CONFIDENTIAL

SECOND SIGHT MEDICAL PRODUCTS, INC.
ARGUS® II RETINAL PROSTHESIS SYSTEM

H110002

SPONSOR EXECUTIVE SUMMARY

PREPARED FOR THE
SEPTEMBER 28, 2012 MEETING OF THE
OPHTHALMIC DEVICES ADVISORY PANEL

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Abbreviated Terms and Definitions

Term or Acronym	Full Term or Definition
AAMI	Association for the Advancement of Medical Instrumentation
ADL	Activities of Daily Living
AE	Adverse event
ANSI	American National Standards Institute
BaGA	Basic Grating Acuity Test
BaLM	Basic Assessment of Light and Motion
BLP	Bare light perception
CRAO	Central Retinal Artery Occlusion
CRVO	Central Retinal Vein Occlusion
CT	Computer Tomography
EC	Ethics Committee
EER	Electrically Evoked Response
EMEA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EtO	Ethylene Oxide
FDA	Food and Drug Administration (U.S.)
FLORA	Functional Low-Vision Observer Rated Assessment
FrACT	Freiburg Visual Acuity and Contrast Test
FST	Full-field Stimulus Threshold
Functional Vision	How the patient performs in vision-related activities of daily living
GLP	Good Laboratory Practice
GDD	Glaucoma drainage device

Term or Acronym	Full Term or Definition
HDE	Humanitarian Device Exemption
HM	Hand motion
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
IMSM	Independent Medical Safety Monitor
IOL	Intraocular lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ISO	International Organization for Standardization
logMAR	log of the Minimum Angle of Resolution
MRI	Magnetic resonance imaging
N/A	Not applicable
NLP	No light perception
Percept	Perceived form of light in response to electrical stimulation
RD	Retinal detachment
RF	Radio frequency
RP	Retinitis Pigmentosa
SAE	Serious adverse event
SE	Standard Error
SMDA	Safe Medical Devices Act
USP	United States Pharmacopeial Convention
VCF	Video Configuration File: This is the program downloaded onto the subject's Video Processing Unit that controls that converts the video image captured by the camera into stimulation commands.
VisQOL	Visual Quality of Life
Visual Function	How the eye, as an organ, works (e.g., visual acuity)
VPU	Video Processing Unit

OVERALL EXECUTIVE SUMMARY

Device Description and Intended Clinical Benefit

Second Sight Medical Products, Inc. is applying for Humanitarian Device Exemption (HDE) approval of the Argus® II Retinal Prosthesis System (Argus II System). This application has been assigned HDE# H110002. The Argus II System consists of an epiretinal implant that is fully implanted in and around the eye (cosmetically undetectable), a video camera mounted on a pair of glasses, and a control unit that is worn or carried by the patient. The system is intended to provide electrical stimulation of the retina to induce visual perception in blind patients. It is indicated for use in patients with severe to profound retinitis pigmentosa with bare or no light perception in both eyes.

The Argus II System provides visual information that can range, depending on the patient, from light detection to simple form detection. Patients are able to use this visual information to perform functional tasks (e.g., locating windows and doors, following lines in a cross walk), to allow them to feel more connected with others (e.g., seeing when a person approaches them or when someone walks away), and to simply enjoy visual perception again (e.g., seeing the changing light levels on a TV, tracking groups of players as they move around the field at an athletic event, being able to locate the moon, etc.). For people with bare or no light perception, even limited restoration of vision can make a significant difference in their lives.

Intended Patient Population

The Argus II System is intended for patients with severe to profound retinitis pigmentosa (RP) with bare or no light perception in both eyes. Retinitis pigmentosa is a rare, hereditary disease that causes progressive degeneration of photoreceptors and retinal pigment epithelium, leading to significant visual impairment and, in some cases, blindness. An estimated 1 in 3037 Americans suffers from retinitis pigmentosa (which equates to an incidence of 1,316 people/year)[1], and the incidence of people with *severe to profound* RP is significantly lower.

[1] This number was calculated assuming a US population of 303,763,031, based on a 2006 US Census Bureau estimate.

The need for treatments for RP is high, given the dramatic impact loss of vision can have on a person's life. In the United States, that need is currently not being met as there are no approved treatments for people with severe to profound retinitis pigmentosa . Numerous experimental research programs are currently underway to slow, stop or reverse the progress of RP, including gene therapy, tissue and cell transplants, and some pharmacologic neuroprotection therapies. However, these approaches so far have had fairly limited success in treating RP patients, some are intended for an extremely small segment of the RP population (e.g., gene therapy for a particular genetic subtype), and most are likely years away from obtaining regulatory approval.

Humanitarian Device

In 1990, with the passage of the Safe Medical Devices Act (SMDA), Congress and the President identified the need to encourage the discovery and use of devices intended to benefit patients with rare diseases. They recognized that for diseases and conditions affecting small populations, a device manufacturer's research and development costs could exceed its market returns, thereby creating an impediment to the development of such devices.[2] In the SMDA, Congress established a regulatory pathway, called the Humanitarian Device Exemption (HDE), which was intended to incentivize companies to develop treatments for rare diseases by reducing the regulatory burden of approving these devices.

