ORIGINAL ARTICLE

Subretinal Photovoltaic Implant to Restore Vision in Geographic Atrophy Due to AMD

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ABSTRACT

BACKGROUND

Geographic atrophy due to age-related macular degeneration (AMD) is the leading cause of irreversible blindness and affects more than 5 million persons worldwide. No therapies to restore vision in such persons currently exist. The photovoltaic retina implant microarray (PRIMA) system combines a subretinal photovoltaic implant and glasses that project near-infrared light to the implant in order to restore sight to areas of central retinal atrophy.

METHODS

We conducted an open-label, multicenter, prospective, single-group, baseline-controlled clinical study in which the vision of participants with geographic atrophy and a visual acuity of at least 1.2 logMAR (logarithm of the minimum angle of resolution) was assessed with PRIMA glasses and without PRIMA glasses at 6 and 12 months. The primary end points were a clinically meaningful improvement in visual acuity (defined as ≥0.2 logMAR) from baseline to month 12 after implantation and the number and severity of serious adverse events related to the procedure or device through month 12.

RESULTS

A total of 38 participants received a PRIMA implant, of whom 32 were assessed at 12 months. Of the 6 participants who were not assessed, 3 had died, 1 had withdrawn, and 2 were unavailable for testing. Among the 32 participants who completed 12 months of follow-up, the PRIMA system led to a clinically meaningful improvement in visual acuity from baseline in 26 (81%; 95% confidence interval, 64 to 93; P<0.001). Using multiple imputation to account for the 6 participants with missing data, we estimated that 80% (95% CI, 66 to 94; P<0.001) of all participants would have had a clinically meaningful improvement at 12 months. A total of 26 serious adverse events occurred in 19 participants. Twenty-one of these events (81%) occurred within 2 months after surgery, of which 20 (95%) resolved within 2 months after onset. The mean natural peripheral visual acuity after implantation was equivalent to that at baseline.

CONCLUSIONS

In this study involving 38 participants with geographic atrophy due to AMD, the PRIMA system restored central vision and led to a significant improvement in visual acuity from baseline to month 12. (Funded by Science Corporation and the Moorfields National Institute for Health and Care Research Biomedical Research Centre; PRIMAvera ClinicalTrials.gov number, NCT04676854.)

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Age-related macular degeneration (AMD) is the most common cause of incurable blindness in older adults.[1,2] Geographic atrophy is an advanced stage of dry (nonexudative) AMD that leads to progressive, irreversible death of photoreceptors and retinal pigment epithelial cells, causing profound vision loss.[3] Geographic atrophy affects approximately 5 million persons worldwide and is responsible for approximately 20% of all cases of legal blindness in North America.[2-4]

The first therapies for geographic atrophy (pegcetacoplan and avacincaptad pegol) were designed to inhibit the complement cascade and slow disease progression. These treatments were recently approved in the United States, and intravitreal injections are needed every 1 or 2 months.[5-7] However, no approved therapies, investigational approaches, or cell therapies have led to a meaningful improvement in vision.[8-12]

In a healthy retina, photoreceptors transduce light into electrical signals, which are then processed by the inner retina and transmitted to the brain. In geographic atrophy, light is not transduced into electrical signals because of a loss of photoreceptors, which leads to an absolute scotoma (blind spot).[3] The photovoltaic retina implant microarray (PRIMA) neurostimulation system replaces the lost photoreceptors.[13]

The PRIMA implant, which has an area of 2 mm by 2 mm and a thickness of 30 μm, is a thin crystalline silicon array comprising 378 photovoltaic pixels that are each 100-μm wide.[14,15] The array is implanted subretinally within the atrophic lesion. A frame-mounted camera on the PRIMA glasses captures images and projects them, after processing, onto the implant with the use of near-infrared light (wavelength, 880 nm) (Fig. 1). The pixels in the implant convert near-infrared light into electrical pulses to stimulate retinal bipolar cells, which restores the flow of visual information.[14] Unlike a wired prosthesis, the photovoltaic nature of the implant enables wireless operation combined with a straightforward implantation technique.[16,17] The lenses in the PRIMA glasses are transparent, so participants have natural vision and prosthetic central vision simultaneously.[18]

After extensive preclinical testing,[18-20] a first-in-human clinical trial evaluated the feasibility of the PRIMA system in five participants with geographic atrophy due to AMD.[21] Although the primary end point of the feasibility trial was light perception with the implant, after optimization and training, three participants reliably recognized sequences of letters and had acuity closely matching the maximum resolution of 20/420 allowed by the pixel width (100 μm).[15] At 4 years, these three participants could read small fonts, with a mean Snellen visual acuity of 20/135.[21] We conducted the PRIMAvera study to assess the efficacy and safety of the PRIMA system in patients with geographic atrophy due to AMD.

