, double vision, night vision problems, and night driving difficulties decreased or remained unchanged after ICL surgery.

Conclusion: Three-year results from this standardized, multicenter clinical investigation support the safety, efficacy, and predictability of ICL surgery to treat moderate to high myopic refractive errors. *Ophthalmology 2004;111:1683–1692 © 2004 by the American Academy of Ophthalmology.*

A previous report by the authors concerning clinical outcomes from the United States Food and Drug Administration (FDA) multicenter STAAR Myopic Implantable Contact Lens (STAAR Surgical, Monrovia, CA) clinical investigation demonstrated the safety and effectiveness of the Myopic Implantable Contact Lens in the treatment of moderate to high myopia (with up to 2 years follow-up in less than half of the eyes studied).[1] This earlier US Investigational Device clinical trial experience, in conjunction with clinical outcomes from a number of international series,[2–12] has documented that an implantable posterior chamber phakic intraocular lens may be a viable alternative to existing refractive laser surgical treatment options for the correction of myopia. The FDA has requested that the term *Implantable Contact Lens* be changed to avoid confusion with corneal contact lenses. Because the Implantable Contact Lens is made of a material referred to as Collamer, a proprietary hydrophilic porcine collagen ($<$0.1%)/hydroxyethyl copolymer containing an ultraviolet chromophore, STAAR Surgical has changed the name to Implantable Collamer Lens (ICL) to retain the ICL acronym, which is well recognized. Common observations with the Myopic ICL include a high level of best-corrected vision preserva-

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*See "Appendix" for group membership.

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Table 1. Summary of Key Efficacy Variables Stratified by Preoperative Spherical Equivalent (SE)*

		Preoperative SE			Total (3–20 D)
		≤7-D Myopia	*>7- to 10-D Myopia*	*>10-D Myopia*	
Uncorrected visual acuity	20/20 or better	68.1%	48.9%	21.9%	40.8%
	20/40 or better	97.2%	86.3%	70%	81.3%
UCVA (if BSCVA≥20/20)	20/20 or better	71.4%	54.2%	32.5%	51.6%
	20/40 or better	98.4%	86.9%	83.8%	88.8%
UCVA for patients with preoperative BSCVA ≥20/20 (for eyes targeting emmetropia)	20/20 or better	72.4%	62.7%	37.5%	59.3%
	20/40 or better	98.3%	92.8%	93.8%	94.7%
Predictability: attempted vs. achieved	± 0.50 D	84.7%	71%	56.9%	67.5%
	± 1.00 D	97.2%	93.1%	80%	88.2%
	± 2.00 D	100%	100%	95.6%	98.1%
Patient satisfaction	Unsatisfied	0%	0%	1.4%	0.6%
	Fairly/moderately satisfied	4.2%	5.7%	10.2%	7.3%
	Very/extremely satisfied	95.8%	94.3%	88.4%	92.1%

BSCVA = best spectacle-corrected visual acuity; D = diopters; UCVA = Uncorrected visual acuity.
*Data from 3 years postoperatively.

tion and even improvement relative to preoperative values, a reduction in patient symptoms in combination with a high patient satisfaction rating, and minimal operative and postoperative complications, with a rapid improvement in uncorrected acuity and refraction that is stable over time.

The purpose of this article is to provide an update on the long-term follow-up through 3 years after ICL implantation from the US Myopic ICL multicenter clinical investigation with the ICL lens design currently under consideration for commercial approval in the US. In comparison to our earlier analysis, data are stratified by degree of preoperative myopia in addition to data from the 3-year examination.

Patients and Methods

Study Design

The US STAAR Myopic ICL clinical study was designed as a prospective, 2-year, multicenter, nonrandomized clinical trial intended to evaluate the safety and efficacy of the ICL to treat moderate to high myopia. The FDA Ophthalmic Devices Advisory Panel, at a recent meeting (August 2, 2002), however, recommended at least a 3-year follow-up for all phakic IOLs before Premarket Approval Application (PMA) submission, so the current study was extended until over 350 eyes had reached the 3-year follow-up window. Assessment of ICL outcomes was based on a comparison of preoperative and postoperative values and the achieved versus expected refractive outcomes postoperatively in conjunction with a complete analysis of adverse events or complications.

Study Outcome Parameters

The primary outcomes parameters for this multicenter clinical study were uncorrected visual acuity (UCVA), refraction, best spectacle-corrected visual acuity (BSCVA), operative and postoperative adverse events and complications, lens opacity analysis (Lens Opacity Classification System III[13]), and subjective patient satisfaction and symptoms.

An endothelial cell density substudy was performed using Emory University as the photographic reading center. The design and protocol for the substudy have been described elsewhere, as have been the results,[14] which will only be briefly summarized.

A contrast sensitivity substudy was performed at 2 of the study centers. The tests were performed under mesopic conditions using the Stereo Optical Optec X 1600F2 Vision Tester (Stereo Optical, Inc., Chicago, IL). Testing was performed with best spectacle correction before and after the operation using light levels of 3 candelas/m^2 after 10 minutes of dark adaptation, with and without a glare source of 10 lux. Testing was performed at 1.5, 3, 6, 12, and 18 cycles per degree.