Under the HDE regulation, a company must demonstrate that the device does not expose patients to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from using the device outweighs the risk of injury or illness from its use. To qualify for the HDE, a device must be used to treat or diagnose a disease or condition that manifests itself in fewer than 4,000 individuals per year in the United States, and there must be no alternative treatments available in the United States.

In May 2009, the FDA's Office of Orphan Product Development designated the Argus II System as a Humanitarian Use Device (HUD), qualifying it for the HDE approval pathway. The Argus II System was assigned HUD designation #09-0216.

History of Device Development

The Argus II System represents the culmination of over 20 years of research and development to design a retinal prosthesis that partially restores vision to individuals with severe to profound retinitis pigmentosa. This research was begun in the early 1990s by Eugene de Juan, MD, Mark Humayun, MD, PhD, Gislin Dagnelie, PhD, Robert Greenberg, MD, PhD and others at the Duke Eye Center at

[2] Federal Register, Vol. 61, No. 124, June 26, 1996, "Medical Devices; Humanitarian Use Devices."

Duke Medical Center (Durham, NC) and the Wilmer Eye Institute at The Johns Hopkins University (Baltimore, MD). These researchers tested the feasibility of directly stimulating the retina of RP patients to elicit a visual percept in series of acute tests performed in the operating room under local anesthesia.[3,4]

Following the success of these acute feasibility studies, Second Sight was founded in 1998 by philanthropists Alfred Mann and Sam Williams to create a retinal prosthesis that could be chronically implanted to partially restore vision to blind individuals. Second Sight, led by Robert Greenberg, MD, PhD, developed the first-generation retinal prosthesis called the Argus I (also referred to as the Argus 16). The Argus I System was developed as a "proof of concept" device intended to evaluate whether a fully-implantable, chronic epiretinal prosthesis could be safely implanted and elicit light percepts in implanted patients. The Argus I device was implanted in 6 subjects between 2002 and 2004. After implantation, all six subjects could detect light and saw percepts. Two of these subjects remain implanted and continue to use their devices today.[5,6,7]

Based on the success of the Argus I device, Second Sight began to develop the Argus II Retinal Prosthesis System (Argus II System), which was designed to be a commercial device. Second Sight submitted its initial Investigational Device Exemption (IDE) application to study the Argus II System in a clinical trial in December, 2005. The Argus II System is the subject of this HDE application.

To date, Second Sight has received 132 U.S. patents, 50 foreign patents, and has invested nearly $100 million in the development of a retinal prosthesis for the blind. Another nearly $30 million of this funding has come from U.S. government-sponsored grants from the National Institutes of Health, National Eye Institute. The Department of Energy sponsored a related program with nearly $75 million, which primarily supported several university partners and five national lab partners.

[3] Humayun, M. S., de Juan, E., Jr., Dagnelie, G., Greenberg, R. J., Propst, R. H., & Phillips, D. H. (1996). Visual perception elicited by electrical stimulation of retina in blind humans. Archives of Ophthalmology, 114(1), 40–46.

[4] Humayun, M. S., de Juan, E., Jr., Weiland, J. D., Dagnelie, G., Katona, S., Greenberg, R. J., et al. (1999).

[5] Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J, Mech B, Cimmarusti V, Van Boemel G, Dagnelie G, de Juan E. Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. Vision Res. 2003 Nov; 43(24):2573-81.

6 Yanai D, Weiland JD, Mahadevappa M, Greenberg RJ, Fine I, Humayun MS. Visual performance using a retinal prosthesis in three subjects with retinitis pigmentosa. Am Jour of Opthal. 2007 May; 143(5): 821-827.

7 Caspi A, Dorn JD, McClure KH, Humayun MS, Greenberg RJ, McMahon MJ. Feasibility study of a retinal prosthesis: spatial vision with a 16-electrode implant. Arch Ophthalmol. 2009 Apr; 127(4):398-401.

Designing the Argus II Clinical Trial

Designing a trial for a small, underserved patient population with distinctly different disease features carries with it recognized challenges, among them the difficulty (or impossibility) of carrying out a large randomized trial, and the lack of accepted, validated endpoint measures. As described in this Executive Summary, Second Sight successfully met each of these challenges. First, while the trial was initially designed as a feasibility study, it was designed to produce sufficient safety and probable benefit data (n=30 subjects) but small enough to enroll in a reasonable time (just over 2 years). It was not powered to demonstrate safety and efficacy (noting that a showing a probable benefit rather than of effectiveness is required to support HDE approval). Second, independent, scientific experts in low vision research helped Second Sight select and design appropriate endpoint measures before the trial commenced, and they helped refine a few of the endpoints during the trial.

Objectives

The objectives of the feasibility trial were to evaluate the safety and probable benefit of the Argus II System for blind subjects with severe to profound retinitis pigmentosa.