Methods

Study Design and Oversight

PRIMAvera was an open-label, prospective, single-group, baseline-controlled, confirmatory clinical efficacy and safety study of the PRIMA system. The study was conducted at 17 clinical sites across five European countries. Full details about the study methods, including the surgical procedure and the training of participants regarding use of the PRIMA system, are provided in the Supplementary Appendix, available with the full text of the article at NEJM.org. The study was designed by Science Corporation with assistance from its advisory board and was approved by local ethics committees. Clinical authors conducted the study; data were analyzed by the clinical authors and staff at Science Corporation and were reviewed by the data and safety monitoring board. The first and last two authors, together with authors from Science Corporation, wrote the manuscript. All the authors reviewed and approved the manuscript for submission. The last two authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol (available at NEJM.org).

Participants

Recruitment activities included chart review, referral by health care providers, and community outreach. Participants were eligible for inclusion if they were 60 years of age or older, had a diagnosis of geographic atrophy due to AMD in both eyes as confirmed on fundus autofluorescence imaging and optical coherence tomography (OCT), had a visual acuity of at least 1.2 logMAR (logarithm of the minimum angle of resolution [smaller values indicate better visual acuity]; Snellen equivalent, 20/320) in the study eye, and had atrophy involving the fovea of the study eye that was larger than the implant (i.e., >2.4 mm in diameter).

All the participants provided written informed consent.

END POINTS

The primary efficacy end point was a clinically meaningful improvement in visual acuity from baseline to month 12 after implantation. Clinically meaningful improvement was defined as an improvement (i.e., decrease) of at least 0.2 logMAR (corresponding to an increase of ≥10 letters) on a standard Early Treatment Diabetic Retinopathy Study chart.[15,21-24] Secondary efficacy end points included a clinically meaningful improvement in visual acuity at 6 months, the mean improvement in visual acuity from baseline to months 6 and 12, visual impairment as assessed with the Impact of Vision Impairment (IVI) questionnaire at 6 and 12 months, and central visual perception (the ability to perceive light obtained with the PRIMA system in the central visual field) at 12 months as assessed with a central visual perception test.[25,26] The IVI questionnaire is used to assess vision-related quality of life with regard to reading and information access, mobility and independence, and emotional well-being as reported by the participant.

The primary safety end points were the number and severity of serious adverse events through month 12 after surgery that were considered by the data and safety monitoring board to be related to the procedure or device. Secondary safety end points were the number and severity of all adverse events related to the procedure or device, the change in the best-corrected natural visual acuity (defined as visual acuity as assessed without the PRIMA glasses) from baseline, and the percentage of compliant implantations (i.e., those in which the implant was placed in the subretinal space within the atrophy-associated scotoma) at week 4 after surgery. Additional follow-up is planned to occur for a period of up to 36 months after surgery.

ASSESSMENT OF VISUAL FUNCTION

An implant-resolution test was conducted after surgery in order to assess the maximum resolution provided by the PRIMA implant. The test assesses resolution independently of external factors such as zoom and image processing by displaying Landolt C optotypes directly onto the PRIMA glasses (i.e., without use of the camera).

We assessed the best-corrected visual acuity of the study eye with PRIMA glasses and without PRIMA glasses at months 6 and 12 after implantation. Participants could adjust the brightness and zoom levels at will.

After month 12, participants answered a 19-question survey regarding the home use of the PRIMA system. The questions assessed the integration of the PRIMA system into daily life and the effects of the system on the ability to perform various visual tasks.

STATISTICAL ANALYSIS

All the participants with an implant were included in the primary efficacy analyses. A binomial test was used to assess the percentage of participants with a clinically meaningful improvement in visual acuity (≥0.2 logMAR) from baseline to month 12 (primary efficacy end point) as compared with the null hypothesis that a primary efficacy end-point event would occur in 50% or fewer participants. Multiple imputation was used in the analysis of the primary efficacy end point in order to account for missing data at month 12; data from the analysis of observed data are also reported. Logit 95% confidence intervals were calculated in the multiple-imputation approach, and exact 95% confidence intervals were calculated in the analysis of observed data. A post hoc analysis with methods similar to those used in the primary efficacy end-point analyses was conducted to assess the percentage of participants with an improvement in visual acuity of at least 0.3 logMAR from baseline to month 12.

A sequential gatekeeping approach was used to compare the mean improvement in visual acuity from baseline to month 12 with the null hypotheses of a mean improvement of zero and a mean improvement of 0.2 logMAR, at a one-sided alpha level of 0.025. Visual acuity was analyzed according to three conditions: without PRIMA glasses, with PRIMA glasses, and participant's choice (the better visual acuity between the assessment without glasses and the assessment with glasses). Exact confidence intervals were calculated for secondary end points.

