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Long-Term Results from an Epiretinal Prosthesis to Restore Sight to the Blind

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Purpose: Retinitis pigmentosa (RP) is a group of inherited retinal degenerations leading to blindness due to photoreceptor loss. Retinitis pigmentosa is a rare disease, affecting only approximately 100 000 people in the United States. There is no cure and no approved medical therapy to slow or reverse RP. The purpose of this clinical trial was to evaluate the safety, reliability, and benefit of the Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc, Sylmar, CA) in restoring some visual function to subjects completely blind from RP. We report clinical trial results at 1 and 3 years after implantation.

Design: The study is a multicenter, single-arm, prospective clinical trial.

Participants: There were 30 subjects in 10 centers in the United States and Europe. Subjects served as their own controls, that is, implanted eye versus fellow eye, and system on versus system off (native residual vision).

Methods: The Argus II System was implanted on and in a single eye (typically the worse-seeing eye) of blind subjects. Subjects wore glasses mounted with a small camera and a video processor that converted images into stimulation patterns sent to the electrode array on the retina.

Main Outcome Measures: The primary outcome measures were safety (the number, seriousness, and relatedness of adverse events) and visual function, as measured by 3 computer-based, objective tests.

Results: A total of 29 of 30 subjects had functioning Argus II Systems implants 3 years after implantation. Eleven subjects experienced a total of 23 serious device- or surgery-related adverse events. All were treated with standard ophthalmic care. As a group, subjects performed significantly better with the system on than off on all visual function tests and functional vision assessments.

Conclusions: The 3-year results of the Argus II trial support the long-term safety profile and benefit of the Argus II System for patients blind from RP. Earlier results from this trial were used to gain approval of the Argus II by the Food and Drug Administration and a CE mark in Europe. The Argus II System is the first and only retinal implant to have both approvals. *Ophthalmology 2015;122:1547-1554 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material is available at www.aaojournal.org.

This study presents 3-year results from the ongoing clinical trial of the Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, CA). The study's purpose is to evaluate the safety and benefit of the Argus II System in providing functional vision to people blind from retinitis pigmentosa (RP).

Several different approaches to restoring sight to those blind from retinal degeneration are currently under investigation, including stem cell therapy,[1] gene therapy,[2,3] and other approaches.[4] Visual prostheses offer the possibility of restoring vision in patients who are severely blinded from RP and other retinal degenerations. Different visual prostheses have been explored, including visual cortex,[5,6] optic nerve,[7] epiretinal,[8] and subretinal[9] devices. Although many approaches show promise, to date, retinal prostheses are the only therapy to have achieved market approval in the United States and Europe. A previous report[8] presented data from this cohort when all subjects had reached 6 months of follow-up. We present complete 1-year and 3-year data from the Argus II clinical trial.

Methods

Study Design

The study is a single-arm, prospective, unmasked clinical trial. Because of the rarity of the eligible patient population, the sample size was 30 subjects, which was determined, with guidance from

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regulatory agencies, to be reasonably achievable and of sufficient power to evaluate safety and probable benefit. These 30 subjects were enrolled at 10 centers in the United States and Europe. Subjects served as their own controls (i.e., tested with the Argus II System turned on vs. using only their residual vision). The trial was and continues to be conducted in accordance with the Declaration of Helsinki and the national regulations for medical device clinical trials in the respective countries where 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.

Inclusion and Exclusion Criteria

Subjects were eligible to enroll if they had a confirmed diagnosis of RP (United States) or outer retinal degeneration (Europe), bare or no light perception in both eyes, functional ganglion cells or optic nerve (confirmed by photoflash detection or measurable electrically evoked response), and a history of useful form vision. Age inclusion criterion was initially $\geq$50 years and was later changed to 25 years in the United States and Switzerland and 18 years in France and the United Kingdom.

Exclusion criteria included diseases or conditions that affected retinal or optic nerve function, ocular structures, or conditions that could prevent successful implantation, and any inability to tolerate the implant surgery or medical/study follow-up. Full inclusion and exclusion criteria are listed at www.clinicaltrials.gov.