Results

Patient Population

A detailed description of the Myopic ICL study cohort, which is comprised of 526 eyes of 294 study subjects (3 eyes of 3 patients have been added to the cohort since the previous report[1]) with preoperative myopia (manifest refraction spherical equivalent [MRSE]) between −3.00 diopters (D) and −20.0 D, was previously reported by the authors.[1] Implantable Collamer Lens implantations took place at 14 US clinical investigational sites between November 1998 and December 2002. All eyes received the current ICL design version (version 4) that is presently under consideration by the FDA for commercial marketing approval.

Of the 294 study subjects, 178 were female (60.3%) and 84.7% were Caucasian. Mean age at the time of implantation (primary eye in bilateral subjects) was 36.5±5.8 years (range, 22–45). Preoperative MRSE for this study cohort averaged −10.06±3.74 D. Only 21.3% of eyes had a preoperative myopia of ≤7.0 D, 33.1% had one of >7.0 D but ≤10 D, 35.7% had one of >10 D but ≤15 D, and 9.9% had one of >15 D.

Subject compliance with postoperative follow-up visit requirements was extremely high. The percent accountability was ≥89% at all prospective study visits through the 2-year visit (89.7%–100%) and 77.2% at the additional 3-year follow-up period. The FDA currently recommends a follow-up of 70% at 3 years as acceptable in their Refractive Implant Guidance document. At 2 years postoperatively, 454 eyes were examined, and 369 eyes were examined at 3 years postoperatively.

Fifteen eyes (2.9%) underwent LASIK procedures after ICL implantation. Although the pre-LASIK refractive data were included, the post-LASIK refractive data were not included in the

predictability analysis. No surgical or perisurgical complications were noted with the LASIK procedures.

Effectiveness Outcomes: Total and Stratified by Preoperative Manifest Refraction Spherical Equivalent

Uncorrected Visual Acuity. Effectiveness outcomes at 3 years postoperatively for the Myopic ICL PMA cohort for the entire group and ≤7-D, >7- to 10-D, and >10-D preoperative MRSE groups are summarized in Table 1.

Uncorrected visual acuity at 3 years postoperatively for the entire population was 20/20 or better in 40.8% of eyes and 20/40 or better in 81.3%. The uncorrected visual results in this "all eyes" group must be put in the context that only 67.6% of these eyes had BSCVA of 20/20 or better at baseline. Furthermore, only 52.1% of the eyes examined at 3 years postoperatively had a BSCVA of 20/20 or better preoperatively and were targeted for emmetropia (±0.5 D). As anticipated, UCVA for the overall Myopic ICL PMA cohort was better with lower levels of preoperative myopia. In the ≤7-D group, 97.2% of eyes had UCVA of 20/40 or better, and 68.1% of eyes had UCVA of 20/20 or better. In the >7- to 10-D group, the proportion of eyes with UCVA 20/40 or better was 86.3%, and 48.9% were 20/20 or better at 3 years. In the high myopia group (>10 D), 70% of eyes had UCVA of 20/40 or better, and 21.9% had UCVA of 20/20 or better.

At 3 years after ICL surgery, in the subset of eyes with good visual potential (BSCVA of 20/20 or better at baseline), the proportion of eyes 20/20 or better uncorrected was 51.6%, and the proportion of eyes 20/40 or better was 88.8%. For the stratified groups, the ≤7-D (98.4%) and >7- to 10-D (86.9%) groups exceeded the FDA recommended target value of 85% of eyes 20/40 or better. Of the high myopes in the Myopic ICL PMA cohort (>10 D), 83.8% reported UCVA of 20/40 or better, a proportion substantially higher than the FDA laser refractive target for >7-D myopes (75%). Predictability outcomes for all 3 stratified groups combined were better than the FDA's overall predictability target values.

As would be expected, an analysis of the subset with a preoperative BSCVA of 20/20 or better where emmetropia was targeted (±0.5 D) shows an even greater improvement in postoperative UCVA outcomes. Uncorrected visual acuity of 20/20 or better occurred in 59.3% of cases, and 94.7% were 20/40 or better. At 3 years postoperatively, 57.5% of patients could see uncorrected postoperatively as well as or better than they could with their best-corrected spectacle correction preoperatively. In the stratified groups, UCVA of 20/40 or better was reported at 3 years postoperatively for 98.3% in the ≤7-D group, 92.8% in the >7- to 10-D group, and 93.8% in the >10-D group. Incidences of UCVA of 20/20 or better were 72.4% in the ≤7-D group, 62.7% in the >7- to 10-D group, and 37.5% in the >10-D group (Fig 1).