Methods

For enrollment in the trial, subjects were required to have confirmed history of retinitis pigmentosa [in the US] or outer retinal degeneration [in Europe] with bare light perception or worse vision in both eyes. Subjects were required to have functional ganglion cells and intact optic nerve (as documented by full-field flash detection or electrically evoked response) and a confirmed history of useful form vision. Minimum age for enrollment in the study was 25 years old [in US and Switzerland] or at least 18 years old [in France and UK].

Subjects were implanted monocularly in their worse-seeing eye. They were followed for 3 years. At the end of 3 years, subjects were offered the opportunity to enroll in a study extension for an additional 2 years (until 5 years post-implant). In the US, the study was recently extended again to allow subjects to remain in the study until 7 years post-implant.

The primary safety endpoint for the study was the number, seriousness, and relatedness of all adverse events, subject to review and adjudication by an Independent Medical Safety Monitor. Throughout the trial, subjects were actively monitored for adverse events at the regular clinical visits through a number of

routine observations and diagnostic tests in order to provide a general check of ocular health and to assist in detecting and understanding adverse events.

Working within the framework of clinical trials for other ophthalmic devices, Second Sight and its team of scientific advisors selected or designed several tests that would address the main elements that should be assessed for these types of devices: visual function (i.e., how the eye, as an organ, works [e.g., visual acuity]), functional vision (i.e., how the patient performs in vision-related activities of daily living), and quality of life. The endpoints that were selected provided a mixture of objective and subjective data. The study design was strengthened by the fact that controlled observations could be obtained by performing assessments both with the Argus II System ON and OFF (i.e., control was available at each time point).

Subjects

Thirty subjects were enrolled and implanted between June 6, 2007 and August 11, 2009. Despite the fact that 10 internationally-recognized eye hospitals were participating in the study, enrollment of the 30 subjects took a little over two years. This was partially due to enrollment having paused midway through for approximately 7 months, but was mostly due to the difficulties of recruiting subjects from a rare patient population.

At the time many RP patients are diagnosed, they are told there are no available treatments for them – and there is no hope of stopping their vision loss or regaining any function. As a result, many abandon routine ophthalmic exams. Without an active connection to a physician, it is very challenging to locate these patients and recruit them for clinical trials.

As of the data cut-off date of March 15, 2012, all subjects were followed a minimum of 2.5 years (with the exception of one subject who was explanted at 14 months). The mean follow-up was 3.5 ± 0.9 years (range 2.6 – 4.8 years). The cumulative subject-experience with the device was 105 subject-years of follow-up.

Twenty-nine (29) subjects had a history of retinitis pigmentosa (one of whom had Leber Congenital Amaurosis) and 1 had choroideremia. The median age of subjects was 57.9 years at time of implant; the range was 28 – 77 years. Thirty percent of subjects were female, and 70% were male. All had bare or no light perception in both eyes.

Results

Twenty-six (26) subjects were implanted in the right eye and 4 subjects were implanted in the left eye. This disparity in the eye implanted was due to the fact that until early 2009, only right eye implants were manufactured and available. The surgery to implant the device lasted an average of 4 hours (range 1:53 – 8:32).

There were no unexpected adverse events. The majority of subjects (n=19 or 63%) did not experience any serious adverse events. Eleven subjects experienced a total of 23 SAEs. The SAEs occurred most often in the first 60 days post-implant and tended to be clustered in a few subjects. All SAEs were manageable and were treated using standard techniques. The majority of SAEs were resolved within 1-2 months through drug treatment and/or surgical intervention. Four SAEs resolved slowly (2-11 months), two were resolved by explanting the device, and 3 remained stable as of this report.

Non-serious adverse events represented the majority of events. Non-serious events were likewise routinely treated with standard techniques (i.e., topical treatment and/or oral medications) or without any intervention at all. It was also demonstrated that the device can be safely removed: one implant (including the retinal tack) was safely explanted to resolve an adverse event, and 3 retinal tacks were safely removed during elective revision surgeries. In general, adverse events did not adversely affect performance with the Argus II System.

All subjects had bare light perception (i.e. could only detect a full-field or photographic flash) or worse vision before implantation. Tests of residual vision throughout the study demonstrated that all but one subject still had bare light perception as of the last follow-up. One subject's vision declined to no light perception in both eyes, indicating this decline was likely due to the natural course of the disease. These results demonstrated
that chronic electrical stimulation did not lead to a significant decline in residual light perception when compared to fellow eyes.

The Argus II System provided all 30 subjects with benefit as measured by high-contrast visual function tests. The degree of benefit naturally varied from subject to subject.

- All subjects were able to see visual percepts when the Argus II was electrically activated.
- On the Square Localization test (i.e., object localization), subjects (on average) performed better with the System ON than OFF at all follow-up time points. At 24 months, on average, subjects missed the target by about 50 pixels with System ON vs. about 250 pixels with the System OFF.

