

Interim Results from the International Trial of Second Sight's Visual Prosthesis

Mark S. Humayun, MD, PhD,¹ Jessy D. Dorn, PhD,² Lyndon da Cruz, MD, PhD,³ Gislín Dagnelie, PhD,⁴ José-Alain Sahel, MD,⁵ Paulo E. Stanga, MD,⁶ Artur V. Cideciyan, PhD,⁷ Jacque L. Duncan, MD,⁸ Dean Elliott, MD,⁹ Eugene Filley, PhD,¹⁰ Allen C. Ho, MD,¹¹ Arturo Santos, MD,¹² Avinoam B. Safran, MD,¹³ Ariès Ardití, PhD,¹⁴ Lucian V. Del Priore, MD,^{4,15} Robert J. Greenberg, MD, PhD,² for the Argus II Study Group*¹

Purpose: This study evaluated the Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, CA) in blind subjects with severe outer retinal degeneration.

Design: Single-arm, prospective, multicenter clinical trial.

Participants: Thirty subjects were enrolled in the United States and Europe between June 6, 2007, and August 11, 2009. All subjects were followed up for a minimum of 6 months and up to 2.7 years.

Methods: The electronic stimulator and antenna of the implant were sutured onto the sclera using an encircling silicone band. Next, a pars plana vitrectomy was performed, and the electrode array and cable were introduced into the eye via a pars plana sclerotomy. The microelectrode array then was tacked to the epiretinal surface.

Main Outcome Measures: The primary safety end points for the trial were the number, severity, and relation of adverse events. Principal performance end points were assessments of visual function as well as performance on orientation and mobility tasks.

Results: Subjects performed statistically better with the system on versus off in the following tasks: object localization (96% of subjects), motion discrimination (57%), and discrimination of oriented gratings (23%). The best recorded visual acuity to date is 20/1260. Subjects' mean performance on orientation and mobility tasks was significantly better when the system was on versus off. Seventy percent of the patients did not have any serious adverse events (SAEs). The most common SAE reported was either conjunctival erosion or dehiscence over the extraocular implant and was treated successfully in all subjects except in one, who required explantation of the device without further complications.

Conclusions: The long-term safety results of Second Sight's retinal prosthesis system are acceptable, and most subjects with profound visual loss perform better on visual tasks with system than without it.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology* 2011;xx:xxx © 2011 by the American Academy of Ophthalmology.



*Group members listed online in Appendix 1.

Several different treatment avenues using biologic and bio-electronic approaches have been proposed to restore sight to the blind.¹⁻⁴ Some of the major challenges for bioelectronic implants include long-term stable performance of the implanted electronics, as well as a safe surgical implantation procedure. Previous studies have shown that electrical stimulation of the retinal ganglion cell side (epiretinal stimulation) can produce discrete phosphenes and that spatial resolution and partial restoration of vision is possible.⁵⁻¹³ Herein, from an ongoing international clinical trial evaluating the Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, CA), is reported the experience with 45.6 cumulative subject-years in 30 subjects implanted at 10 clinical centers.

Patients and Methods

Statement of Compliance

This multicenter feasibility study for Second Sight's retinal prosthesis system is being conducted in accordance with the Declara-

tion of Helsinki and the national regulations for medical device clinical trials in the countries in which the study is being conducted. The study has been approved by the national ministries of health in these countries and the ethics committees or institutional review boards of participating institutions. All subjects signed informed consent to participate. The clinical trial is posted on www.clinicaltrials.gov, trial registration number NCT00407602.

Purpose of Study and Description of Subjects

The study is a single-arm, prospective, unmasked study to evaluate the safety and usefulness of the prosthesis in providing functional vision to blind subjects with end-stage outer retinal degenerations. A total of 32 subjects have been implanted with the prosthesis. The first 2 subjects were part of a pilot study in Mexico (the first country to grant regulatory approval for clinical use); because these subjects received a significantly different device (the electrode array was placed outside of the macula), this report focuses on the 30 subjects who received an electrode array that could be placed at least partly in the macular region. These 30 subjects were 50 years of age or older (18 or older at some clinical sites) with a diagnosis of retinitis pigmentosa (or other outer retinal degeneration at some sites; 1 participant had Leber congenital amaurosis

and 1 had choroideremia) with remaining vision of bare or no light perception (visual acuity worse than 2.9 logarithm of the minimum angle of resolution [logMAR] in both eyes). All subjects had a history of useful form vision. Exclusion criteria addressed any inability to implant the device physically, concurrent complicating ocular pathologic features, and any inability to commit to the expectations and duration of the study. Refer to www.clinicaltrials.gov for full subject selection criteria.

Subjects had a median age of 57.5 ± 9.9 years (range, 27–77 years) at the time of implantation, and all but 1 subject were at least 45 years of age. Thirty percent of subjects were female and 70% were male. Some subjects (33%) had undergone previous cataract removal surgery in the implanted eye, and 1 subject had had several previous ocular surgeries in the implanted eye (prior pars plana vitrectomy to clear vitreous debris and subconjunctival placental tissue injections). The last 15 subjects were implanted with a modified device that was slightly re-engineered to have a more flexible cable and an electrode array that allowed closer apposition of the electrodes to the underlying retina. All subjects were followed up for a minimum of 6 months and up to 2.7 years.

Description of Device

The Argus II Retinal Prosthesis System consists of an active implantable device surgically implanted on and in the eye and an external unit worn by the user. The external unit consists of a small camera and transmitter mounted on glasses and a video processor and battery worn on the belt or a shoulder strap (Fig 1A).

The implanted portion (Fig 1B) consists of a receiving and transmitting coil and electronics case that are fixed to the sclera outside of the eye and an electrode array (60 electrodes) that is positioned surgically onto the surface of the retina by a retinal tack. The electrode array is connected to the electronics case by a metallized polymer ribbon cable that penetrates the sclera in the pars plana. The camera captures video and sends the information to the processor, which converts the image to electronic signals that are then sent to the transmitter coil on the glasses. The episcleral implanted receiver coil and antenna wirelessly receives these data and sends the signals via the ribbon cable to the electrode array, where electrical stimulation pulses are emitted. The spatially controlled microelectrode electrical stimulation of the retinal cells induces cellular responses in the retina that travel through the optic nerve to the central visual system, resulting in visual percepts.

Although magnification or zoom is possible in the system, for this study, the field of view of the camera was cropped to match the predicted visual field of the array on the retina (assuming 1° visual angle = $300 \mu\text{m}$ on the retina).¹⁴ The cropped image then was downsampled to 10×6 pixels. The pixels were mapped 1:1 onto the electrodes of the implanted array, so the chosen field of view of the camera matched the field of view of the array—approximately 20° on the diagonal.