Predictability of Manifest Refraction (Attempted versus Achieved). Myopic lenses were available from −3.0 D to −20.0 D. It is noteworthy that not all eyes were targeted for emmetropia, as discussed previously, because 9.5% of eyes required a ≥20-D implant power and were therefore intentionally undercorrected. Thus, the following predictability outcomes provide a more accurate assessment of refraction accuracy than the postoperative MRSE outcomes. At 3 years postoperatively, 67.5% of eyes were within 0.50 D and 88.8% within 1.0 D of attempted correction. In the stratified groups, attempted versus achieved outcomes were within 1.0 D in 97.2% of the ≤7-D group, 93.1% of the >0.7- to 10-D group, and 80% of the >10-D group; this compares very favorably with the overall FDA target of 75% within 1.0 D and >7-D refractive laser target of 60% (Fig 2). For the Myopic ICL PMA cohort, 84.7% of the ≤7-D group, 71.0% of the >7- to 10-D group, and 56.9% of the >10-D group achieved at 3 years a refractive outcome within 0.50 D of the intended correction. This compares favorably with the FDA refractive implant target of 50% within 0.5 D for all eyes and 30% for eyes with >7 D of refractive error for refractive lasers.

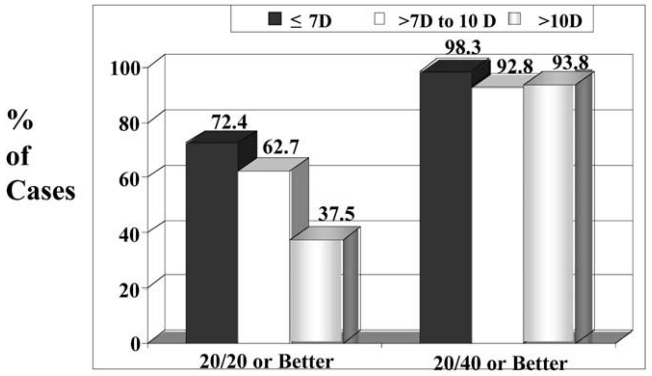

Figure 1. Three-year postoperative uncorrected visual acuity stratified by preoperative myopia in the subset of patients with preoperative best spectacle-corrected visual acuity of 20/20 or better and in those targeted to within 0.5 diopters (D) of emmetropia.

Subjective Assessments. At 3 years postoperatively, 92.1% reported that they were very or extremely satisfied with the results of their surgery, 7.3% were moderately to fairly satisfied, and only 0.6% reported that they were unsatisfied. Three years after ICL surgery, 97.1% of patients reported that they would choose ICL implantation again. Subjective patient satisfaction was excellent for all 3 preoperative MRSE groups, with slightly lower values in the highest myopia group (>10 D). Patients were very or extremely satisfied for 95.8% of eyes in the ≤7-D group, 94.3% in the >7- to 10-D group, and 88.4% in the high myopia group (>10 D). In both the low and middle myopic groups, no patients reported being unsatisfied, and dissatisfaction was reported for only 2 eyes (1.4%) in the high myopia group.

Best Spectacle-Corrected Visual Acuity

Best Spectacle-Corrected Visual Acuity over Time. Best spectacle-corrected visual acuity in the study cohort improved after ICL implantation over preoperative levels. At the 2- and 3-year follow-up windows, 82.3% and 84.8% of eyes, respectively, had BSCVA of 20/20 or better, an improvement over the baseline level

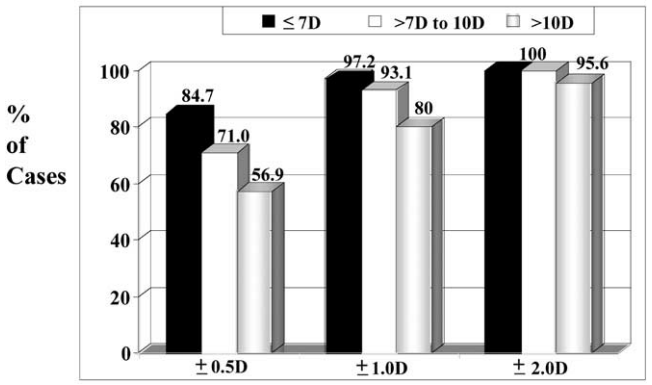

Figure 2. Attempted versus achieved correction (±0.5 diopters [D], ±1.0 D, and ±2.0 D) at 3 years postoperatively stratified by preoperative myopia.

Table 2. Change in Subjective Patient Symptoms (before to 3 Years after the Operation)

	Glare		Halos		Double Vision		Night Vision		Night Driving	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Improved 2 categories	10	2.8	8	2.3	0	0	11	3.1	12	3.6
Improved 1 category	32	9.1	24	6.9	4	1.1	31	8.9	34	10.1
No change	275	78.3	278	79.4	341	97.2	266	76.0	255	76.1
Worsened 1 category	30	8.5	30	8.6	6	1.7	34	9.7	25	7.5
Worsened 2 categories	4	1.1	10	2.9	0	0	8	2.3	9	2.7

of 67.7%. Further, BSCVA 20/40 or better values were 98.2% and 98.6% at 2 and 3 years postoperatively, compared with 97.0% preoperatively.

Change in Best Spectacle-Corrected Visual Acuity. Overall, there was an improvement in BSCVA at all follow-up visits over preoperative levels. The mean improvement in BSCVA ranged between 0.5 and 0.6 lines between 1 and 3 years postoperatively. At 3 years after ICL implantation, 3 eyes (0.8%) decreased by ≥2 lines, in contrast to 40 eyes (10.8%) that improved by a similar amount.

