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One-Year Safety and Performance Assessment of the Argus II Retinal Prosthesis
A Postapproval Study

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IMPORTANCE The Argus II Retinal Prosthesis System is indicated for patients with vision loss due to severe to profound outer retinal degeneration, a group with few treatment options.

OBJECTIVES To collect postapproval safety and visual function data for the Argus II.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, postapproval clinical trial conducted at 9 sites in Germany and Italy. Data were collected from December 2, 2011, to September 30, 2017, and patients were followed-up for 12 months or longer. Patients were 25 years or older with severe to profound outer retinal degeneration, some residual light perception or the ability of the retina to respond to electrical stimulation, and a history of useful form vision and were already planning to undergo Argus II implantation.

MAIN OUTCOMES AND MEASURES The primary end point of this study was the nature and rate of adverse events. Secondary end points included 3 visual function tests: square localization (SL), direction of motion, and grating visual acuity (GVA).

RESULTS Forty-seven patients were followed for 12 months or longer after implant. Mean (SD) age was 56 (12) years, 37 (79%) had retinitis pigmentosa, and 27 (57%) were male. Through the first 12 months postimplantation, 23 patients (49%) experienced 51 nonserious adverse events and 12 (26%) experienced 13 serious adverse events (SAEs), 9 of which were judged to be related to the Argus II, and 4 of which were judged to be related to the procedure. The most common SAE was conjunctival erosion, reported in 4 patients. No significance testing was done for group analysis for the SL or direction-of-motion tests. When averaged across the group, patients' accuracy on the SL test, but not on the direction-of-motion test, appeared better when the Argus II was on than when it was switched off. For GVA, more patients at each point in time achieved the 2.9 GVA cutoff in the implanted eye when the Argus II was on compared with it switched off.

CONCLUSIONS AND RELEVANCE Safety and visual function outcomes in this clinical practice setting cohort of patients with Argus II implants were consistent with previously reported results. Longer follow-up of these patients and data from additional patients are required to better outline the risks and benefits of this approach to addressing blindness secondary to severe-to-profound outer retinal degeneration.

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Supplemental content

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Nearly 1.5 million older Americans have low vision (best-corrected visual acuity in the eye with worse vision, <20/60) and approximately 1 million are blind (best-corrected visual acuity,<20/200).[1] The consequences of visual impairment on activities of daily living can be substantial. In a study examining the association of low vision with health-related quality of life, individuals with low vision had more difficulties completing activities of daily living compared with an age-matched reference population, as well as reference populations with specific chronic conditions, including asthma, migraine, and heart disease.[2] Moreover, visual impairment may also be associated with worse mental well-being. A study with more than 5000 blind individuals found that they were more likely to have mental health disorders than age- and sex-matched control participants, including depression, anxiety, and alcohol abuse.[3]

Investigators have explored a wide array of approaches to mitigate the devastating effects of blindness, including gene therapy,[4] stem cell transplant,[5] and electronic neural ocular implants, but only the last strategy has been commercialized, as retinal prostheses. In 2011, the Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc) became the first retinal prosthesis to receive the CE Mark to be approved for use in the European Economic Area. This approval was based on safety data and visual function of patients with retinitis pigmentosa (a group of inherited ocular disorders that, in the most severe forms, is characterized by progressive and irreversible vision loss)[6] who received the Argus II implant as part of a phase 1/2 feasibility study. At 1 year postimplantation, 14 of 30 patients (47%) scored 2.9 logMAR or better on grating visual acuity (GVA) with the system on in the implanted eye; none of these patients had scored 2.9 logMAR in the same eye at baseline.[7] The Argus II is approved for patients with severe to profound outer retinal degeneration who meet the following criteria: (1) 25 years or older; (2) some or no residual light perception in both eyes (if the patient has no residual light perception in either eye, the retina must be able to respond to electrical stimulation); and (3) history of useful form vision.[8] In addition, Argus II is one of the few implants that have received positive CE certification. This device is approved for use in the European Economic Area, in Canada, in the United States, and several other countries.