The data and safety monitoring board reviewed all serious adverse events and all adverse events that could potentially be related to the procedure or device. The primary safety analyses were conducted with the use of observed data without imputation and included all serious adverse events that were considered by the data and safety moni-

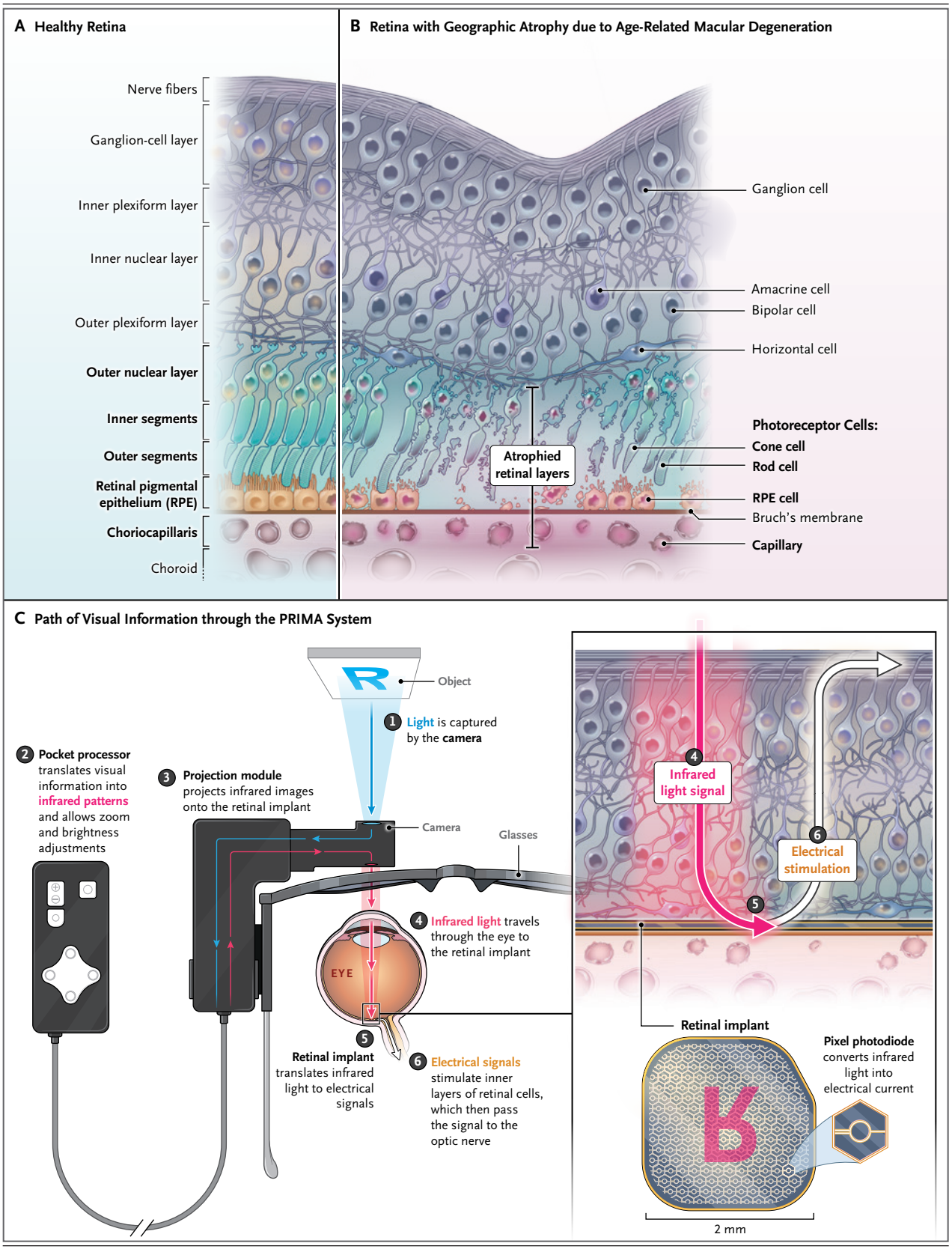
A Healthy Retina
Nerve fibers
Ganglion-cell layer
Inner plexiform layer
Inner nuclear layer
Outer plexiform layer
Outer nuclear layer
Inner segments
Outer segments
Retinal pigmental epithelium (RPE)
Choriocapillaris
Choroid
B Retina with Geographic Atrophy due to Age-Related Macular Degeneration
Ganglion cell
Amacrine cell
Bipolar cell
Horizontal cell
Atrophied retinal layers
Photoreceptor Cells:
Cone cell
Rod cell
RPE cell
Bruch's membrane
Capillary
C Path of Visual Information through the PRIMA System
Object
1 Light is captured by the camera
2 Pocket processor translates visual information into infrared patterns and allows zoom and brightness adjustments
3 Projection module projects infrared images onto the retinal implant
Camera
Glasses
4 Infrared light travels through the eye to the retinal implant
EYE
5 Retinal implant translates infrared light to electrical signals
6 Electrical signals stimulate inner layers of retinal cells, which then pass the signal to the optic nerve
4 Infrared light signal
6 Electrical stimulation
5
Retinal implant
Pixel photodiode converts infrared light into electrical current
2 mm