Best spectacle-corrected vision was well preserved after ICL surgery, with only 5 eyes (1%) losing ≥2 lines at last visit with the ICL in place. Three of the 5 eyes were associated with nuclear opacities that developed during follow-up (between 1 and 3 years postoperatively). One of these eyes had undergone cataract extraction, with a final BSCVA of 20/25 (pre-ICL BSCVA, 20/30). The fourth eye lost vision as a result of macular involvement and cataract formation; a retinal detachment (RD) was repaired with silicone oil. The fifth case was the result of inadvertent intraoperative irrigation with a preservative-containing carbachol solution with severe inflammation and development of an anterior subcapsular cataract. After cataract extraction, BSCVA in this case was 20/20.

Secondary Implantable Contact Lens–Related Surgeries

Since the initial report,[1] 3 additional ICL replacements and 1 removal with cataract extraction were performed, for a total of 16 (3.0%) secondary surgical interventions. Secondary ICL-related surgical procedures had little or, for the most part, no effect on either safety or efficacy final outcomes at last visit. Of the 16 eyes that underwent secondary surgical procedures, only 1 had a decrease in BSCVA at last visit (1 line loss), 1 eye gained 2 lines, 8 eyes (50%) gained 1 line of BSCVA, and 6 eyes (37.5%) had no change in BSCVA. Only 3 eyes underwent cataract surgery (0.6% of the entire cohort). These 3 eyes had a mean preoperative spherical equivalent of 15.8 D (12.8–18 D). The remaining 13 eyes (81%) remained phakic; 12 of 13 (92%) kept their ICL. Uncorrected acuity in these 12 eyes with the ICL in place was 20/40 or better in 83% of eyes.

Postoperative Complications

Since the initial report,[1] 2 additional RDs were reported, for a total of 3 in the entire series (0.6%; 95% confidence interval, 0.4%–0.8%). The average preoperative myopia in these eyes was 14.5 D.

Lens Opacity Classification System III Opacities

Nuclear Opacities. Since the previous report,[1] a total of 5 eyes (0.9%) of 3 patients developed nuclear opacities of grade >2 at 2 to 3 years postoperatively. The first patient, a 42-year-old Hispanic female with a preoperative spherical equivalent of −16.25 D, had a clear lens until 31 months postoperatively, when an RD involving the macula developed. Repair was achieved with silicone oil. Six months after silicone oil had been in contact with the crystalline lens, the patient had >4 nuclear color, >4 nuclear opalescence, and a >4 posterior subcapsular opacity. Final visual acuity was counting fingers.

The second patient was a 32-year-old Hispanic female with preoperative spherical equivalents of −16.75 D in the first eye and −14 D in the secondary eye. The crystalline lens was completely clear in each eye at the 2-year postoperative visit; however, the patient presented at the 3-year postoperative visit with bilateral >2.5 nuclear opalescence, and a loss of 2 and 3 lines of BSCVA in the primary (right) and secondary (left) eye, respectively.

The third patient was a 40-year-old male with preoperative spherical equivalents of −16.75 D and −16.63 D in the primary and fellow eyes, respectively. The patient presented with a >0.5 nuclear opacity preoperatively in both eyes, and a >0.5 anterior subcapsular opacity was observed at 3 months postoperatively in the primary eye; this remained stable through the 1-year postoperative visit. Surgery was performed in the fellow eye 1 year after ICL placement in the primary eye. The fellow eye was observed to have the same >0.5 anterior subcapsular opacity preoperatively as was observed in the primary eye at the 3-month postoperative visit. This opacity in the fellow eye was not present a year earlier when the primary eye underwent surgery. Two years after the primary eye's operation and 1 year after the fellow eye's, both eyes had a >1.5 nuclear opacity and a >1 anterior subcapsular opacity. Thirty-one months after the primary eye's operation and 19 months after the fellow eye's, both eyes demonstrated a >3 nuclear opacity and the development of a >1 cortical change. The primary eye also presented with a progression of an anterior subcapsular opacity (>1.5), and the development of a posterior subcapsular opacity (>1) associated with significant glare symptoms and cataract extraction was planned. Cataract extraction had already been performed on the fellow eye, resulting in a 1-line improvement in BSCVA from before the operation, 20/30 to 20/25. The average preoperative myopia of the eyes with nuclear opacities was 16 D (range, −14 to −16.75 D).

Posterior Subcapsular Opacities. Only 2 posterior subcapsular opacities of trace or greater were observed at any of the postoperative visits. They were both associated with nuclear opacities already described.

Anterior Subcapsular Opacities. Since the initial report,[1] no additional anterior subcapsular opacities greater than or equal to trace were reported. At the last available visit in the 14 eyes with anterior subcapsular opacities, 2 eyes lost 1 line of BSCVA (20/20–20/25 and 20/15–20/20), 9 eyes had no change in BSCVA, 2 eyes had an improvement of 1 line of BSCVA, and 1 eye had an improvement of 2 lines of BSCVA.