Surgery

At the start of the implant procedure, 8 mg dexamethasone (to reduce inflammation) and 1 g cefazolin (or equivalents) were administered by intravenous injection. In phakic eyes, the lens was removed via clear cornea phacoemulsification (with the exception of pars plana lensectomy in 1 subject). Next, a 360° limbal conjunctival peritomy was performed followed by isolating the rectus muscles using 2–0 black silk.

The coil was placed temporally on the globe and was centered under the lateral rectus muscle. The electronics package was centered in the superior temporal quadrant. The inferior part of the scleral band was passed under the inferior and the medial rectus

muscles, and the superior portion of the band was passed under the superior rectus muscle. The implant was fixed to the eye via sutures passed through suture tabs on the implant in both temporal quadrants and with the use of mattress sutures around the encircling band in the nasal quadrants with the Watzke sleeve (Labi-cian Ophthalmics, Inc., Oakville, Canada) positioned in the supranasal quadrant.

Core and peripheral vitrectomies were performed and were followed by dissection of any epiretinal membrane in the area where the surgeon intended to tack the array. The microelectrode array then was inserted through a temporal sclerotomy (approximately 5 mm in width) and was placed onto the retina in the macula and then tacked using a custom retinal tack (Second Sight Medical Products, Inc.). The extraocular portion of the cable was sutured to the sclera and all sclerotomies were sutured.

An allograft (Tutoplast; IOP, Inc., Costa Mesa, CA), or a suitable alternative in countries where allografts were not permitted, was sutured and draped over the electronics package to reduce the likelihood of conjunctival irritation. Finally, the Tenon's capsule and the conjunctiva were sutured.

At the end of the surgery, 2 mg dexamethasone, 100 mg cefazolin, and 2 ml lidocaine (or equivalents) were injected under the conjunctiva. Midway through the trial, to reduce the likelihood of endophthalmitis, the surgical procedure was modified by the addition of prophylactic intravitreal injections of antibiotics (0.1 ml intravitreal vancomycin [1 mg/0.1 ml] and ceftazidime [2.25 mg/0.1 ml]) at the end of the implant procedure.

After surgery, the following medications were administered per protocol: 500 mg ciprofloxacin twice daily for 7 to 14 days, 1 drop gatifloxacin 4 times daily for 7 to 14 days, 60 mg daily prednisolone (orally) for 2 weeks, immediately followed by a methylprednisolone (Medrol; Pfizer, Inc., New York, NY) taper pack (8 mg), until the pack was completed (or equivalent taper of prednisolone), 1 drop Pred Forte (Allergan, Inc., Irvine, CA) 1% 4 times daily for 2 weeks, and 1 drop daily atropine 1% for 2 weeks.

Clinical Evaluation

Subjects were evaluated on day 1, weeks 1, 2, and 4, and months 3, 6, 9, 12, 18, 24, 30, and 36. At each of these follow-up time points, complete eye examinations (including measurement of intraocular pressure [IOP]), retinal fundus photography, fluorescein angiography, and optical coherence tomography were performed.

Serious device- or surgery-related events were reported to the relevant competent authorities and ethics committees in accordance with the local reporting requirements. During the trial, all adverse events were subject to detailed review by an independent medical safety monitor, both as individual events and collated data.

Subjects were allowed to use the system outside the outpatient clinical setting in their daily lives after it was individually programmed and they had completed training (usually after the first month after implantation).

Full-field Stimulus Light Threshold

Subjects' residual native light perception (i.e., without the use of the prosthesis) was measured before and after implantation using the following protocol. The subjects' eyes were dilated and dark adapted for 30 minutes. Monocular thresholds were obtained by patching the other eye during testing. Dark-adapted light thresholds of implanted and fellow eyes to full-field white light stimuli were measured using the Espion D-FST test within the commercially available E2 clinical electrophysiology software package (version 5.0; Diagnosys LLC, Littleton, MA). In one center,

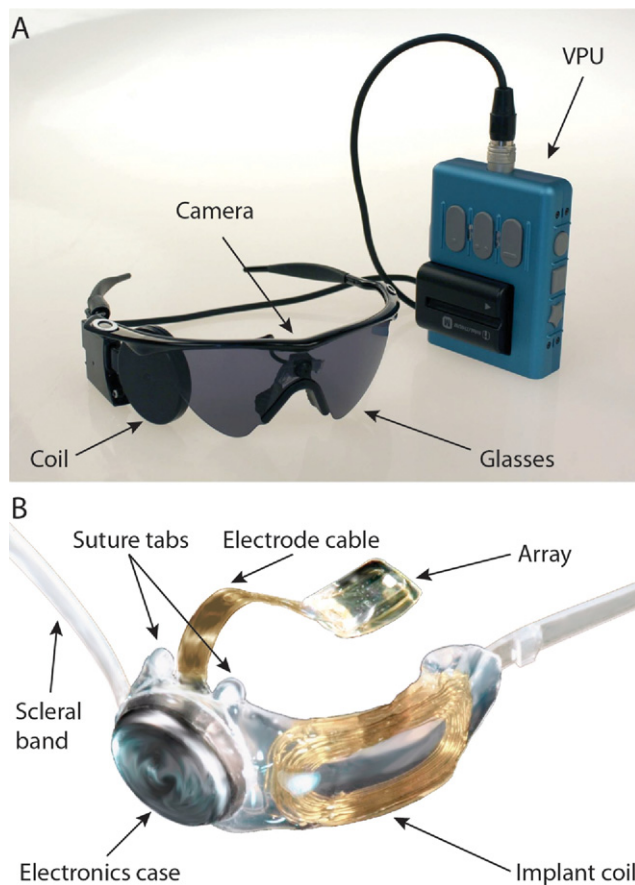


Figure 1. A, Photograph of the external portion of the Argus II prosthesis system (Second Sight Medical Products, Inc., Sylmar, CA) including glasses-mounted video camera, radio-frequency (RF) coil, and video processing unit (VPU) with rechargeable battery. B, Photograph of the implanted portion of Argus II prosthesis system including the 6×10 electrode array, electronics case, and implant RF coil.

custom-written software was used to obtain full-field stimulus testing thresholds.^{15,16} Further details are provided in Appendix 2 (available at <http://aaojournal.org>). Subjects at sites without an Espion system or with no measurable threshold below the maximum luminance provided by the system were tested for having residual bare light perception (BLP) using a photographic camera flash (Uniblitz 82ABSZ; Vincent Associates, Rochester, NY). This method used a forced-choice paradigm with 20 blocks, with 4 presentations per block. A 95% significance criterion was used to determine if a subject was BLP (i.e., $\geq 9/20$ correct blocks). According to the binomial distribution, given a chance rate of 0.25, the probability (P) of scoring 9 or more correct of 20 by chance is less than 0.05.