The current multicenter, prospective, case series evaluated the postapproval outcomes of the Argus II Retinal Prosthesis System. The objectives of this study were, through the collection of postapproval surveillance data for this retinal prosthesis system, to monitor its safety and its associations with visual function.

Key Points

Question What are the safety and visual outcomes associated with the Argus II Retinal Prosthesis System in a postapproval cohort of patients?

Findings In the first year of this postapproval study of 47 adults with Argus II implants, 49% experienced 51 nonserious adverse events and 26% experienced 13 serious adverse events, 9 of which were judged to be device related. On average, patients performed better on the square localization test and grating visual acuity in the implanted eye when the device was on than with it switched off.

Meaning Safety and visual function outcomes in this clinical practice setting cohort of patients with Argus II implantations were consistent with previously reported results.

Methods

Study Design

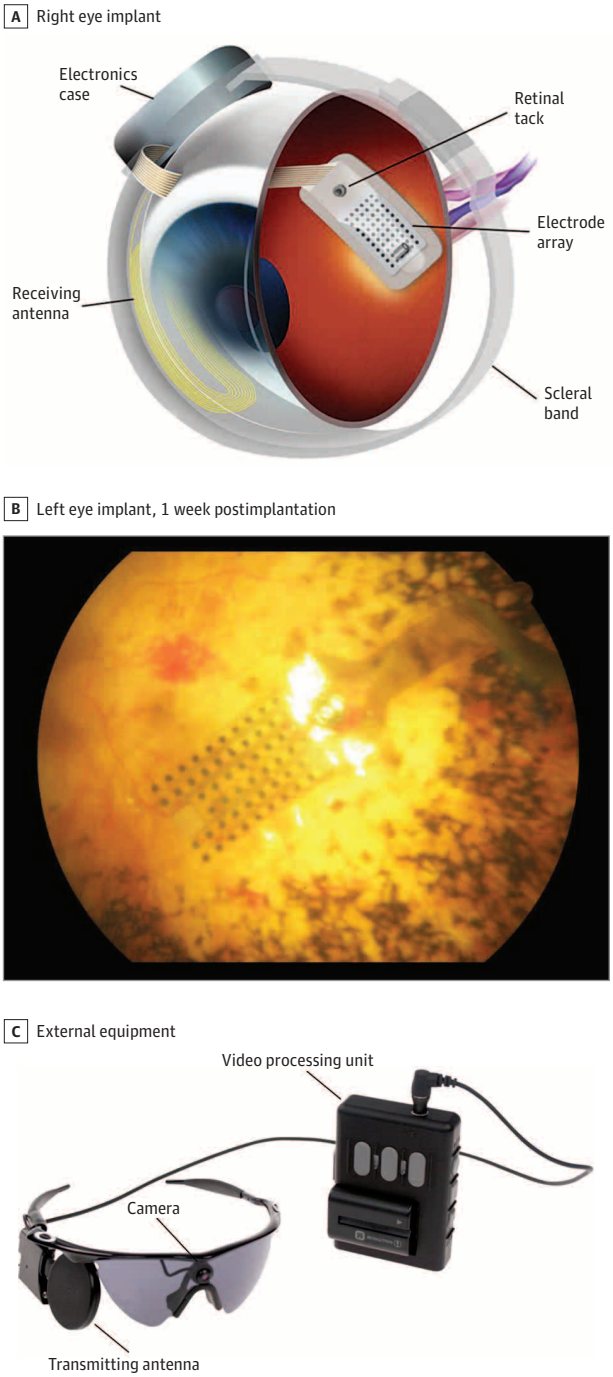
This was a multicenter, postapproval clinical trial of adult blind patients with severe-to-profound outer retinal degeneration (excluding age-related macular degeneration [AMD]) with a history of usable vision and either some residual light perception or retinal response to electrical stimulation. Data for this report were collected between December 2, 2011, and September 30, 2017. At the baseline visit, which took place between 7 and 21 days after surgical implantation of the Argus II, patient history data were collected and the following tests were performed: eye examination; medical evaluation, ocular imaging (if scans taken fewer than 120 days before implantation were not available), and tests of residual vision (if tests administered fewer than 120 days before implantation were not available). The protocol was approved by the ethics committees at each of the 9 participating sites. The study was performed in compliance with the ethical principles of the 1996 version of the Declaration of Helsinki[9] and the International Conference on Harmonisation Good Clinical Practice.[10] Patients provided written informed consent at the baseline visit.