The overall incidence of anterior subcapsular opacities of trace or more in this series was 14/526 (2.7%). Nine of 19 investigators reported anterior subcapsular opacities; 1 investigator reported 6

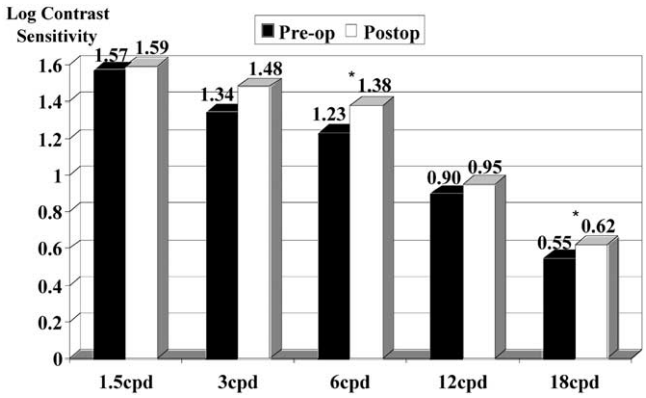

Figure 3. Log contrast sensitivity under mesopic illumination (3 candelas/m^2) without a glare source. cpd = cycles per degree. *Statistically significantly different at a level of 0.05.

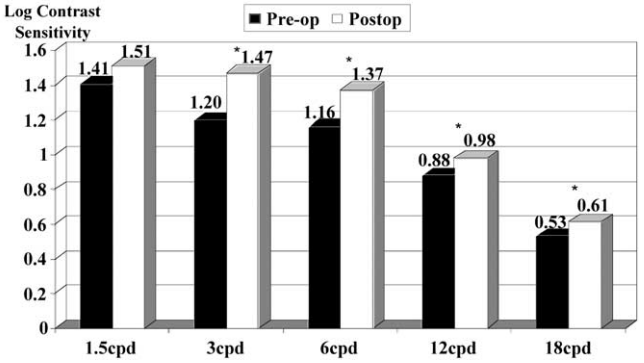

Figure 4. Log contrast sensitivity under mesopic illumination (3 candelas/m^2) with a glare source (10 lux). cpd = cycles per degree. *Statistically significantly different at a level of 0.05.

opacities, and 8 investigators reported 1 each. Although the investigator reporting 6 opacities implanted only 12% of the ICLs (64/526), these opacities represent 43% of the anterior subcapsular opacities graded trace or greater. Although the incidence of opacities at this site was 6/64 (9.4%), the remainder of the investigators had a total of 8 events in 462 eyes, or 1.7% ($P = 0.003$). This investigator also reported both of the clinically significant anterior subcapsular cataracts. The incidence of clinically significant anterior subcapsular cataract at this site was 2/64 (3.1%), whereas there were no reports at the other sites ($P = 0.01$).

Subjective Symptom Assessment

The incidence of glare, halos, double vision, night vision problems, and night driving difficulties decreased or remained unchanged from before the operation after ICL surgery (Table 2). There was no marked increase in any of these patient symptoms after ICL implantation.

Endothelial Cell Substudy

Endothelial cell density measurements were obtained in over 200 eyes at each of the preoperative and 3-month, 1-year, 2-year, and 3-year postoperative visits; 67 eyes were also evaluated at 4 years postoperatively. Cumulative cell loss over the first 3 postoperative years was 8.4% to 9.7%, depending upon the method of analysis. There were 57 eyes that were examined at both 3 and 4 years postoperatively; the mean endothelial cell densities were 2354 cells/mm^2 and 2355 cells/mm^2, respectively. The 3- to 4-year percentage cell loss was a 0.1% gain (90% confidence intervals, −1.4%–1.6%). There was no decrease in percentage hexago-

Table 3. Summary of Key Safety Variables Stratified By Preoperative Spherical Equivalent (SE)

Safety Events	Preoperative SE ≤7 D (n = 112)	Preoperative SE >7–10 D (n = 174)	Preoperative SE >10 D (n = 240)	Total (3–20 D) (n = 526)
Best spectacle-corrected visual acuity worse than 20/40 at 1–3 yrs postoperatively (if 20/20 or better preoperatively)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Loss of ≥2 lines BSCVA (persistent)	0 (0%)	0 (0%)	5 (2.1%)	5 (1.0%)
Increase > 2 D cylinder (3 yrs postoperatively)	0 (0%)	0 (0%)	2 (0.8%)	2 (0.4%)
Implantable Collamer Lens repositioning	1 (0.9%)	0 (0%)	3 (1.2%)	4 (0.8%)
Implantable Collamer Lens replacement, then removal	0 (0%)	1 (0.6%)	0 (0%)	1 (0.2%)
Implantable Collamer Lens replacement	3 (2.7%)	4 (2.3%)	1 (0.4%)	8 (1.5%)
Implantable Collamer Lens removal/cataract extraction/with/without IOL	0 (0%)	0 (0%)	3 (1.2%)	3 (0.6%)
Lens Opacities Classification System ≥ trace, anterior subcapsular	1 (0.9%)	7 (4%)	6 (2.5%)	14 (2.7%)
Clinically significant cataract*				
Anterior subcapsular	0 (0%)	0 (0%)	2 (0.8%)	2 (0.4%)
Nuclear	0 (0%)	0 (0%)	5 (2.1%)	5 (1.0%)
Intraocular pressure > 25 mmHg or > 10 mmHg Increase from before the operation (at last visit†)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)
Endophthalmitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased IOP on medications	0 (0%)	1 (0.6%)	1 (0.4%)	2 (0.4%)
Corneal haze/edema (after 1 wk postoperatively)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Retinal detachment	0 (0%)	1 (0.6%)	2 (0.8%)	3 (0.6%)