Figure 1 (facing page). The Photovoltaic Retina Implant Microarray (PRIMA) System.

Shown is the anatomy of a healthy retina (Panel A) and a retina with geographic atrophy due to age-related macular degeneration (Panel B). The PRIMA system (Panel C) combines a subretinal photovoltaic implant, a pocket processor, and glasses that project near-infrared light to the implant to restore sight to areas of central retinal atrophy. The camera captures light reflecting from an image (e.g., a letter R) and sends the visual information to the pocket processor. Processed information is then sent to the glasses and projected onto the implant by means of near-infrared light (wavelength 880 nm); the letter R on the implant is shown in red to indicate that the wavelength of the projected image differs from that of the light reflected by the original letter R. To achieve continuous, uninterrupted central visual perception, the projector operates at a frame rate of 30 Hz, and the processor adjusts perceptual brightness by controlling the pulse duration from 0.7 to 9.8 ms at a peak irradiance of 3.5 mW per square millimeter. The implant has an area of 2 mm by 2 mm and is composed of pixels with a width of 100 μm. Each pixel includes an active electrode in the center, a hexagonal return electrode mesh, and two photodiodes filling the space between the active and the return electrode. The photodiodes convert the near-infrared light into electrical current in order to stimulate the nearby inner retinal neurons, which process the electrical information in the retina. This information is then transferred via the optic nerve to the brain, where it is interpreted as a visual image.

toring board to be related to the procedure or device (as defined according to standard ISO 14155 of the International Organization for Standardization).

Analyses of secondary end points were not adjusted for multiplicity, and confidence intervals should not be used in place of hypothesis testing or to infer definitive treatment effects. All statistical analyses were performed with SAS software, version 9.4. Additional details about the statistical analysis plan are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

The PRIMA array was implanted in 38 participants. A total of 18 participants were men and 20 were women, and the mean (±SD) age was 78.9±6.4 years (Table S4). The participants were broadly representative of the worldwide population with geographic atrophy (Table S5).

A representative set of fundus and OCT images obtained before and after implantation is shown in Figure 2. At 12 months, 32 participants were available for primary efficacy evaluation (Fig. S1). Six participants were not assessed because of death (in 3 participants), withdrawal from the study (in 1), or unavailability for testing (in 2) (Table S6).

PROSTHETIC VISION

Of the 32 participants who were assessed with the central visual perception test at 12 months, 30 had central visual perception with the PRIMA system (see the Supplementary Appendix). Among the 33 participants who were assessed with the implant-resolution test at month 12, the mean visual acuity was 1.32±0.16 logMAR (Snellen equivalent, 20/417) (Table S7). This value matches the theoretical resolution achievable with the 100-μm-wide pixels in the PRIMA implant (1.32 logMAR) (see the Supplementary Appendix).

EFFICACY

At 12 months, 26 of 32 participants (81%; 95% confidence interval [CI], 64 to 93; P<0.001) had a clinically meaningful improvement in visual acuity (≥0.2 logMAR). Using multiple imputation with prespecified covariates to account for missing data from 6 participants in the analysis of the primary efficacy end point, we estimated that 80% (95% CI, 66 to 94) of all participants would have had a clinically meaningful improvement at 12 months (P<0.001) (Table 1).

The mean improvement in visual acuity at 12 months was 0.49 logMAR (95% CI, 0.35 to 0.63; range, −0.32 to 1.18) with PRIMA glasses and 0.51 logMAR (95% CI, 0.39 to 0.64; range, −0.04 to 1.18) with participant's choice; these findings corresponded to improvements of 24.5 and 25.5 letters, respectively (Fig. 3A). The analysis of the participant's choice condition at 12 months included four participants whose best visual acuity occurred without glasses; none of the four had a clinically meaningful improvement from baseline to month 12 (mean change from baseline, −0.01 logMAR; range, −0.04 to 0.02). The mean improvement in visual acuity at 12 months with participant's choice was significantly greater than the prespecified null hypotheses of 0 logMAR and 0.2 logMAR (P<0.001 by the sequential t-test for both comparisons) (Table S9). The maximum improvement at 12 months with the PRIMA glasses was 1.18 logMAR (59 letters) (Fig. 3B).