- On the Direction of Motion test, which tested subjects' ability to determine the direction of a moving bar, subjects showed higher mean accuracy with the System ON than they did with it OFF at all time points, indicating that the Argus II System improved their performance on a spatial vision task. At 24 months, the mean response error was about 60° with the System ON vs. more than 80° -- nearly the error expected by chance -- with the System OFF.
- On the Grating Visual Acuity test, which assessed subjects' visual acuity using the principles of acuity charts but designed for extremely low vision subjects, 27% of subjects were able to score on the scale (between 1.6 and 2.9 logMAR) at least once with the System ON, while none of the Argus II subjects were able to score on the scale with the System OFF.
- Research into subjects' ability to recognize alphanumeric characters demonstrated that a large number of subjects were able to recognize large letters and numbers with the System ON (but not with the System OFF). The median percent correct with the System ON was approximately 50% higher than with the System OFF. In addition, the four best performers could use the System to read short words, while these 4 subjects were not able to do this task with the System OFF.

The Argus II System was also able to provide subjects with clinical probable benefit as measured by objectively-scored functional vision tests. Subjects performed better with the Argus II System ON vs. OFF on orientation and mobility tests (finding a door and following a line) and on functional vision tasks (sorting white, black and grey socks; following an outdoor sidewalk; and determining the direction of a person walking by). Self-report questionnaires on functional vision and quality of life indicated mild improvement (Massof Activity Inventory) or no significant change (VisQOL).

An assessment of Argus II subjects' functional vision in and around their home by independent, certified low-vision rehabilitation specialists was also performed (The assessment was called the Functional Low-vision Observer Rated Assessment, or FLORA.). In no cases did the assessors report that the Argus II System had a negative impact on subjects. In 77% of cases, assessors determined that the subject was receiving (or had received at one time) functional vision and/or well-being benefit from the Argus II System.

Risk-Benefit Analysis

The Argus II System is intended for use in blind patients with severe to profound retinitis pigmentosa with bare or no light perception in both eyes. The Argus II device is implanted in the worse-seeing eye. Typically with an ophthalmic implant, the main risk is loss of residual vision. With the Argus II implant, this risk is limited since the patients have minimal to no residual vision, i.e., **this is an intervention performed on a blind eye**. The Argus II device is safely explantable, further limiting the risk. Finally, if permanent damage were to happen to the implanted eye, the fellow eye (with comparable or better residual vision) would be unaffected, preserving it for future potential treatments with an alternative therapy. These factors combine to make the baseline risk of the Argus II implant low.

All subjects in the study reached a minimum of 2.5 years follow-up (with the exception of one subject who was explanted at 14 months). Data were available on approximately one-half of the subjects out to 3 years post-implant, and approximately one-quarter of the subjects out to 4 years post-implant. In total, the subject experience was 105 subject-years of follow-up. This represented a very robust amount of follow-up data for an HDE-designated implantable device.

The safety review concluded that the Argus II System has a reasonable safety profile for an ophthalmic device that requires vitreoretinal surgery to implant. **All adverse events were treatable with standard practices, and no catastrophic adverse events (e.g., lost eyes) occurred.** With the exception of one device that had to be explanted due to adverse events, all subjects were able to use the Argus II System despite adverse events.

These risks were acceptable given the benefits provided by the Argus II System. Results from the clinical trial provided objective, quantitative evidence that **subjects' visual function and orientation and mobility were improved with the Argus II System for over two years**. Subjects were able to detect light better with the System ON vs. OFF, and they were able to perform tasks that require spatial vision (i.e., detecting the direction of motion, grating visual acuity, and reading letters and short words) with the System ON, while they were unable to do these tasks with the System OFF. Subjects were also able to locate a door and follow a line better with the System ON vs. OFF. The objective visual function test results are clinically meaningful as they indicate the potential of the Argus II System to provide useful vision to patients, while the door and line orientation and mobility tasks mimic two important real-world activities that are challenging for blind individuals (i.e., locating a door in an unfamiliar room and crossing the street at a crosswalk without veering).

The Functional Low-vision Observer Rated Assessment (FLORA) provided a qualitative, subjective assessment of the benefit the Argus II System provided to subjects in their everyday lives (as judged by expert, trained low vision therapists).

Analysis of the FLORA results showed that **three-quarters of the subjects had received a positive benefit in terms of well-being and/or functional vision, while none had experienced a negative effect**.

The results from this clinical trial demonstrate that the Argus II System provided benefits for these blind subjects in terms of visual function, functional vision, and well-being. The study also demonstrated that the Argus II System does not pose an unacceptable risk to blind patients with severe to profound RP with bare or no light perception in both eyes.

In considering the overall risk-benefit of the Argus II System, one must also consider the patient's perspective on benefit and tolerance for risk. Patients who are blind due to severe to profound RP currently have no effective treatments available to them. Because of their unique circumstances, such patients may be willing to take greater risks to receive new treatments, and they should be afforded that choice.