BSCVA = best spectacle-corrected visual acuity; D = diopters; ICL = Implantable Collamer Lens; IOP = intraocular pressure; LOCS = Lens Opacities Classification System.
*Any anterior subcapsular/posterior subcapsular score of trace or more at any postoperative visit with increase in glare, ≥2-line loss BSCVA, or nuclear opalescence ≥ 2.0 also symptomatic.
†Includes IOP from unscheduled visit 3 mos or more after the operation.

Table 4. Comparison of the STAAR Implantable Collamer Lens (ICL)

Sponsor	STAAR	Nidek*	Autonomous†	Summit‡
Procedure	Myopia	Myopia/astigmatism LASIK	Myopia/astigmatism LASIK	Myopia/astigmatism LASIK
Device	ICL	Nidek EC-5000	LADARVision	Apex Plus
Study population	N = 112 (≤7 D)	N = 664 eyes (<7 D)	N = 153 eyes (<7 D; sphere only)	N = 176 eyes at 6 (≤−7 D; sphere only)
Mean age (yrs)	37.9	42.4	39.8	38.8
Mean preoperative SE (D)	−5.3	Not reported	−3.4	Not reported
Preoperative BSCVA	20/100 or better	20/40 or better	20/40 or better	Criteria not reported
Target correction	UCVA analysis only of eyes with emmetropia target; target *not* emmetropia in all eyes	Target *not* emmetropia in all eyes	UCVA analysis only of eyes with emmetropia target; target *not* emmetropia in all eyes	Not reported
Postoperative time reported	6 mos	6 and 12 mos	3 mos	6 mos
UCVA 20/20 or better	70.5%‡‡	Not reported	64.2%	69.1%
UCVA 20/40 or better	98.9%‡‡	Not reported	93.4%	95.4%
MRSE ±0.5 D	88.8%	67.1% (6 mos)	81.3%	70.9%
MRSE ±1.0 D	99%	90.0% (6 mos) 89.7% (12 mos)	94.5%	89.7%
MRSE ±2.0 D	100%	99.6% (6 mos) 100% (12 mos)	100%	98.2%

*U.S. Food and Drug Administration, Center for Devices and Radiological Health. Premarket Approval Application (PMA) summary of safety and Available at: http://www.fda.gov/cdrh/pdf/p970053s002.html. Accessed April 27, 2004.
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#U.S. Food and Drug Administration, Center for Devices and Radiological Health. Premarket Approval Application (PMA) summary of safety and http://www.fda.gov/cdrh/pdf/p970049.html. Accessed April 27, 2004.
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††U.S. Food and Drug Administration, Center for Devices and Radiological Health. Premarket Approval Application (PMA) summary of safety and 2001. Available at http://www.fda.gov/cdrh/pdf/p980008s005.html. Accessed April 27, 2004.
‡‡BSCVA 20/20 or better.

nality or increase in coefficient of variation at any interval studied.

Contrast Sensitivity Substudy

Figure 3 demonstrates the mesopic contrast sensitivity results without glare, demonstrating no loss of contrast at any spatial frequency and a statistically significant improvement in contrast value at 6 and 18 cycles per degree. Contrast sensitivity with glare (Fig 4) demonstrated a significant improvement in contrast sensitivity at 4 of the 5 spatial frequencies tested (except 1.5 cycles per degree).

Summary of Key Safety Variables Stratified by Preoperative Manifest Refraction Spherical Equivalent

As shown in Table 3, in general, the higher the degree of preoperative myopia (MRSE), the greater the incidence of complications or adverse events. Specifically, all 5 of the eyes with persistent loss of ≥2 lines of BSCVA occurred in the >10-D group. In addition, both cases of a >2-D increase of cylinder at 3 years postoperatively also occurred in the high myopic individual (>10-D myopia) group. Consistent with these outcomes, all of the cataract extractions and 3 of 4 of the ICL repositionings occurred in the >10-D myopia group. Anterior opacities were observed in 6 eyes (2.5%) in the >10-D group, 7 eyes (4%) in the >7- to 10-D group, and in only 1 case (0.9%) in the ≤7-D group. All clinically significant cataracts, both nuclear and anterior subcapsular, occurred in the >10-D myopic individual group (7 of 7 eyes). The only eye with an intraocular pressure (IOP) of >25 mmHg (last visit) or an increase in IOP from baseline of 10 mmHg (last visit) was in the >10-D group, with no eyes (0%) in either the ≤7-D or the >7- to 10-D subsets. One eye with increased IOP on medication was in the >7- to 10-D group, and 1 was in the >10-D subset. Two of the 3 reported patients with an RD occurred in the >10-D group, and the third case was a −9.5-D myopic individual.