Outside Outpatient Clinic Use

An important objective in the months after implantation was to have the subjects start using their system outside the outpatient clinical setting. As soon as possible after implantation, subjects were trained to set up and use the system independently and to respond to audible alarm states (e.g., low battery alarm). Subjects also were trained to use the system to perform activities of daily living (Videos 1 and 2 showing subjects using their systems to

perform tasks both indoors and outdoors are available at <http://aaojournal.org>).

Electrode Reliability

Although all microelectrode arrays comprised 60 electrodes, the number of enabled electrodes (i.e., electrodes available for stimulation) in the delivered, finished device in this clinical trial varied from 46 to 60 because of a conservative policy of shutting off electrodes that did not meet stringent electrical stimulation criteria. The median number of enabled electrodes at the time of implant was 55. After implantation, impedance measurements on each electrode were used to determine if additional electrodes should be disabled or if previously disabled electrodes should be re-enabled.

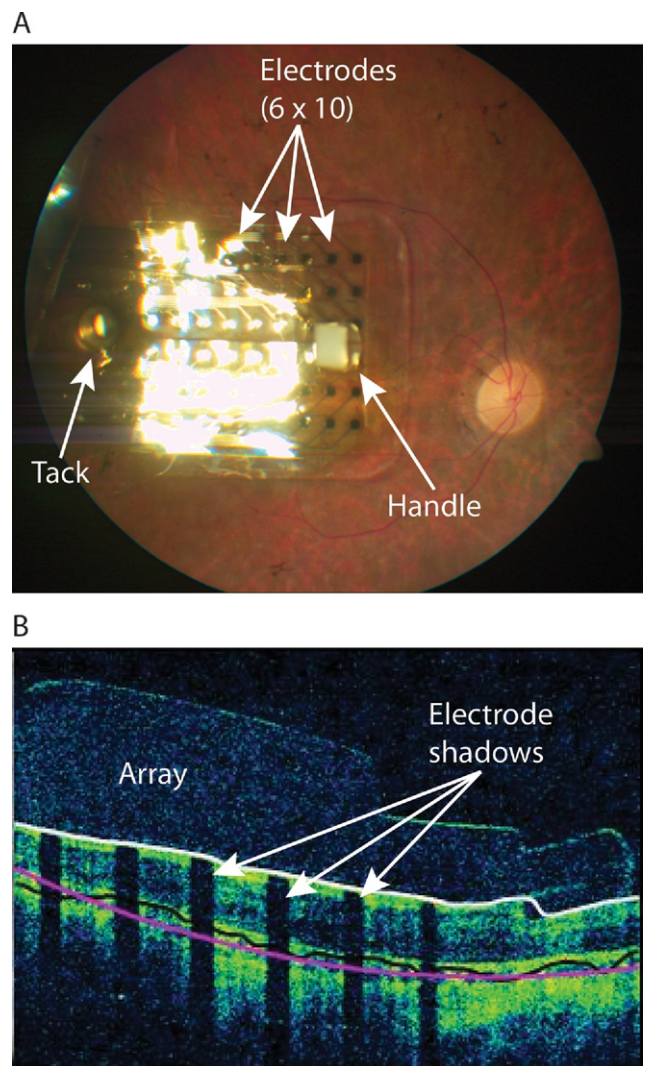


Figure 2. A, Fundus photograph of implanted Argus II array (Second Sight Medical Products, Inc., Sylmar, CA) in the macular region. The electrode array is secured to the retina with a retinal tack; the white square visible on the distal side of the array is an opaque section of tubing (the handle) used by the surgeon to position the array. B, Optical coherence tomography image of an implanted Argus II array. Shadows cast on the retinal image (white arrows) are the result of occlusion of the scanning light source by the metal electrodes.

Tests of Visual Acuity and Real-World Usefulness

Three types of visual acuity tests were performed using computer monitors. In square localization, subjects were asked to localize a white square on a black background; in direction of motion, subjects were asked to indicate the path of a white line swept across a black background; and in grating visual acuity, subjects were asked to differentiate the orientation of black and white bars of a range of widths. Two types of real-world utility tests were performed. In the door test, subjects were asked to find a door across a room, and in the line test, subjects were asked to follow a white line on the floor. For further details on these testing methods, please see Appendix 2 (available online at <http://aoajournal.org>).

Results

Surgery

If the subjects' eyes did not have equal visual acuity at baseline, implantation was performed in the worse-seeing eye. If the subjects' eyes had equal visual acuity, the right eye was selected for implantation. Twenty-six subjects were implanted in the right eye, and 4 were implanted in the left eye.

During the implantation procedure, 67% of subjects had their natural lens removed via clear cornea phacoemulsification (with the exception of pars plana lensectomy in 2 cases) and they were left aphakic (no lens). Patients with lens implants (i.e., pseudophakic) did not undergo lens explantation with the exception of 1 patient in whom the intraocular lens was subluxed before surgery, necessitating its removal. The width of the sclerotomy where the cable was inserted averaged 5.0 ± 0.5 mm (range, 4.5–6.0 mm). Fifty-seven percent of subjects had a well-adhered posterior hyaloid, an epiretinal membrane that required peeling, or both. Most subjects had an allograft (either Tutoplast sclera [57%] or Tutoplast pericardium [30%]) placed over the extraocular portion of the device (under the conjunctiva) at the end of the surgery. France does not permit the use of these allografts, so the subjects in France received either a polytetrafluoroethylene patch (1 subject) or an autologous aponeurosis graft (3 subjects).

The median implant surgery time was 4 hours and 4 minutes (range, 1 hour 53 minutes–8 hours 32 minutes). The longest implant procedure was prolonged by the fact that the subject had undergone several previous surgeries on the implanted eye (prior pars plana vitrectomy to clear vitreous debris and subconjunctival placental injections), which resulted in extensive conjunctival scar-

ring. In addition, this subject's lateral rectus muscle was fibrosed and disinserted in these prior surgeries and required reinsertion. Figure 2A shows a fundus photograph of an implanted array, and Figure 2B shows an optical coherence tomography image of an implanted array.