Patients returned for additional visits during which the following assessments were performed: eye examination, medical evaluation; retinal photography; optical coherence tomography[11]; ultrasonographic B-scan; photographic flash test; array scanning, which tests functionality of the device and sensitivity of the retina's response to electrical stimulation; visual function tests (square localization [SL], direction of motion, GVA); and adverse event (AE) collection.

Participants

Patients from 9 sites throughout Germany and Italy who were already planning to receive the Argus II implant were recruited by investigators to participate in this study. Inclusion criteria included age 25 years or older, severe to profound outer retinal degeneration, some residual light perception or the ability of the retina to respond to electrical stimulation, history of useful form vision, the absence of nonophthalmic serious adverse events (SAEs) at the baseline visit, and surgical implantation of Argus II 7 to 21 days before study enrollment. Key exclusion criteria included AMD, ocular conditions that could prevent successful implantation or function of the Argus II or that could prevent adequate healing from surgery, ocular conditions other than cataracts that prevent adequate visualization of the inner structures of the eye, predisposition to eye rubbing, and pregnancy or desire to become pregnant during the course of the study.

Figure 1. Argus II Retinal Prosthesis System



A, Conceptual illustration of a right eye implant. B, Fundus photograph of a left eye implant at 1 week postimplantation. C, Argus II external equipment.

Preenrollment Implantation

One to 3 weeks before enrollment, patients underwent surgical implantation of the Argus II Retinal Prosthesis System. The Argus II is designed to provide visual function to individuals with severe to profound vision loss due to outer retinal degeneration. It consists of implanted and external components. The implant is an epiretinal prosthesis that includes a receiver, electronics, and an electrode array that is surgically implanted in and around the eye (**Figure 1**). The array is attached to the retina over the macula with a tack. The external equipment includes glasses, the Argus II Video Processing Unit (VPU), and a cable. The glasses include a miniature video camera, which captures video images, and a coil that sends data and stimulation commands to the implant. The VPU, which is worn on the body, converts the video images into stimulation commands. The cable connects the glasses to the VPU. The Argus II Clinician Programming System is used in the clinic to test and program the Argus II Implant and external equipment.

Study End Points

The primary end point of this study was the nature and rate of AEs. Secondary end points were all related to visual function, as measured by the SL, direction of motion, and GVA tests.

Statistical Methods

This single-arm trial was designed to evaluate the safety and performance of the Argus II Retinal Prosthesis System. Data on AEs were collected throughout the study beginning with the day of surgery. For several performance measures, patients served in 3 ways as their own control: comparisons were performed, where applicable, between the Argus II System turned on and off, between implanted eyes and fellow eyes, and between presurgery and postsurgery performance. All patients with follow-up data after the baseline visit who had reached at least 12 months postimplantation were included in the analyses.

Descriptive summaries were provided for all data. Where testing was conducted with the system on and off, comparison was made between participant performances under both conditions. Where testing was conducted with the implanted and nonimplanted eyes separately, comparison was executed between participant performances using each eye. Where data were collected for testing both before surgery and after surgery, comparison was carried out between participant performances at each point. Significance testing for visual function tests was performed within individuals, with 2-tailed t tests assuming unequal variances within individuals. Statistical calculations were performed with Microsoft Excel 2013 (Microsoft).