Another consideration is the upgradeable nature of the Argus II System design. The external software and hardware can be easily upgraded as future research and computer technology advances. For example, better image processing techniques and color perception are active areas of research. This has been important in the field of cochlear implants where external hardware and software improvements have enabled performance gains.

It should also be noted that use of the Argus II System in the commercial setting would be closely monitored. First, per the HDE regulations, Second Sight will be responsible for obtaining initial and continuing IRB approval at each center where the Argus II System is used. Second, Second Sight intends to continue to collect long-term follow-up of the subjects currently enrolled in the Argus II clinical trial. Finally, Second Sight intends to conduct a post-approval study of the Argus II System.

Conclusions

For a device to be approved as an HDE, the sponsor must demonstrate the safety of the device. Whereas a PMA (Pre-Market Approval) requires that a device must also demonstrate a "reasonable assurance of effectiveness", the HDE approval requires that the sponsor demonstrate that the device has a "probable benefit," taking into account alternative therapies. The results of the clinical trial of the Argus II System demonstrate that the System provides a probable benefit with a low risk to patients.

Approval of the Argus II System can provide, for the first time, a treatment option for blind patients who have bare or no light perception due to retinitis pigmentosa. In doing so, this device can fill an important unmet need for patients who currently have no other hope of any vision recovery.

1 DISEASE BACKGROUND AND ALTERNATIVE PRACTICES

RP is the most common type of a large and heterogeneous group of hereditary retinal degenerations that cause progressive impairment of photoreceptors and retinal pigment epithelium. The progression of the disease is generally slow, but the eventual impact on vision and quality of life is often devastating. Affected individuals first experience defective dark adaptation or nyctalopia (night blindness), followed by reduction of the peripheral visual field (known as tunnel vision). For example, patients afflicted with RP for 25 years are usually left with a visual field of 10 degrees or less. As the disease progresses and further photoreceptor loss occurs, even this constricted field may be lost. This progression of vision loss is illustrated in Figure 1.

Figure 1: Progression of Vision Loss in Patients with Retinitis Pigmentosa

Images courtesy of National Eye Institute, National Institutes of Health

Population indicated for the Argus II System

As one would expect, loss of visual field is associated with a marked decrease in physical mobility and an increase in the number of bumps and injuries, including hip fractures.[8] The gradual onset and the relatively late age at which most RP patients become legally blind adds to personal and familial difficulties in adjusting

[8] Turano KA, Broman AT, Bandeen-Roche K, et al. Association of Visual Field Loss and Mobility Performance in Older Adults: Salisbury Eye Evaluation Study. Optometry & Vision Science 2004; 81(5):298-307.

to being blind.[9] Blindness later in life is also associated with significant incidence of depression and anxiety at a rate higher than observed for many other disabling chronic diseases.[10]

Currently, no other treatments (devices, drugs or biologics) are commercially available in the United States to treat individuals for whom the Argus II System is indicated. Traditionally, the approach to vision rehabilitation in patients with RP has been to use the remaining vision with optical aides. If no vision remains, auditory or tactile information is substituted (e.g., through the use of braille, cane travel, etc.). Numerous experimental research programs are examining a variety of approaches for slowing, stopping or reversing the progress of RP, including gene therapy, tissue and cell transplants, and pharmacologic neuroprotection therapies.[11] However, these approaches so far have had fairly limited success in treating the intended target population. More recently, visual prostheses have been developed to address the extreme low vision population with retinal degenerations such as RP by providing electrical stimulation at neuronal locations in the eye.[12] As a visual prosthesis, the Argus II System offers patients with advanced stages of RP the opportunity to regain some visual function.

It is estimated that 100,000 people in the United States (US) have RP, mainly caused by mutated genes inherited from one or both parents.[13] This equates to a prevalence of 1/3037 Americans (assuming a US population of 303,763,031 based on a 2006 US Census Bureau estimate) and an incidence of 1,316 people/year. Since the Argus II System is intended for blind individuals with late-stage RP with bare light perception or worse, the target population for this device is considerably less than that of the overall RP population (i.e., less than 1 in 3037).

2 DEVICE DESCRIPTION

2.1 INDICATION FOR USE

The Argus II System is intended to provide electrical stimulation of the retina to induce visual perception in blind patients. It is indicated for use in patients with

[9] Leinhaas MA, Hedstrom NJ. Low vision: how to assess and treat its emotional impact. Geriatrics 1994; 49(5): 53-56

[10] Brody BL, Gamst AC, Williams RA, et al. Depression, Visual Acuity, Comorbidity, and Disability Associated with Age-related Macular Degeneration. Ophthalmology 2001; 108(10): 1893-1900.

[11] Delyfer MN, Leveillard T, Mohand-Said S, et al. Inherited retinal degenerations: therapeutic prospects. Biol Cell 2004; 96(4): 261-269.

[12] Weiland JD, Cho AK, Humayun MS. Retinal prostheses: current clinical results and future needs. Ophthalmology. 2011 Nov; 118(11):2227-37.