Clinical Safety

Serious Adverse Events. Serious adverse events (SAEs) were defined according to ISO 14155 as medical occurrences that either caused death; were life threatening; caused permanent impairment of a body function or permanent damage to body structure, or necessitated medical or surgical intervention to preclude such impairment or damage; required hospitalization or prolonged hospitalization; or caused fetal death or abnormality (although pregnancy was an exclusion criterion). There were 17 SAEs that were determined to be device or surgery related as of March 1, 2010. Table 1 presents a summary of these events. The SAEs often were clustered (i.e., more than 1 event occurred in the same subject), and 70% of subjects did not experience any SAEs.

The vast majority of SAEs occurred within the first 6 months after implantation. Eighty-two percent (14/17) of SAEs occurred within the first 6 months after implantation, and 70% (12/17) occurred within the first 3 months after implantation. Subjects enrolled later in the study experienced fewer SAEs ($n = 4$ SAEs in 2 subjects) than those enrolled earlier in the study ($n = 13$ SAEs in 7 subjects). This improvement was attributed to improvements in the surgical technique and minor design improvements made midway through the study.

Conjunctival erosion and dehiscence over the extraocular implant, when combined, were the most common occurrences and were treated in all but 1 subject with additional sutures, placement of additional tissue (conjunctiva or sclera), or both. In 1 subject, the suture tab on the device was damaged during the repair, precluding the ability to restore the device; after recurrent erosions, this device was explanted without any further complications.

Culture-negative presumed endophthalmitis occurred and resolved in 3 subjects in the first group of 15 subjects. None of the cases were associated with observed pre-existing conjunctival erosion or hypotony. All cases were treated with intravitreal (0.1 ml vancomycin [1 mg/0.1 ml] and ceftazidime [2.25 mg/0.1 ml]) subconjunctival, topical, and systemic antibiotics.

The first endophthalmitis case developed in the very immediate postoperative period in a subject from a United States site. The subject was treated with intravitreal vancomycin and ceftazidime as well as oral tablets of moxifloxacin. At week 1, antibiotics (moxifloxacin tablets and topical gatfloxacin) were tapered and

Table 1. Serious Adverse Events (Device or Surgery Related)

| Serious Adverse Events | All Subjects (n = 30) | | Last Subjects Enrolled in Study (n = 15) |
|-----------------------------------|----------------------------|-------------------------|--|
| | No. of Subjects with Event | 95% Confidence Interval | No. Subjects with Event |
| Conjunctival dehiscence | 3 | 2.1%–26.5% | 1 |
| Conjunctival erosion | 2 | 0.8%–22.1% | 0 |
| Presumed endophthalmitis | 3 | 2.1%–26.5% | 0 |
| Hypotony | 3 | 2.1%–26.5% | 1 |
| Retack | 2 | 0.8%–22.1% | 1 |
| Rhegmatogenous retinal detachment | 1 | 0.1%–17.2% | 1 |
| Tractional retinal detachment | 1 | 0.1%–17.2% | 0 |
| Retinal tear | 1 | 0.1%–17.2% | 0 |
| Inflammatory uveitis | 1 | 0.1%–17.2% | 0 |

Pred Forte (prednisolone acetate) was given over the next week. The second and third endophthalmitis cases developed approximately 5 and 8 weeks after surgery. These subjects were implanted at the same center in the United Kingdom on the same day. The first of these subjects was treated with intravitreal injections of amikacin and vancomycin, topical application of chloramphenicol and dexamethasone, and oral tablets of moxifloxacin. The final subject with endophthalmitis was treated with intravitreal vancomycin, ceftazidime, and amphotericin B. Although the second and third subjects were implanted at the same center on the same day, the intravitreal antibiotics chosen for the second subject were different from the third. The principal investigator consulted with the infectious disease specialist, who recommended the use of ceftazidime instead of amikacin and the addition of an antifungal. The subject also continued oral tablets of moxifloxacin and prednisolone, as well as topical chloramphenicol and dexamethasone. Four days later, the subject received a second round of intravitreal vancomycin and ceftazidime.

None of the presumed endophthalmitis cases required explantation of the device, and none occurred in subjects implanted later in the trial (the last 15 subjects) after a protocol change was implemented that included prophylactic intravitreal antibiotics at the end of the case.

In the trial, hypotony was defined as IOP of less than 5 mmHg that persisted for more than 2 weeks or for shorter duration if the low IOP was associated with appositional choroidals or with a flat anterior chamber. Three subjects had hypotony that required surgical intervention. Of these 3 cases, 2 occurred within the first 6 months (at 1 and 4 months) of implantation and the third occurred at 1 year in the patient whose suture to secure the implant had broken and whose device had migrated anteriorly. As described previously, this third subject's device eventually was explanted, which led to normalization of the IOP. Of the other 2 subjects, 1 was treated with intraocular silicone oil tamponade, which normalized the IOP. The second had an associated rhegmatogenous retinal detachment requiring repair; the subject later was treated with silicone oil tamponade, which resulted in stabilization of the IOP between 6 and 7 mmHg.

Two cases of retinal detachment, which eventually required surgical intervention to treat, occurred during the 5 to 6 months after implantation. The first had a rhegmatogenous detachment associated with 360 circumferential bands and choroidal effusion; this is the same subject described above. At approximately 5 months after surgery, a second subject incurred blunt trauma to the implanted eye, resulting in proliferative vitreoretinopathy that progressed to a tractional retinal detachment. The retinal detachment was repaired successfully with vitrectomy, partial retinectomy, and silicone oil.

Two subjects required the array to be retacked to the retina shortly after the implant surgery. In both cases, it became apparent in the first few days after surgery that the tack was not implanted securely at the time of the initial surgery. In both cases, the tack was reattached successfully near the same retinal site.

Nonserious Adverse Events. Nonserious adverse events (non-SAEs) were those events related to the device or surgery that did not require surgical intervention (they resolved after treatment with topical or oral medications or did not require any treatment). Conjunctival edema that was considered to be more extensive or lasting longer than what is seen typically after surgery occurred in 10 subjects and was considered a non-SAE. The following non-SAEs occurred in 5 to 7 subjects: intraocular inflammation, hypotony without significant choroidal detachments, suture irritation, and ocular pain (mostly foreign body sensation). The following non-SAEs occurred in 2 to 3 people: inflammatory conjunctivitis, corneal filaments, epiretinal membrane, high IOP controlled by topical antiglaucoma medications, epiphora, mild hyphema, in-

flammatory uveitis with few keratic precipitates, and mild vitreous hemorrhage. The following non-SAEs had only a single occurrence and resolved: limited conjunctival dehiscence, corneal abrasion, mild peripheral corneal vascularization, cystoid macular edema, decrease in light perception, dry eye, transient headache, iris vessel engorgement that receded secondary to surgery to resuture sclerotomy (to treat hypotony), a stable tractional retinal detachment, transient nausea, transient increased nystagmus, scleritis, and transient vertigo.