This interim analysis was performed to evaluate th study results when at least 30 participants completed a minimum of 1 year of follow-up. Because the objective of this study was to actively monitor the safety of the Argus II in the clinical practice setting, the target sample size of 60 (which was expanded from the original target of 45) approximates as closely as possible the number of participants receiving the device, doubling the premarket approval experience with the device, which had a sample size of 30. This report describes the interim analysis focused on safety and visual function of the 47 patients with results up to 12 months postimplantation.

Table 1. Patient Demographic, Ocular, and Surgical Characteristics

Characteristic	Argus II (n = 47), No. (%)
Sex	
Male	27 (57)
Female	20 (43)
Age, y	
Mean (SD) [range]	56 (12) [31-78]
Diagnosis	
Retinitis pigmentosa	37 (79)
Nonsyndromic retinitis pigmentosa	33 (70)
Usher syndrome	4 (9)
Rod/cone dystrophy	1 (2)
Choroideremia	1 (2)
Missing diagnosis	8 (17)
Axial length	
Mean (SD) [range], mm	23.5 (1.3) [20.5-25.9]
Posterior coats thickness of the implant eye, mm	
No.	31
Mean (SD) [range]	1.4 (0.4) [0.5-2.0]
Implanted eye	
Left eye	19 (40)
Right eye	28 (60)
Surgery duration	
Mean (SD) [range], h:min	2:47 (0:48) [1:32-5:00]

Results

Participant Characteristics and Flow

Among the 47 patients enrolled, mean (SD) age was 56 (12) years and 27 (57%) were male. The total of 47 patients enrolled across 9 German and Italian sites accounts for 78% of the 60-patient target enrollment. Surgical implantation of the Argus II took a mean of 2 hours 47 minutes (**Table 1**). Thirty-seven (79%) of the patients had retinitis pigmentosa. Patients included in this analysis had worn the implant for a mean (SD) of 3.5 (1.5) years, with a range of 0.5 years to 5.8 years. This includes 1 patient who withdrew from the study after 3 months and subsequently died 6 months after receiving the implant. As of the time of analysis, the sum of implant duration among all participants was 162.4 patient-years. As of September 30, 2017, 26 patients had completed the study, 10 were still monitored, 9 withdrew early, and 2 had the device explanted before study completion. One patient (included in the 26 patients completing the study) had the device explanted because of device failure (ie, a progressive inability to establish radiofrequency link with the implant) and underwent reimplantation of the device in the same eye, concluding the study with the second implant. Reasons for withdrawal were lost to follow-up (n = 4), refusal to use device or travel to the clinic (n = 4), and planning to become pregnant (n = 1).

Safety

A total of 23 patients (49%) experienced 51 nonserious AEs through the first 12 months postimplantation (**Table 2**).

Table 2. Nonserious Adverse Events Through 12 Months Postimplantation

Adverse Event	Patients With Adverse Event (n = 47), No. (%)
Ocular	
Ocular pain	6 (13)
Conjunctival irritation	3 (6)
Retinoschisis	3 (6)
Ocular inflammation	3 (6)
Suture irritation	2 (4)
Irregular pupil	2 (4)
Subconjunctival hemorrhage	2 (4)
High IOP	2 (4)
Retinal tear	2 (4)
Vitreous hemorrhage	2 (4)
Decrease in light perception	2 (4)
Eyelid inflammation	1 (2)
Corneal edema	1 (2)
Corneal epithelial defect	1 (2)
Corneal opacity	1 (2)
Foreign body sensation	1 (2)
Conjunctival congestion	1 (2)
Conjunctival erosion	1 (2)
Infectious conjunctivitis	1 (2)
Rubeosis iridis	1 (2)
Episcleritis	1 (2)
Anterior chamber inflammation	1 (2)
Uveitis anterior	1 (2)
Elective revision surgery	1 (2)
Nonocular	
Headache	2 (4)
Nausea/vomiting	2 (4)
Syncope	2 (4)
Syncope and vomiting	1 (2)
Vertigo	1 (2)
Skin irritation	1 (2)

Abbreviations: AE, adverse event; IOP, intraocular pressure.