[13] Foundation for Fighting Blindness (http://blindness.org/index.php)

severe to profound retinitis pigmentosa who meet the following criteria:

- Adults, age 25 years or older.
- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation.

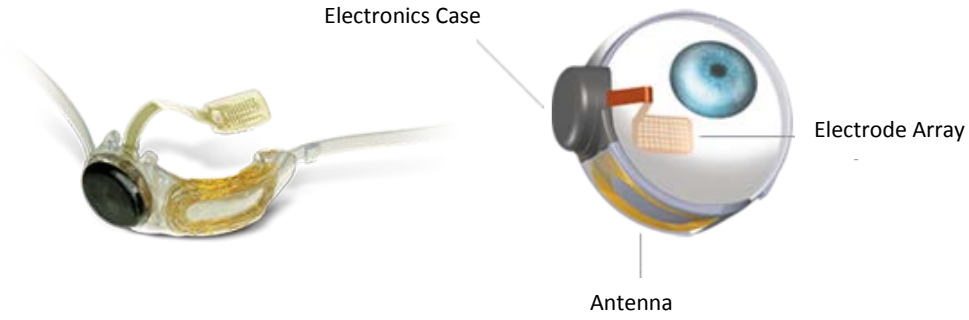
The Argus II implant is intended to be implanted in a single eye, typically the worse-seeing eye.

2.2 DEVICE DESCRIPTION

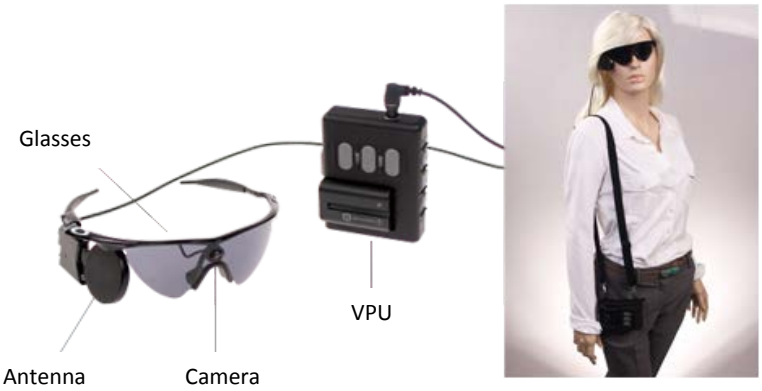
The Argus II System consists of three primary components (1) an epiretinal prosthesis that is fully implanted on and in the eye (i.e., there are no percutaneous leads), (2) an external unit worn by the user, and (3) a clinician fitting system that is periodically used to perform diagnostic tests with the System and to custom-program the external unit for use by an individual subject. Refer to Figure 2.

Figure 2: Argus II Retinal Prosthesis System

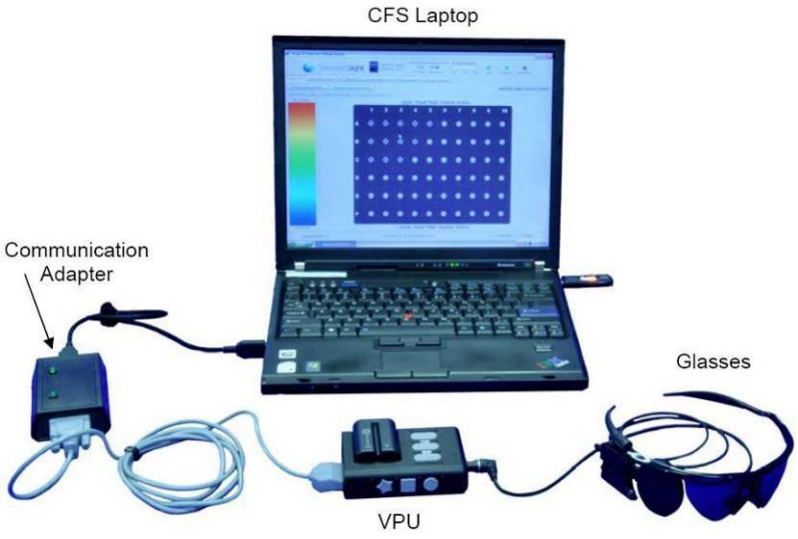
Implant



Externals



Fitting System
(Typical Configuration)



Implant

The retinal prosthesis implant is responsible for receiving information from the external components of the system and electrically stimulating the retina to induce visual perception

The implant consists of: (a) a receiving coil for receiving information and power from the external components of the Argus II System; (b) electronics to drive stimulation of the electrodes; and (c) an electrode array. The receiving coil and electronics are secured to the outside of the eye using a standard scleral band and sutures, while the electrode array is secured to the surface of the retina inside the eye by a retinal tack. A cable, which passes through the eye wall, connects the electronics to the electrode array.