At 6 months, 20 of 35 participants with available data had an improvement of at least 0.2 logMAR. The mean improvement from baseline to month 6 was 0.32 logMAR (95% CI, 0.16 to 0.47) with PRIMA glasses and 0.38 logMAR (95% CI, 0.25 to 0.51) with participant's choice (Fig. 3A). Without PRIMA glasses, the change in visual acuity from baseline was 0.01 logMAR (95% CI, −0.04 to 0.06) at month 6 and 0.00 logMAR (95% CI, −0.05 to 0.04) at month 12.

A video showing use of the PRIMA system in vision-related activities is available at NEJM.org

Participants dynamically adjusted zoom settings (range, 1× to 12× original magnification) and brightness during assessment of visual acuity; Table S8 shows the maximum zoom level used by the participants. Figure S2 and Tables S10 and S11 show changes in visual acuity in individual participants and findings from other assessments of visual acuity, which included subgroup analyses of the mean change in visual acuity from baseline to month 12 according to the time since AMD diagnosis.

Digital-enhancement features applied to the camera feed, which included contrast, brightness, and zoom, helped participants see a wide range of visual stimuli. At 12 months, 84% of the participants (27 of 32) could read letters, numbers, and words with prosthetic vision at home (Video 1); 69% (22 of 32) reported medium-to-high user satisfaction with the PRIMA system. However, analyses of data from the IVI questionnaire did not indicate changes in behavior from baseline to months 6 or 12 (Table S12).

POST HOC ANALYSIS

After the primary analysis, we conducted a post hoc analysis using a threshold for improvement of at least 0.3 logMAR from baseline to month 12. In this analysis, 25 of 32 participants (78%;

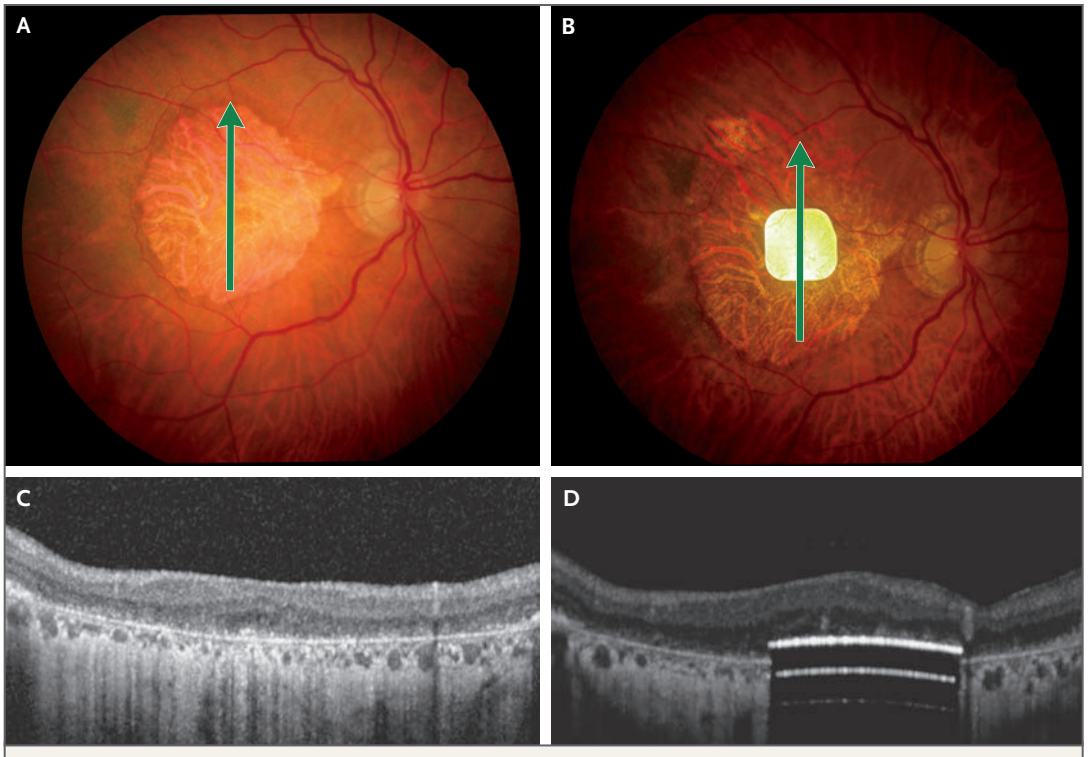

Figure 2. Retinal Imaging before and after Implantation.