Table 3. Serious Adverse Events Through 12 Months After Implant

Serious Adverse Event	Patients With Serious Adverse Event (n = 47), No. (%)
Conjunctival erosion	4 (9)
Hypotony	2 (4)
Explant	2 (4)
Episcleritis	1 (2)
Inflammation-ocular	1 (2)
Retinal detachment	1 (2)
Retinal detachment-rhegmatogenous	1 (2)
Retinal detachment-tractional	1 (2)

Twelve patients (26%) experienced 13 device- or procedure-related SAEs during the same time period (**Table 3**). The most common SAE was conjunctival erosion, experienced by 4 patients. The second-most common SAE was retinal detachment (RD) when combining unspecified RD type,

rhegmatogenous, and tractional (1 patient each, for a total of 3). Hypotony and explantation were experienced by 2 patients each. One patient underwent explantation of the Argus II owing to device failure and the other owing to ocular pain. Nine of the 13 SAEs were judged by the investigator to be related to the Argus II, with the remaining 4 SAEs judged to be procedure related. Most SAEs were resolved; 1 patient had an ongoing SAE at the cutoff time for data acquisition for the present article (hypotony, with a duration of 8 months) and another patient had an SAE (rhegmatogenous retinal detachment) that was deemed permanent by the investigator and the independent medical safety monitor.

Visual Function

The number of patients for whom data were available differed across points in time for each of the visual function tests, owing to missed visits and technical issues related to data capture. Number of participants are presented at each point in time in each of the figures displaying visual function test results (**Figure 2**) (eFigures 1-3 in the Supplement).

Square Localization

The SL test measures the patient's accuracy at locating a white square on a black computer screen across a total of 40 trials. Using binocular vision, patients took this test twice at each point in time, once with the Argus II on and once with it off. When averaged across the group, patients' accuracy at localizing the square appeared better when the Argus II was on than when it was off (Figure 2A). This was true at each postimplant point in time.

No significance testing was performed for group analysis for the SL test. When analyzed individually, 16 of 35 patients showed a significant benefit from having the Argus II switched on at the 12-month visit when performing SL (2-tailed *t* test assuming unequal variances, $P < .05$) (eFigure 1 in the Supplement). Of the remaining 19 patients, 15 showed no significant difference between on and off and 4 showed a significant benefit from having the Argus II off.

Direction of Motion

The direction of motion test measures accuracy in determining the direction of an object moving in the visual field across a total of 80 trials. Using binocular vision, patients took this test twice at each point in time, once with the Argus II on and once with it off. When averaged over the group, patients' accuracy at identifying the direction of movement was not substantially improved at any point in time when the Argus II was on compared with it switched off (Figure 2B).

No significance testing was performed for group analysis for the direction-of-motion test. Twelve of 34 patients individually showed a significant benefit from having the Argus II on at the 12-month visit when performing direction of motion (2-tailed *t* test assuming unequal variances, $P < .05$) (eFigure 2 in the Supplement). Of the remaining 22 patients, 14 showed no significant difference between on and off and 8 showed a significant benefit from having the Argus II off.

Grating Visual Acuity

The GVA is an adaptive, forced-choice test of up to 95 trials in which patients report the orientation of black and white bars presented in 1 of 4 orientations. Using a single eye for each test, participants took this test 3 times at each point in time, once for the study eye with the Argus II on, once for the study eye with it off, and once for the fellow eye (with the Argus II off). At each point in time, more patients had measurable acuity at or better than 2.9 logMAR in the implanted eye when the Argus II was on than with it switched off (Figure 2C). With the system off, more patients measured 2.9 logMAR or better acuity in the fellow eye than in the implanted eye, indicating that the Argus II was implanted in the eye with worse vision, as recommended by the manufacturer.

Data Sets

Baseline data from these visual function tests were incomplete, owing to technical issues related to data capture. To determine whether this fact substantially altered the outcomes presented above, results are presented in eFigure 3 in the Supplement using data at each point in time restricted to patients with available baseline data. This assessment showed similar results to those reported in the overall population, except the difference between on performance and off performance was greater for SL and direction of motion (eFigure 3A and 3B in the Supplement) than shown in the entire data set (Figure 2A and B), and no patients in this data subset scored 2.9 logMAR or better on GVA with the system off in the study eye (eFigure 3C in the Supplement).