Full-field Stimulus Light Threshold

Across all subjects measured, there was no significant difference between threshold obtained before and after surgery for both implanted and fellow eyes ($P > 0.05$, student 2-tailed, paired *t* test). All but 1 subject had BLP in both eyes before implantation. The 1 subject who had no light perception recorded in 1 eye before implantation subsequently was categorized as BLP in that eye after implantation, when the photographic flash test was available. Ninety-three percent of subjects still had BLP in both eyes as of the latest follow-up time point (as of November 30, 2010). Of the 2 whose vision declined from BLP to no light perception, 1 showed the decline in both eyes, and 1 declined only in the nonimplanted eye. For subjects with quantifiable light thresholds in both eyes, implanted and fellow eye thresholds were correlated ($R^2 = 0.41$; $P < 0.01$), thus providing validation of method.

Outside Outpatient Clinical Use

Subjects took the system home at an average of 2.3 ± 0.7 months after implantation (range, 1.4–3.7 months; median, 2.1 months). As of March 1, 2010, 29 of 30 subjects were using the system at home (1 subject's device was explanted as described above), and subjects had been using their systems at home for an average of 15.8 ± 9.7 months (range, 4.2–28.8 months; median, 14.3 months).

Electrode Reliability

The implants are designed with an electrode array that contains 60 electrodes arranged in a rectangular grid of 6×10 . Of the electrodes that were enabled at the time of implantation, 94.4% remained enabled and functional throughout the study (as of March 1, 2010).

Perception Thresholds for Electrical Stimulation

All subjects (100%) were able to perceive light when their systems were stimulated (thresholds were measurable on at least 1 electrode). An average of 55.5% (standard deviation, 32.0%) of all enabled electrodes across subjects had measurable thresholds of less than a charge density of 1.0 mC/cm^2 .

Square Localization

Figure 3 shows the mean distance from the center of the target (accuracy) for system on and off for each subject at the latest follow-up time point (the smaller the mean distance, the closer the subject's response was to the target). These data show that, as of the most recent follow-up time point, 27 of 28 subjects (96%) performed this test better with the system on versus off, and no subjects performed significantly better with the system off.

Direction of Motion

Figure 4 shows the mean response error (stimulus angle minus the response angle) with the system on and off for each subject at the

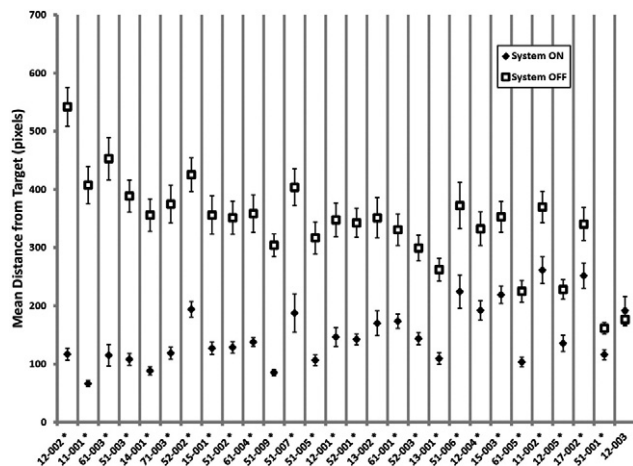


Figure 3. Graph showing the mean accuracy on the square localization task for each subject, system on (filled diamonds) and off (open squares). Subjects are ordered along the x-axis from greatest difference between on and off performance to least difference. Error bars indicate standard error. Asterisks indicate subjects for whom the mean system on performance was significantly different from the mean system off performance ($P < 0.05$, 2-tailed t test assuming unequal variances). Data are the latest available for each subject as of March 1, 2010.

latest follow-up time point (the smaller the mean response error, the closer the subject's response was to the stimulus direction). These data show that 16 of 28 subjects (57%) performed this test better with the system on versus off.

Grading Visual Acuity

Per the protocol inclusion criteria, all subjects' visual acuity was measured at worse than 2.9 logMAR—off the acuity scale used for this test—in both eyes before implantation (at month 0). To date, none of the subjects have been able to score reliably on the visual acuity scale in either eye with the system off. Seven subjects have been able to score reliably on the scale (with visual acuity between 2.9 and 1.6 logMAR) with the system on. The best result to date is 1.8 logMAR (Snellen equivalent, 20/1262). Note that, these tests were performed without magnification or zoom.

Orientation and Mobility

The observed results at each time point for the on-versus-off conditions are shown in Figures 5 and 6 for the door and line tasks, respectively. A repeated measures analysis of variance model was used to compute and compare the difference between the mean success rates (over all subjects) for the door task with the system on and off at each follow-up time point. These results are provided in Tables 2 and 3. This analysis demonstrated that, with the exception of the 12-month time point, subjects' performance on the door test was significantly better with the system on compared with the system off ($P < 0.05$; indicated with asterisks). This analysis demonstrated that subjects' performance on the line task with the system on was significantly better ($P < 0.05$; indicated with asterisks) than it was with the system off at all follow-up time points.

Discussion

This study represents 45.6 cumulative subject-years in 30 human subjects implanted with the Argus II Retinal Pro-

sthesis System. There are no other suitable retinal prostheses with which the safety or efficacy of this system can be compared. Although other retinal prostheses currently are being developed by both commercial and academic entities, none of these devices are commercially approved, none are approved for longer than 1 month's implantation, few are even being subject to clinical trial testing, and none have been the subject of published long-term clinical results or multicenter data. However, there are other commercially available ophthalmic devices that have some similar characteristics (e.g., extraocular or intraocular components, requirement for vitrectomy to install, among others) as this system. But even in this comparison, the adverse event rates quoted are reflective of rates for established and practiced therapies; the rates of adverse events for these same therapies at the time they were introduced to the market (similar to this device at this stage) likely would have been higher.

As an example, to help evaluate the incidence of conjunctival erosion in prosthesis subjects, glaucoma drainage devices (or shunts) are a potentially useful comparator device because, like this system, they have an intraocular and extraocular portion and have a portion of similar volume implanted under the conjunctiva. Studies conducted by Lankaranian et al¹⁷ and Gedde et al¹⁸ report the rate of conjunctival erosion of glaucoma drainage devices as 5% to 16%. Gedde et al reported that wound dehiscence also occurred at a rate of 11%. In this trial, there were 2 cases of conjunctival erosion (6.7%) and 3 cases of conjunctival dehiscence (10.0%), which are within the range of those seen with glaucoma drainage devices.