Device

The Argus II System consists of an active device implanted on and in the eye and external equipment worn by the user. The implanted portion of the system includes a receiving antenna and an electronics case that are fixed outside the eye with sutures and a scleral band, and an intraocular 6 $\times$ 10 electrode array that is tacked over the macula epiretinally (i.e., on the retinal ganglion cell side) (Fig 1A). The external portion of the system includes a glasses-mounted video camera and a small video processing unit (VPU) (Fig 1B) that can be worn on a shoulder strap or belt (not shown). The camera collects visual information and sends it to the VPU, which down-samples and processes the image. Several buttons on the VPU allow user control of various image-processing algorithms, for example, enhancing contrast. Data and power are sent wirelessly from a transmitting antenna on the glasses to the internal receiving antenna. The electrodes in the array emit pulses of electricity whose amplitude corresponds to the brightness of the scene in that location. Stimulation of the remaining retinal cells induces cellular responses that travel through the proximal visual system, resulting in visual percepts that subjects learned to interpret.

Surgical Procedure

Subjects received the Argus II Retinal Prosthesis System in 1 eye, typically the worse-seeing eye. The surgical procedure is summarized as follows; a more detailed description of the procedure and medication regimen is in the online Appendix (available at www.aaojournal.org).

To implant the device, a 360-degree limbal conjunctival peritomy was performed. The rectus muscles were isolated, and the coil was inserted temporally on the globe and centered under the lateral rectus muscle. The electronics package was centered in the superotemporal 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 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 a Watzke sleeve (Labtician Ophthalmics, Inc, Oakville, Ontario, Canada) and mattress sutures or scleral tunneling were used to secure the scleral band in the nasal quadrants.

A core and peripheral vitrectomy were conducted. The array was then inserted through a temporal sclerotomy. The electrode array was placed on the retina in the macular region and then tacked using a custom retinal tack (Second Sight Medical Products, Inc, Sylmar, CA). The extraocular portion of the cable was sutured to the sclera, and all sclerotomies were closed.

An allograft (or suitable alternative in countries where allografts were not permitted) was fixed over the device to reduce the likelihood of conjunctival irritation. Finally, the Tenon's capsule and the conjunctiva were closed.

Assessment of Safety: Primary End Point

All adverse events were collected and reported as necessary to the relevant authorities and ethics committees. Adverse events were classified by relatedness (device- or surgery-related, or subject-related) and whether they met the regulatory definition of "serious" (i.e., adverse events that required medical or surgical intervention or hospitalization to prevent permanent injury). Serious adverse events (SAEs) were distinguished from those for which treatment was unnecessary or noninvasive (nonserious). Therefore, a particular type of adverse event, such as hypotony, may have been considered nonserious or serious, depending on how or whether that particular event was treated. All adverse events were subject to detailed review and adjudication by an independent medical safety monitor.

Assessment of Visual Function: Primary End Point

The primary end point for the evaluation of benefit was visual function. This was assessed with 3 computer-based, objective tests of basic visual skills developed by Second Sight with input from the low-vision research community to cover the range of low vision restored by a retinal implant.

In "Square Localization," subjects had to locate and touch a white square in random locations on a black touchscreen monitor. The response error (the distance between the subject's response and the center of the target square in centimeters) was recorded and averaged over 40 trials. The mean error with the system on and off for each subject was evaluated with a 2-tailed t test assuming unequal variances to determine whether the on and off results were significantly different.

In "Direction of Motion," a white bar moved across the same black touch screen and subjects drew the direction they perceived the bar to be moving. The response error (the difference between the subject's response angle and the target bar's angle in degrees) was recorded and averaged over 80 trials. A 2-tailed t test was performed to determine whether the mean errors with the system on and off were significantly different.

Finally, "Grating Visual Acuity" measured subjects' visual acuity on a scale of 2.9 to 1.6 logarithm of the minimum angle of resolution (logMAR) (20/15887−20/796 in Snellen notation) using black and white gratings displayed for 5 seconds. In a 4-alternative forced-choice test, subjects indicated the perceived orientation (horizontal, vertical, diagonal left/right); the program adaptively reduced or increased the spatial frequency of the gratings on the basis of the number of correct and incorrect answers. Subjects whose performance was no better than chance were scored as acuity "worse than 2.9 logMAR."