Discussion

Patients in this clinical practice setting study had had the Argus II for a mean (range) of 3.5 (0.5-5.8) years at the time of this analysis, and these patients will continue to be tracked for 3 years postimplantation. One device failed during the study.

The safety data from this study (13 SAEs among 47 enrolled patients) were generally similar to 1-year safety results from the Argus II clinical trial, which reported 18 SAEs among 30 enrolled patients.[12] Three SAEs were identified in the postmarket study that were not seen in the premarket study: episcleritis, explantation, and ocular inflammation. (However, 1 explantation did occur in the premarket study before 3 years postimplantation[12]; and scleritis and ocular inflammation were both reported as nonserious events according to online supplemental material.) However, 8 SAEs reported in the premarket population within 1 year of implantation[12] were not seen in this postapproval data set, including conjunctival dehiscence, corneal melt, corneal opacity, infective keratitis, presumed endophthalmitis, retack of the array, retinal tear, and uveitis.

The lack of new AEs or SAEs (except those captured as serious rather than nonserious) compared with the preapp-

proval study reports, although the limited number of cases evaluated limits the ability to rule out safety problems that occur 5% or less often.[13] Overall, 26% of patients in the current postapproval study had 1 SAE within the first year, compared with 33% of patients from the Argus II clinical trial.

Across postimplantation points in time, as a group, patients in the current study were able to localize light better when the Argus II was on than with it switched off. On the more difficult tasks of determining the direction of motion, the difference in performance with the system on and off, on average, was smaller but still present. On GVA, the hardest task, more patients could perform at 2.9 logMAR or better with their implanted eye with the system on than with it off. As shown by the variability in performance of square localization and direction-of-motion tests when the system was on (eFigures 1 and 2 in the Supplement), the amount of visual function with the system varied across patients on these 2 assessments.

Variability in outcomes among patients is likely owing to many factors such as genetic subtype of retinal disease, age at time of implant, age at time of total vision loss, apposition of the array and retinal surface, and many others. Given the small sample size in this study, even when combined with the preapproval study, no clearly predictive factors have been identified to date, although the question has been and continues to be investigated.[14-17]