The electrode array contains 60 electrodes arranged in a 6 x 10 grid. The array provides a visual field of approximately 20° (diagonal). Based on the spacing of the electrodes, the theoretical limit of resolution of the Argus II System is 20/2094 (or 2.0 logMAR). However, in the clinical trial, one subject achieved a resolution better than this (i.e., 20/1262 or 1.8 logMAR), likely due to head scanning.

It is technologically challenging to build a device as small as the Argus II implant with all 60 electrodes meeting all of the many specifications imposed. In light of this, after discussions with the FDA and considering the desire to provide a consistent product to patients, the implant intended for commercial sale will have 55 of the 60 electrodes enabled (i.e., available for use).[14] A diagram of the implant is provided in Figure 3.

[14] The average number of electrodes enabled at the time of implant in the clinical trial was also 55.

Figure 3: Argus II Implant and Tack (Right Eye Implant Shown)

The implant receives power and data commands wirelessly from an external unit described below. The implant is provided in both left and right eye configurations. The device is only implanted in one eye. It is important to note that the Argus II implant can be fully explanted.

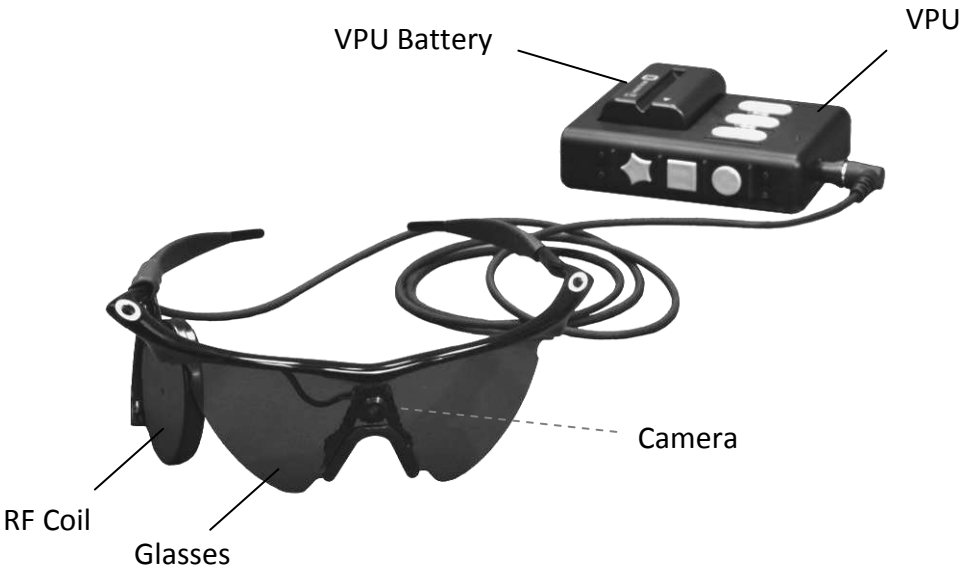
Externals

The externals are composed of the Argus II Glasses and the Argus II Video Processing Unit. A small, light-weight video camera and transmitting coil are mounted on the glasses. The telemetry coils and radio-frequency system are mounted on the temple arm of the glasses for transmitting data from the VPU to the implant.

The glasses are connected to a video processing unit (Argus II VPU) by a cable. The VPU is worn by the patient, typically, on a belt or a strap. The VPU is used to process the images from the video camera and convert the images into electrical stimulation commands which are transmitted wirelessly to the implant. These system components are shown in Figure 4.

Both the VPU and Glasses are upgradeable to allow patients to benefit from future improvements in the software and hardware.

Figure 4: Argus II External Equipment



Fitting System

To be able to use the Argus II System, a subject's VPU needs to be custom-programmed. This process, which is called "fitting," occurs in the clinic shortly after implant surgery and then periodically thereafter as needed. To perform the fitting process, the subject's Video Processing Unit is connected to Communication Adaptor (which provides electrical isolation) and then to the Clinician Fitting System. The Clinician Fitting System consists of software with a graphical user interface running on a laptop computer. The Clinician Fitting System is used to run a series of tests to determine the most appropriate stimulation parameters to be used to process the video images from the camera. The subject-specific files developed from the fitting process, called Video Configuration Files (VCFs), are downloaded to the VPU where they are available for use by the patient. The clinician also uses the Clinician Fitting System to run diagnostic tests (e.g., to obtain electrode and impedance waveform measurements or to check the radio-frequency link between the implant and external unit).

2.2.1 DEVICE MODIFICATIONS

As one would expect for a study of a novel medical device that took three years to enroll, minor refinements were made to the system during the study based on clinical feedback. However, all subjects received an Argus II System that functioned under the same principle of operation. The main surgical steps and locations were unchanged (e.g., lensectomy, pars plana vitrectomy, scleral buckling, insertion of retinal tack, etc). Further, a subgroup analysis of the most significant device changes (single vs. dual metal) demonstrated a trend toward

improved safety and benefit for the later cohort (dual metal) that incorporates the refinements that will be present in the marketed product. Refer to 6.11.1.1 (Design Changes and Associated Sub-Group Analysis) for a description of these changes and a discussion of their impact.