The incidence of presumed endophthalmitis was 10% (3 of 30) and occurred within 2 months after implantation. In all 3 subjects, clinical symptoms were reported and signs of endophthalmitis were observed, although no positive cul-

Figure 4. Graph showing the mean response error for each subject on the direction of motion task, system on (filled diamonds) and system off (empty squares). Subjects are ordered along the x-axis from greatest difference between on and off performance to least difference. Single asterisks indicate subjects for whom the system on mean was significantly different (smaller) than the system off mean, and the double asterisk indicates a subject for whom system off was significantly different (smaller) than system on ($P < 0.05$, 2-tailed t test assuming unequal variances). Data are the latest available for each subject as of March 1, 2010.

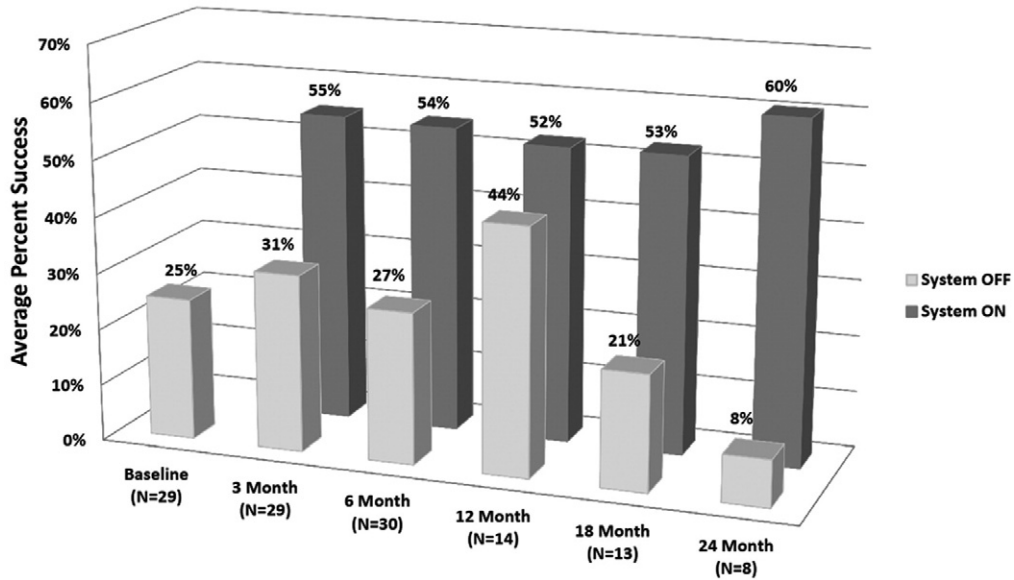
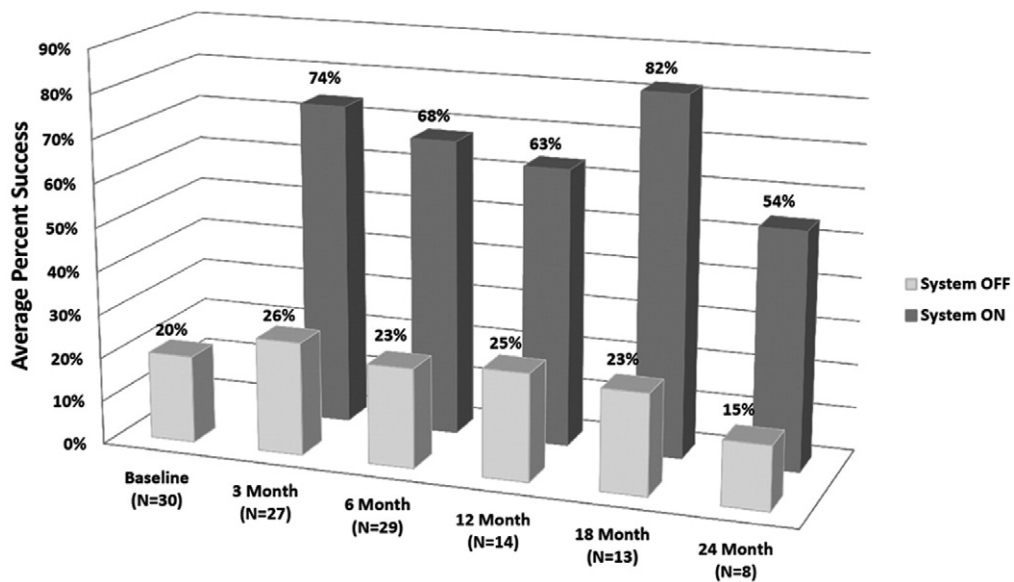


Figure 5. Bar graph showing the average percent success at each clinical visit for the find-the-door orientation and mobility task.

tures were identified and all 3 patients demonstrated resolution. Although a comprehensive investigation was conducted for each incidence of presumed endophthalmitis, no conclusive source of infection could be determined. Potential contributing factors included slightly longer surgical times than average in these cases and a greater-than-usual number of personnel moving in and out of the operating room, some of whom did not wear face masks. Typically, the incidence of postsurgical endophthalmitis in ophthalmic procedures is low because of the sterile surgical technique. The literature reveals an endophthalmitis rate of 1% to 5% of subjects with glaucoma drainage devices.^{18,19}

With the addition of a temporary sleeve to cover the array region before it is introduced intraocularly; stricter

sterile techniques during implantation procedures, especially in the handling of the implant; reduction in the number of observers present; and the routine use of prophylactic intraoperative broad-spectrum antibiotics, the risk of endophthalmitis has been reduced. In fact, no cases of endophthalmitis were observed after these procedural changes (n = 15 cases). None of these subjects' implants were explanted and that all remained functional after the presumed endophthalmitis events were treated with antibiotics. The presumed endophthalmitis cases occurred early (within 2 months after implantation) and were not associated with conjunctival erosions, so it is not likely that the conjunctival erosions led to the infections, as has been seen in glaucoma filtering procedures. Moreover, there was no pocket of



Figures 6. Bar graph showing the average percent success at each clinical visit for the follow-the-line orientation and mobility task.

Table 2. Repeated Measures Analysis of Variance: Door Task

| Door Task | Baseline | 3 Months* | 6 Months* | 12 Months | 18 Months* | 24 Months* |
|--|----------------|-----------|-----------|-----------|------------|------------|
| RM ANOVA difference (on-off) in mean % success | Not applicable | 24% | 27% | 10% | 32% | 48% |
| P value | Not applicable | 0.001 | 0.0001 | N/S | 0.002 | 0.0004 |

RM ANOVA = repeated measures analysis of variance.