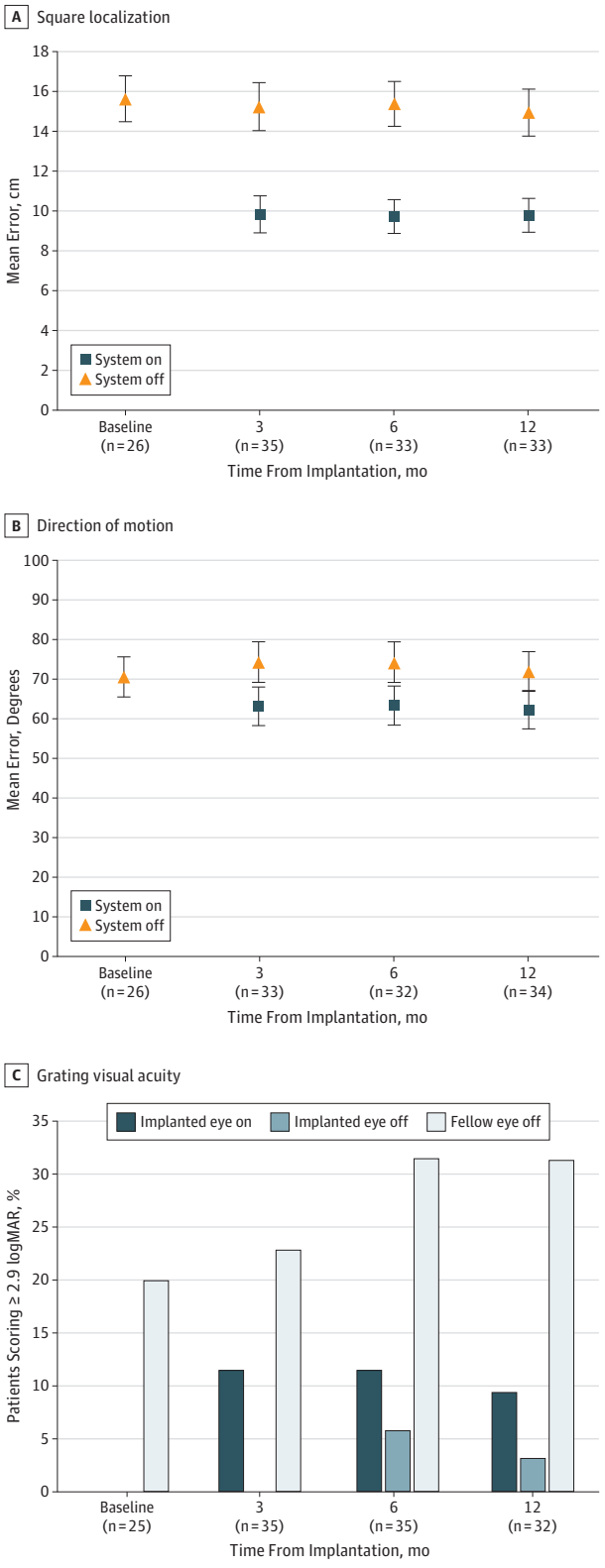
Strengths and Limitations

This postapproval study assessed safety and visual function outcomes in a group of blind patients receiving a commercial medical device in a clinical practice setting, rather than among a group of participants volunteering for an experimental treatment. Strengths of this study include the ability to turn the Argus II on and off, which allows within-subject control data to be collected, unlike in most surveillance studies. Weaknesses and limitations include the small sample size, enrolling only 47 patients to date, which limits the ability to identify additional AEs that occur in 5% or fewer patients.[13] The lack of ability to mask participants to device condition (on or off) owing to the nature of the device (eg, the audio and visual prompts that occur when the system is on) also limits our ability to interpret visual function improvements. Finally, although these computerized visual function tests allow for objective measurement of visual function, they do not provide a clear assessment of clinically meaningful benefit for each patient.

Conclusions

The efficacy and safety data presented in this postapproval study of the Argus II Retinal Prosthesis System demonstrate that the Argus II provides improvements in visual functioning with no additional safety concerns identified since the preapproval study. Longer follow-up with these patients, records from additional patients, and data regarding activities of daily living and quality of life measures are warranted to further enlarge our knowledge on the risk-benefit profile of the Argus II implant.

Figure 2. Group Visual Function Test Results



A, Square localization test at 12 months postimplantation with the Argus II on and off. Points indicate mean error; bars indicate standard error. B, Direction of motion test at 12 months postimplantation with the Argus II on and off. Points indicate mean error; bars indicate standard error. C. Grating visual acuity.

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Author Contributions: Dr Dorn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Schellhase, Walter, Augustin, Kirchhof, Szurman, Richard, Greenberg, Dorn, Rizzo.
Acquisition, analysis, or interpretation of data: Schaffrath, Walter, Augustin, Chizzolini, Grisanti, Wiedemann, Szurman, Richard, Greenberg, Dorn, Parmeggiani.
Drafting of the manuscript: Augustin, Szurman, Richard, Dorn.
Critical revision of the manuscript for important intellectual content: Schaffrath, Schellhase, Walter, Chizzolini, Kirchhof, Grisanti, Wiedemann, Szurman, Richard, Greenberg, Dorn, Parmeggiani, Rizzo.
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Administrative, technical, or material support: Walter, Chizzolini, Grisanti, Wiedemann, Szurman, Richard, Greenberg, Parmeggiani.
Supervision: Schellhase, Walter, Augustin, Chizzolini, Szurman, Richard, Greenberg, Dorn, Rizzo.

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