Discussion

The FDA granted the ICL file "expedited review" status for high myopia. The FDA's guidance document on expedited

Food and Drug Administration (FDA) Trial to FDA LASIK Clinical Trials

Photomed§	Bausch & Lomb‖	Visx¶	Dishler#	Alcon**	LaserSight††
Myopia/astigmatism LASIK	Myopia/astigmatism LASIK	Myopia/astigmatism LASIK	Myopia/astigmatism LASIK	Myopia/astigmatism LASIK	Myopia/astigmatism LASIK
Kremer excimer laser	Technolas 217A	STAR S2	Dishler excimer laser	LADARVision-Wavefront	LaserScan LSX
N = 476 eyes (<7 D)	N = 110 eyes (<7 D; sphere only)	N = 267 eyes (≤7 D sphere only)	N = 367 eyes (<7 D sphere only)	N = 139 eyes	N = 109 eyes (≤6 D)
Not reported	36.8	42.0	40.0	38.1	39.8
−3.9	−3.9	Not reported	Not reported	−3.2	Not reported
Criteria not reported	20/40 or better	20/40 or better	20/40 or better	20/25 or better	20/25 or better
Undercorrection allowed; target not emmetropia in all eyes	Target not emmetropia in all eyes	Undercorrection allowed; target not emmetropia in all eyes	UCVA analysis only eyes with emmetropia target; target not emmetropia in all eyes	Emmetropia in all eyes	UCVA analysis only eyes with emmetropia target; target not emmetropia in all eyes
6 mos	3 mos	6 mos	6 mos	6 mos	12 mos
36.3%	90%	58.6%	58.6%	79.9%	51.8%
86.6%	100%	97.0%	87.9%	98.6%	97.6%
66.4%	50.0%	77.8%	70.7%	74.8%	67.9%
84.2%	80%	94.4%	87.5%	95.7%	86.8%
98.1%	100%	99.8%	100%	Not reported	96.8%

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effectiveness data (PMA P970043/S005). LADARVision excimer laser system. Rockville, MD: Center for Devices and Radiological Health; 2000.

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effectiveness data (PMA P970005). Kremer excimer laser system serial no. KEA940202 for laser in situ keratomileusis (LASIK) for the correction of
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effectiveness data (PMA P970049). Dishler excimer laser system. Rockville, MD: Center for Devices and Radiological Health; 1999. Available at:

effectiveness data (PMA P970043/S010). Alcon Laboratories, Inc. LADARVision 4000 excimer laser system. Rockville, MD: Center for Devices and

effectiveness data (PMA P980008/S005). LaserSight LaserScan LSX excimer laser system. Rockville, MD: Center for Devices and Radiological Health;

review[15] states, "Expedited review will generally be considered when a device offers a potential for clinically meaningful benefit as compared to the existing alternatives (preventative, diagnostic, or therapeutic) or when the new medical device promises to provide a revolutionary advance (not incremental advantage) over currently available alternative modalities." On October 3, 2003, the Ophthalmic Devices Advisory Panel to the FDA determined that the ICL for myopia of −3 D to −20 D was approvable for commercial use in the United States. If approved by the FDA, this will be the first IOL of any kind to be approved for patients younger than 60 years, the first phakic IOL approved in the US, the first intraocular device and procedure approved for a refractive indication, the widest range of myopia approved for any refractive procedure, and the first refractive procedure to be approved for patients with myopia of ≥15 D.

Since the first report describing this series of patients, 2 types of late complications have been reported with greater frequency: clinically significant nuclear opacities in 5 eyes of 3 patients (none reported previously) and 2 additional RDs (one reported previously).

With regard to nuclear opacities, in one eye the nuclear opacity was first observed 6 months after RD repair with silicone oil, which is known to induce lens opacities.[16,17] The other 2 nuclear opacities were observed to occur bilaterally in 2 patients with preoperative myopia of ≥14 D in all 4 eyes. A number of epidemiologic studies have documented a direct relationship between the development of nuclear opacities and myopia.[18–21] The average age of our study population was 36.5 years (range, 22–45). The development of lens opacities or the progression of myopic retinopathy may differ in an older population, and our results may not be applicable to that older group.

With regard to the RD, the 3 eyes in this series had preoperative myopia of −9.50 D, −16.25 D, and −17.75 D. Perkins[22] has estimated that the expected risk of RD in phakic myopes is as high as 0.68% per year. Given the current follow-up of this reported series of high myopes, as many as 9 RDs would be expected, whereas only 3 were

observed. Thus, it is unlikely that the ICL caused this particular complication. Interestingly, one of these detachments involved the only patient with severe nonreversible visual loss in the entire reported series.

With regard to anterior subcapsular opacities, in the previous report of this series, 14 opacities of trace or more, 2 of which were clinically significant, were observed. These numbers have remained unchanged despite a 2-year follow-up on an additional 196 eyes and a previously unreported follow-up on 369 eyes at 3 years postoperatively.