Mean percent rates of success with the system; minus the mean percent rate of success with the system off (over all subjects) at each time point. Means were computed using a repeated measures analysis of variance model as described in Appendix B. The mean percent differences were tested against 0 for each time point (i.e., differences significantly greater than 0 indicate that the outcome was significantly better with the system on compared with off). Means were significantly different for all time points except at 12 months after implant (asterisks). Because of different enrollment times and a method change part way through the study (to make the task more difficult to perform by chance), the 12-month clinical visit consisted of a larger proportion of subjects using the new (more difficult) method.

localized infection seen either at the scleral entry site of the cable or around the extraocular device.

In 1 of the 2 subjects (2/30; 6.7%) with retinal detachments, the subject had experienced a blunt trauma to the eye that most likely caused the retinal detachment. The second subject was young (27 years of age) with very adherent hyaloid, which led to incomplete vitreous removal from the posterior retina and subsequent tractional retinal detachment.

Again, it is difficult to find a large clinical trial in which the surgical procedure is similar to the one required for implantation of a retinal prosthesis. But in an effort to draw some comparisons, the following are the results from more complex procedures with implants. The rate of retinal detachment for sclerally fixated intraocular lenses is reported to be between 8.5% and 9.5%.^{20,21} The rate of retinal detachment with Retisert (Bausch & Lomb, Rochester, NY) implantation is between 1.5% and 2.2%,^{22,23} and that with the Vitrasert (Bausch & Lomb) implant has been reported to be as high as 13.8%.²⁴ One must consider that the target subject population for the Vitrasert (AIDS-related cytomegalovirus) carried with it a higher risk of retinal detachment.

Finally, it is worth noting that there were 2 dislodged retinal tacks in this trial (6.7%). This is comparable with the percentage of dislodged retinal tacks reported in the literature (5.3%).²⁵

As discussed previously, the safety profile of the prosthesis, an active implantable device, is encouraging. The SAE rates are comparable with those of similar implantable devices, particularly when considering that the comparator devices are mature, established therapies. Furthermore, in later enrollees (the second group of 15 subjects), there was a lower rate of adverse events, suggesting an improving safety profile even over the course of this study.

The stability of dark-adapted light perception of implanted and fellow eyes speaks to the stable mechanical and electrical interface between the electrode array and the underlying retina. Three of the 4 subjects who went from BLP to no light perception as determined by the photographic flash test did so in both implanted and fellow eyes, suggesting that the loss in sensitivity may be the result of the natural time course of disease progression. Note that in all 4 subjects, the system has remained functional despite loss of light sensitivity.

Performance data are encouraging: threshold testing demonstrated that all subjects were able to perceive percepts when their implant was activated and that they were able to do this throughout their entire follow-up duration to date. Reliability of the prosthesis also was high. Over the follow-up period of this study, all but one device remained implanted and the vast majority of electrodes (94.4%) remained functional. All subjects who received an implant use

Table 3. Repeated Measures Analysis of Variance: Line Task

| Line Task | Baseline | 3 Months* | 6 Months* | 12 Months* | 18 Months* | 24 Months* |
|--|----------------|-----------|-----------|------------|------------|------------|
| RM ANOVA difference (on-off) in mean % success | Not applicable | 48% | 45% | 44% | 65% | 42% |
| P value | Not applicable | <0.0001 | <0.0001 | 0.0002 | <0.0001 | 0.005 |

RM ANOVA = repeated measures analysis of variance.

Mean percent rates of success with the system on minus the mean percent rates of success with the system off (over all subjects) at each time point. Means were computed using a repeated measures analysis of variance model as described in Appendix B. The mean percent differences were tested against 0 for each time point (i.e., differences significantly greater than 0 indicate that the outcome was significantly better with the system on compared with off. Means were significantly different at all time points (asterisks).

their systems outside of outpatient clinical setting. In addition, 96% of subjects can localize high-contrast objects on a computer screen significantly better with the system on than off; 57% can detect the direction of motion of a high-contrast bar significantly better with the system on than off; 23% were able to score on a grading visual acuity test; and subjects performed 2 orientation and mobility tasks significantly better with the system on than off at all but 1 time point (12 months after implantation for the door task). The exception was likely the result of the change in method. Part way through the trial, the task was made harder to perform by chance (as described in Appendix 2, available at <http://aaojournal.org>). Because subjects were implanted over the course of 2 years, each time point represents a slightly different population of subjects. Because of the time at which the method was changed, nearly all of the 14 subjects represented in the 12 months after implantation time point were tested with the old method. The corresponding higher chance rate (reflected in the higher average success rate with the system off seen in Fig 5) resulted in no significant difference between on and off performance at this 1 time point.

In conclusion, the prosthesis system is reliable over the long term (45.6 subject-years so far in this study) and provided benefit to implanted subjects during this period. The data in this report suggest that, on average, prosthesis subjects have improved visual acuity from light perception to at least hand movements, with some improving to at least counting fingers.^{26,27} These visual acuity data combined with the safety and other performance results to date (e.g., da Cruz et al, Invest Ophthalmol Vis Sci ARVO E-Abstract, 2010) demonstrate the ability of this retinal implant to provide meaningful visual perception and usefulness to subjects blind as a result of end-stage outer retinal degenerations.

Acknowledgment. The authors thank Suber Huang, MD, the independent medical safety monitor for this study.