Shown are images before and after implantation of the PRIMA photovoltaic array in a study participant's eye. The size of retinal atrophy was 21.49 mm^2 at baseline, and the array was implanted 5 years after the diagnosis of acute macular degeneration. Images obtained with color fundus photography show geographic atrophy before implantation (Panel A) and the subretinal implant 12 months after surgery (Panel B). Arrows indicate the direction of optical coherence tomographic scanning. Also shown are optical coherence tomographic images of the degenerated retina before implantation (Panel C) and the implant under the degenerated retina in proximity to the inner nuclear layer at month 12 (Panel D). The implant is not transparent and therefore creates a shadow, which covers the underlying choroid. The multiple lines below the implant surface are artifacts due to multiple reflections within the implant.

Table 1. Efficacy Analyses.*

Variable	Primary Analyses: ≥0.2 logMAR Improvement		Post Hoc Analyses: ≥0.3 logMAR Improvement	
	no. with event/ total no.	*% with event (95% CI)*	*no. with event/ total no.*	*% with event (95% CI)*
Analysis of observed data†	26/32	81 (64–93)‡	25/32	78 (60–91)
Multiple imputation§	NA	80 (66–94)‡	NA	77 (62–92)

* A binomial test was used to assess the percentage of participants with a clinically meaningful improvement in visual acuity from baseline to month 12 (primary efficacy end point) as compared with the null hypothesis that a primary efficacy end-point event would occur in 50% or fewer participants. Clinically meaningful improvement was defined as an improvement (i.e., decrease) of at least 0.2 logMAR (logarithm of the minimum angle of resolution; corresponding to an increase of ≥10 letters) on a standard Early Treatment Diabetic Retinopathy Study chart. Multiple imputation was used in the analysis of the primary efficacy end point in order to account for missing data at month 12; data from the analysis of observed data are also reported. A post hoc analysis with methods similar to those used in the primary efficacy end-point analysis was conducted to assess the percentage of participants with an improvement in visual acuity of at least 0.3 logMAR from baseline to month 12. NA denotes not applicable.

† The analyses included 32 participants with nonmissing data at 12 months. Exact 95% confidence intervals were computed in the primary and post hoc analyses.

‡ $P<0.001$ for comparison with the null hypothesis.

§ The analyses included 38 participants, of whom 6 had missing data at month 12. The missing data were estimated with a multiple-imputation approach, which does not provide the exact percentage of participants with an end-point event but rather an estimated percentage computed over 100 imputed datasets. Logit 95% confidence intervals were computed in the primary and post hoc analyses.

95% CI, 60 to 91) had an improvement of at least 0.3 logMAR (Table 1).

SAFETY

Twenty-six serious adverse events considered by the data and safety monitoring board to be related to the device or the procedure occurred in 19 participants within 12 months after surgery (Table 2). All serious adverse events were related to the implantation procedure alone or to the procedure and the device; no serious adverse event was related to the device alone. A total of 21 serious adverse events (81%) occurred within 2 months after surgery, of which 20 (95%) resolved within 2 months after onset. Twenty-two serious adverse events (85%) were classified as mild or moderate in severity, and 4 (15%) were classified as severe (full-thickness macular hole, ocular hypertension, retinal detachment, and proliferative vitreoretinopathy).

The most common serious adverse event was ocular hypertension (six events; 23%); onset occurred between day 1 and week 3 after implantation, and all cases resolved. Peripheral retinal breaks occurred in five participants; all events were treated intraoperatively, and none resulted in rhegmatogenous retinal detachment. Three participants had a subretinal hemorrhage during implantation; the hemorrhage stopped spontaneously or after an increase in infusion pressure. One participant had recurrent subretinal hemorrhage associated with choroidal neovascularization at 9 months. This participant and another participant, who also had choroidal neovascularization, were treated with intravitreal anti–vascular endothelial growth factor (VEGF). Three serious adverse events were full-thickness macular holes; two of these events led to the repositioning of the implant away from the hole in order to improve the functionality of the device. Choroidal fold, retinal detachment, and proliferative vitreoretinopathy occurred in the same participant but were successfully treated with surgery and silicone oil tamponade.