Myopic ICL results to date have compared favorably with clinical outcomes with the latest refractive laser surgical treatments. A recent comparative analysis of the safety and effectiveness outcomes from this FDA multicenter ICL clinical study with clinical study results using LASIK for 8- to 12-D myopes demonstrated that every index of BSCVA, UCVA, predictability of refraction, and stability favored the ICL over the LASIK procedure.[23] The ICL was also equivalent or better by every parameter in a separate series of 4- to <8-D myopes.[24]

In the previous report we compared the results of the ICL series to FDA clinical trials of photorefractive keratectomy and LASIK with preoperative myopia of >6 D or >7D, because the ICL series had a mean preoperative myopia of >10 D. In this report, we stratified the data by preoperative myopia so that it might be instructive to compare corneal refractive surgery (LASIK) to ICL outcomes in the ≤7-D preoperative myopia group, a range generally accepted to be optimum for excimer refractive procedures.

Comparison of Implantable Collamer Lens with Approved LASIK ≤7-Diopter Myopia Clinical Trials

We compared the efficacy outcomes in the FDA ICL Clinical Study for Myopia with the effectiveness data available for FDA-approved LASIK investigational device clinical studies. The excimer refractive surgery outcomes reported here were all published by the FDA in the summaries of safety and effectiveness data of the approved Premarket Approval Applications through the Freedom of Information Act.[25–33] We chose the FDA clinical trials of LASIK to compare with the ICL because they are the most well-controlled and monitored studies available.

Table 4 is an overview of the primary efficacy variables for all myopic or myopic astigmatism LASIK clinical investigations in which the data have been stratified by the level of preoperative MRSE to allow an evaluation of low myopia outcomes (≤7 D). The goal of this overall analysis was to assess the value of the ICL at the present time for the potential refractive surgical candidate seeking a permanent correction of his or her low to moderate myopia.

The LASIK studies required the patients to be followed up with the end point being the point of refractive stability, the demonstration of which required meeting strict criteria developed by the FDA. In 6 of the 9 LASIK series, refractive stability was demonstrated at 6 months postoperatively; in 2 series, at 3 months postoperatively; and in 1 series, at 12 months postoperatively. As expected, the ICL demonstrated refractive stability early in the postoperative course, between 1 and 3 months postoperatively. We used 6-month ICL data for this comparison to LASIK so that the duration of follow-up would be similar; however, once refractive stability occurred, there was little difference in outcome. The LASIK and ICL series are comparable with regard to baseline patient age, with all series' populations having an average age in the late 30s or early 40s. Although all series, ICL and LASIK, had <7 D of myopia, the average spherical equivalent was higher in the ICL series (−5.3 D), whereas the LASIK series averaged between −3.2 D and −3.9 D. If anything, this difference tends to bias the comparison of visual and refractive outcomes in favor of the LASIK series because it is widely accepted that refractive procedures are more predictable as one decreases the amount of preoperative myopia.

Effectiveness of the STAAR Implantable Collamer Lens versus LASIK

Uncorrected visual acuity represents the primary efficacy variable for the ICL clinical study and the majority of refractive laser surgery clinical investigations. The dramatic improvement in UCVA after ICL surgery in the subset of eyes with low myopia exceeded all FDA targets and was better than or comparable to all approved LASIK clinical study results. The proportion of eyes in the ICL study with 20/20 or better UCVA at 6 months after ICL implantation if BSCVA was 20/20 or better was 70.5%, compared with the low myopia LASIK study 3- to 6-month outcomes (36.3%, 51.8%, 58.6%, 58.6%, 64.2%, 69.1%, 79.9%, and 90%). At 20/40 or better, the ICL (98.9%) continued to show long-term results comparable to or better than the early 3- to 6-month LASIK values (range, 86.6%–100%).

Predictability outcomes were excellent during the ICL for Myopia clinical study and, specifically, for the subset of eyes with myopic refractive errors of ≤7 D. Predictability with the ICL was better at all values when compared with currently approved LASIK devices. The proportion of eyes within 0.50 D in the approved LASIK studies ranged from 50.0% to 81.3% (50.0%, 66.4%, 67.1%, 67.9%, 70.7%, 70.9%, 74.8%, 77.8%, and 81.3%), falling short of the 88.8% 6-month outcome reported with the ICL. Predictability within 1.0 D showed a similar trend with the ICL result (99%), exceeding all LASIK outcomes (80.0%, 84.2%, 86.8%, 87.5%, 89.7%, 90.0%, 94.4%, 94.5%, and 95.7%).

The efficacy of the ICL procedure has been shown to be superior to that of LASIK for myopia between −8 and −12 D.[22] These data suggest that the ICL should be given serious consideration for use in eyes with ≤7 D of myopia.

Clinical study outcomes presented in this study substantiate the overall safety of the Myopic ICL in this moderate to high myopia patient population. The low incidence of complications or adverse events reported with the Myopic ICL should be taken in the context of the potential alternative refractive surgical procedures available to myopes with between −3.0- and −20.0-D refractive errors. In general, the greater the level of preoperative myopia, the higher the incidence of complications or adverse events. In particular, for the highest myopia group (>10 D), lack of safe and efficacious alternative refractive surgery options combined

with the low overall incidence of safety events with the Myopic ICL results in a risk–benefit ratio that supports the use of the Myopic ICL across this full patient population.

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Appendix: The ITM Study Group

The participants in the ITM Study Group, as of October 2003, are as follows:

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