References

- MacLaren RE, Pearson RA. Stem cell therapy and the retina. *Eye (Lond)* 2007;21:1352–9.
- Radtke ND, Aramant RB, Petry HM, et al. Vision improvement in retinal degeneration patients by implantation of retina together with retinal pigment epithelium. *Am J Ophthalmol* 2008;146:172–82.
- Dobelle WH, Mladejovsky MG, Girvin JP. Artificial vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis. *Science* 1974;183:440–4.
- Veraart C, Raftopoulos C, Mortimer JT, et al. Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. *Brain Res* 1998;813:181–6.
- Humayun MS, de Juan E Jr, Dagnelie G, et al. Visual perception elicited by electrical stimulation of retina in blind humans. *Arch Ophthalmol* 1996;114:40–6.
- Humayun MS, de Juan E Jr, Weiland JD, et al. Pattern electrical stimulation of the human retina. *Vision Res* 1999;39:2569–76.
- Rizzo JF III, Wyatt J, Loewenstein J, et al. Methods and perceptual thresholds for short-term electrical stimulation of human retina with microelectrode arrays. *Invest Ophthalmol Vis Sci* 2003;44:5355–61.
- Humayun MS, Weiland JD, Fujii GY, et al. Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. *Vision Res* 2003;43:2573–81.
- de Balthasar C, Patel S, Roy A, et al. Factors affecting perceptual thresholds in epiretinal prostheses. *Invest Ophthalmol Vis Sci* 2008;49:2303–14.
- Yanai D, Weiland JD, Mahadevappa M, et al. Visual performance using a retinal prosthesis in three subjects with retinitis pigmentosa. *Am J Ophthalmol* 2007;143:820–7.
- Caspi A, Dorn JD, McClure KH, et al. Feasibility study of a retinal prosthesis: spatial vision with a 16-electrode implant. *Arch Ophthalmol* 2009;127:398–401.
- Greenwald SH, Horsager A, Humayun MS, et al. Brightness as a function of current amplitude in human retinal electrical stimulation. *Invest Ophthalmol Vis Sci* 2009;50:5017–25.
- Horsager A, Greenwald SH, Weiland JD, et al. Predicting visual sensitivity in retinal prosthesis patients. *Invest Ophthalmol Vis Sci* 2009;50:1483–91.
- Oyster CW. *The Human Eye: Structure and Function*. Sunderland, MA: Sinauer Associates; 1999:660.
- Roman AJ, Schwartz SB, Aleman TS, et al. Quantifying rod photoreceptor-mediated vision in retinal degenerations: dark-adapted thresholds as outcome measures. *Exp Eye Res* 2005;80:259–72.
- Roman AJ, Cideciyan AV, Aleman TS, Jacobson SG. Full-field stimulus testing (FST) to quantify visual perception in severely blind candidates for treatment trials. *Physiol Meas* 2007;28:N51–6.
- Lankaranian D, Reis R, Henderer JD, et al. Comparison of single thickness and double thickness processed pericardium patch graft in glaucoma drainage device surgery: a single surgeon comparison of outcome. *J Glaucoma* 2008;17:48–51.
- Gedde SJ, Schiffman JC, Feuer WJ, et al; Tube Versus Trabeculectomy Study Group. Three-year follow-up of the Tube Versus Trabeculectomy Study. *Am J Ophthalmol* 2009;148:670–84.
- Ang GS, Varga Z, Shaarawy T. Postoperative infection in penetrating versus non-penetrating glaucoma surgery. *Br J Ophthalmol* 2010;94:1571–6.
- Bading G, Hillenkamp J, Sachs HG, et al. Long-term safety and functional outcome of combined pars plana vitrectomy and scleral-fixated sutured posterior chamber lens implantation. *Am J Ophthalmol* 2007;144:371–7.
- Kim SW, Kim MJ, Yang KS, et al. Risk factors for pseudophakic retinal detachment after intraocular lens scleral fixation with or without pars plana vitrectomy. *Retina* 2009;29:1479–85.
- Jaffe GJ, Martin D, Callanan D, et al; Fluocinolone Acetonide Uveitis Study Group. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study. *Ophthalmology* 2006;113:1020–7.
- Pavesio C, Zierhut M, Bairi K, et al; Fluocinolone Acetonide Uveitis Study Group. Evaluation of an intravitreal fluocinolone acetonide implant versus standard systemic therapy in noninfectious posterior uveitis. *Ophthalmology* 2010;117:567–75.
- Kappel PJ, Charonis AC, Holland GN, et al; Southern California HIV/Eye Consortium. Outcomes associated with ganciclovir implants in patients with AIDS-related cytomegalovirus retinitis. *Ophthalmology* 2006;113:673–83.

25. Abrams GW, Williams GA, Neuwirth J, McDonald HR. Clinical results of titanium retinal tacks with pneumatic insertion. *Am J Ophthalmol* 1986;102:13–9.
26. Lange C, Feltgen N, Junker B, et al. Resolving the clinical acuity categories “hand motion” and “counting fingers” using the Freiburg Visual Acuity Test (FrACT). *Graefes Arch Clin Exp Ophthalmol* 2009;247:137–42.
27. Bach M, Wilke M, Wilhelm B, et al. Basic quantitative assessment of visual performance in patients with very low vision. *Invest Ophthalmol Vis Sci* 2010;51:1255–60.

Footnotes and Financial Disclosures

Originally received: March 10, 2011.

Final revision: September 14, 2011.

Accepted: September 15, 2011.

Available online: ●●●.

Manuscript no. 2011-408.

¹ Doheny Eye Institute, University of Southern California, Los Angeles, California.

² Second Sight Medical Products, Inc., Sylmar, California.

³ Moorfields Eye Hospital, NIHR Biomedical Research Centre for Ophthalmology, London, United Kingdom.

⁴ Lions Vision Research and Rehab Center, Johns Hopkins University, Baltimore, Maryland.

⁵ Hospitalier National d’Ophthalmologie des Quinze-Vingts, Paris, France.

⁶ Manchester Royal Eye Hospital, Manchester Biomedical Research Centre, University of Manchester, Manchester, United Kingdom.

⁷ Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

⁸ University of California, San Francisco, San Francisco, California.

⁹ Massachusetts Eye & Ear Infirmary, Harvard Medical School, Boston, Massachusetts.

¹⁰ Retina Foundation of the Southwest, Dallas, Texas.

¹¹ Wills Eye Hospital, Philadelphia, Pennsylvania.

¹² Centro de Retina Medica y Quirúrgica, SC, Escuela de Medicina, Tec de Monterrey Campus Guadalajara, Guadalajara, Mexico.

¹³ Hôpitaux Universitaires de Genève, Geneva, Switzerland.

¹⁴ Lighthouse International, New York, New York.

¹⁵ Columbia University, New York, New York.

The members of the Argus II Study Group are listed in Appendix 1 (available online at <http://aaojournal.org>).

Financial Disclosure(s):

Mark S. Humayun - Equity owner - Second Sight Medical Products, Inc.;

Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Jessy D. Dorn - Employee and Equity owner - Second Sight Medical Products, Inc.

Robert J. Greenberg - Employee and Equity owner - Second Sight Medical Products, Inc.

Aries Arditi - Consultant - Second Sight Medical Products, Inc.; Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Artur V. Cideciyan - Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Lyndon da Cruz - Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Gislin Dagnelie - Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Dean Elliott - Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Eugene Filley - Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Avinoam B. Safran - Employee - an institution that receives funds from Second Sight Medical Products, Inc.

José-Alain Sahel - Employee - an institution that receives funds from Second Sight Medical Products, Inc.

Supported by the National Institutes of Health, Bethesda, Maryland (grant no.: 5R01EY012893-10 [RJG]). Sponsored by Second Sight Medical Products, Inc., Sylmar, California. The sponsor participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, preparation, and review of the manuscript.

Correspondence:

Mark S. Humayun, MD, PhD, DVRC 117, 1355 San Pablo Street, Los Angeles, CA 90033. E-mail: humayun@usc.edu.