OCT and fundus photography showed that the inner retinal structure in the atrophic area did not appear to have been altered by the subretinal placement of the implant (Fig. 2). The mean area of atrophy among the study eyes increased by 8.5 mm^2 from baseline to 12 months, as compared with an increase of 2.5 mm^2 in eyes without the implant; in the study eyes, the increase was attributed to atrophy associated with subretinal surgery, including retinotomy and bleb formation. Without the glasses, the mean visual acuity among the study eyes was similar at baseline and month 12 (Fig. 3). Among the 32 participants who were evaluated at 12 months, the

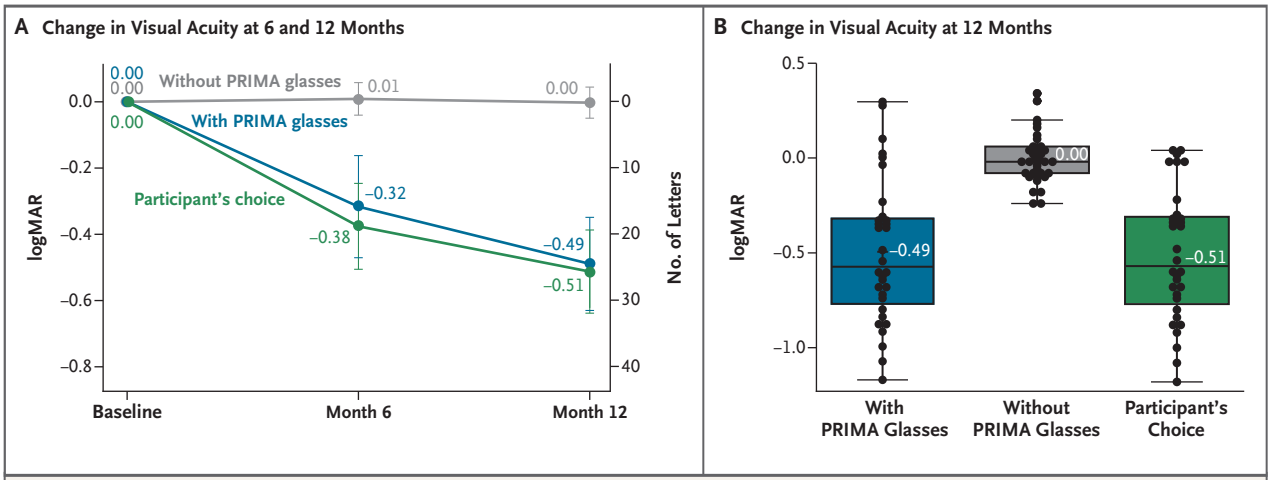

Figure 3. Change from Baseline in Visual Acuity.

The best-corrected visual acuity without PRIMA glasses and with PRIMA glasses was assessed at months 6 and 12 after implantation of the PRIMA photovoltaic array. The mean change from baseline to months 6 and 12 was analyzed according to three conditions: with PRIMA glasses (blue line), without PRIMA glasses (gray line), and participant's choice (the better visual acuity between the assessment without glasses and the assessment with glasses; green line) (Panel A). Mean changes are expressed as logMAR (logarithm of the minimum angle of resolution) values (y axis on left) and number of letters (y axis on right) on a standard Early Treatment Diabetic Retinopathy Study chart. Negative logMAR values indicate improvements from baseline, and the I bars indicate exact 95% confidence intervals. The confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing or to infer definitive treatment effects. Also shown (Panel B) are the changes from baseline to month 12 in visual acuity with PRIMA glasses (blue), without PRIMA glasses (gray), and with participant's choice (green) overall and in individual participants. Negative logMAR values indicate improvements from baseline. In the box-and-whisker plots, the white numbers indicate the mean, the center lines the median, the top and bottom of the boxes the interquartile range, the I bars 1.5 times the interquartile range, and the black dots values for individual participants.

PRIMA system led to an improvement of at least 0.2 logMAR at month 12 in 11 of 14 (79%) with serious adverse events and in 15 of 18 (83%) without serious adverse events.

All serious adverse events that were related to the procedure or device were prespecified in the risk analysis, and none were life-threatening. On review of these and other data obtained in this study, the data and safety monitoring board concluded that the benefits of the PRIMA system outweighed the risks of implantation.

DISCUSSION

In the current study, the PRIMA system resulted in meaningful improvement in vision in a representative sample of participants with profound vision loss due to AMD-induced geographic atrophy with foveal involvement.[27] Visual acuity improved from baseline to month 12 after implantation by at least 0.2 logMAR (≥10 letters) in 81% of the participants and by at least 0.3 logMAR (≥15 letters) in 78% with the PRIMA system. The mean improvement from baseline at 12 months was 0.51 logMAR (25.5 letters), and the maximum improvement was 1.18 logMAR (59 letters). Moreover, 84% of the participants reported using the device at home for reading letters, numbers, or words. With the use of digital enhancements offered by the PRIMA glasses, such as the zoom function, these participants were able to read fonts smaller (Snellen equivalent, up to 20/42) than the theoretical resolution achievable with the 100-μm pixels (Snellen equivalent, approximately 20/400).

Other assistive devices for low vision, such as extraocular magnifiers or implantable telescopes, enlarge images to enable use of the retina beyond the edges of atrophy,[24,28] typically lead to a mean improvement in visual acuity of 0.24 logMAR,[24] and magnify the full visual field. In contrast, the PRIMA system restores vision to the area of scotoma and only magnifies prosthetic central vision, leaving natural peripheral vision unaffected.[14] The mean native resolution (i.e., the resolution independent of external factors) among the participants as assessed with the implant-resolution test

was similar to the theoretical resolution achievable with the PRIMA implant (approximately 1.3 logMAR), and the ability to zoom, enhance contrast, and make other modifications to the image allowed the participants to improve visual acuity beyond this resolution.

Prosthetic vision was previously attempted with the epiretinal implant Argus II,[16,17] the subretinal implant Alpha IMS,[29] and a 44-channel suprachoroidal implant.[30] The resolution with Argus II was limited because it had a large center-to-center distance between electrodes (maximum reported visual acuity, 1.8 logMAR)[31] and stimulated axons from remote retinal ganglion cells, which resulted in a distorted retinotopic map.[32,33] Suprachoroidal implants are relatively far from the retinal neurons and therefore provide a resolution of approximately 3.0 logMAR, which is lower than that with epiretinal implants.[30]

With the PRIMA system, eye movement as opposed to head movement[23] can be used to reorient the implant. Eye movement improves resolution beyond the theoretical resolution achievable by the 100-μm pixels in the PRIMA implant[34-36]; this improvement is presumably due to methods similar to those of the super-resolution algorithms used in conventional cameras to obtain higher resolution than the camera pixel size allows.[37] Unlike epiretinal implants, the PRIMA implant stimulates bipolar cells rather than ganglia, which preserves features of inner retinal signal processing.[18,38]

Our data, collected over a period of 12 months, showed that the PRIMA array can be safely implanted under the atrophic macula and restore central vision while preserving residual natural peripheral vision. Our previous feasibility study involving five participants showed a stable retinal anatomy after implantation, with minimal decrease in the thickness of the inner retina over a period of 36 months, and a mean improvement in visual acuity of 0.64 logMAR (32 letters) from baseline to month 48.[21,39] The wireless design simplifies implantation and reduces the risk of surgical and postoperative adverse events as compared with wired retinal implants with permanent openings in the eye globe.[31] The PRIMA implant is thin (approximately half the height of a photoreceptor) and integrates with the retina without mechanical-fixation hardware, such as the retinal tacks used in some other retinal implants.[24]

The cases of subretinal hemorrhage and choroidal neovascularization in the current study are consistent with the complications associated with vitrectomy and subretinal surgery.[40,41] Choroidal neovascularization developed in two participants (5%) and was successfully treated with intravitreal anti-VEGF therapy on an as-needed basis. This condition can occur in geographic atrophy even without any intervention[5] and has also been observed in patients after retinal surgical procedures. The incidence of choroidal neovascularization was 16% among dry eyes with AMD at 2.6 years after treatment with vitrectomy.[42] The implantation of a subretinal prosthesis may benefit from advanced intraoperative imaging techniques. In several study eyes, the increased atrophy occurred in areas of retinal bleb formation and retinotomy. Natural peripheral visual acuity after implantation did not differ substantially from that at baseline. The current study was not powered to assess the change from baseline in visual impairment as assessed with the IVI questionnaire, and the questionnaire may be insufficiently sensitive to detect such a change in this cohort with extremely low vision.

The data at 12 months in this clinical study showed that the PRIMA subretinal implant restored meaningful central vision in persons with geographic atrophy due to AMD, thus enabling the performance of visual tasks such as reading

Table 2. Serious Adverse Events.*

Event	Participants (N=38)	Serious Adverse Events
	no. (%)	*no.*
Ocular hypertension	6 (16)	6
Peripheral retinal break	5 (13)	5
Macular hole	3 (8)	3
Subretinal hemorrhage	3 (8)	4
Choroidal neovascularization	2 (5)	2
Choroidal hemorrhage	1 (3)	1
Choroidal fold	1 (3)	1
Proliferative vitreoretinopathy	1 (3)	1
Retinal detachment	1 (3)	1
Retinal hemorrhage	1 (3)	1
Thrombophlebitis	1 (3)	1

* Shown are serious adverse events through month 12 after surgery that were considered by the data and safety monitoring board to be related to the procedure or device. A total of 26 serious adverse events occurred in 19 participants.

and writing. Although no retinal implants have been explanted in humans, the wireless design allows for replacement with higher resolution next-generation implants[43,44] or implantation of multiple arrays in a tiled pattern at the atrophic area with minimal incision.[45]

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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