2.3 PRINCIPLE OF OPERATION AND MECHANISM OF ACTION

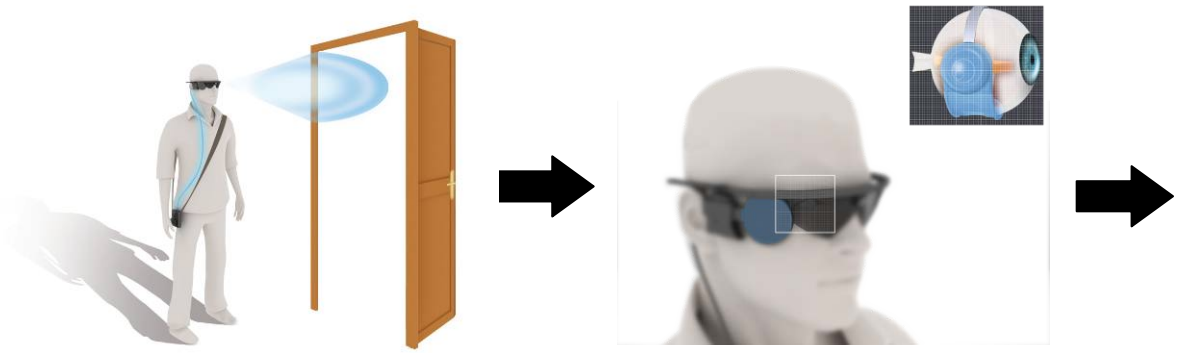
The principle of operation and mechanism of action of the Argus II System is similar to that of a cochlear implant, except that the Argus II System provides stimulation to the retina of a blind person to induce visual perception whereas a cochlear implant provides stimulation to the cochlea to induce hearing in a deaf person.

In the Argus II System, the video camera on the patient-worn glasses captures a video image. The camera signal is sent to the Video Processing Unit (VPU) which processes the camera image and transforms it into electrical stimulation patterns. The electrical stimulation data are then sent to a transmitter coil mounted on the glasses. The transmitter coil sends both data and power via radio-frequency (RF) telemetry to the implanted retinal prosthesis. The implant receives the radio-frequency commands and delivers stimulation to the retina via an array of electrodes that is secured to the retina with a retinal tack.

In patients with retinitis pigmentosa, the photoreceptor cells in the retina, which normally transduce incoming light into an electro-chemical signal, have lost most of their function. The stimulation pulses delivered to the retina via the electrode array of the Argus II Retinal Prosthesis are intended to mimic the function of these degenerated photoreceptor cells. These pulses induce cellular responses in the remaining, viable retinal nerve cells that travel through the optic nerve to the visual cortex, where they are perceived as phosphenes (spots of light). Patients learn to interpret the visual patterns produced by these phosphenes (See “Clinical Utility” below).

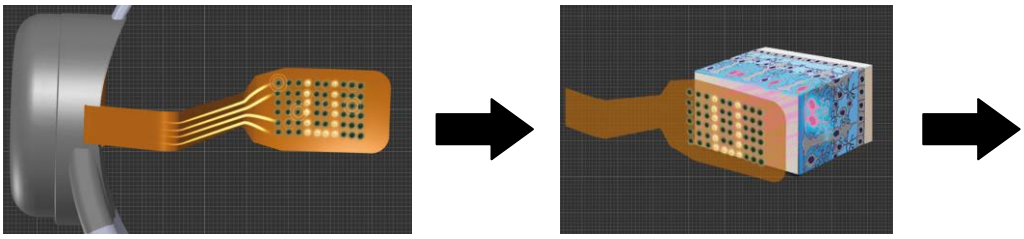
The principle of operation of the Argus II System is shown in Figure 5.

Figure 5: Schematic Overview of the Argus II System Principle of Operation



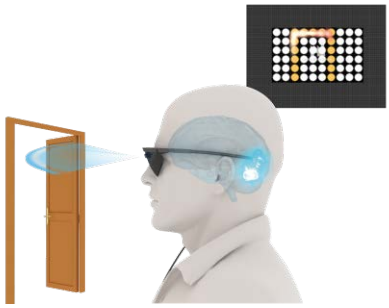
Video camera captures an image and sends data to VPU.

VPU converts image into stimulation commands which are wirelessly transmitted to the implant.



Stimulation commands are converted into electrical signals which are sent to the electrode array.

Array delivers stimulation to the retinal cells



Nerve signals are sent to the brain. Brain perceives patterns of light. Patient learns to interpret the meaning of these light patterns. (See section “Intended Clinical Benefit” below)

2.4 INTENDED CLINICAL BENEFIT

The Argus II System provides an artificial form of vision that affords a range of visual function that can vary from patient-to-patient, ranging from simple light detection to basic form vision. While this level of restored vision cannot yet allow a patient to recognize faces or read at a normal speed, it can improve a patient's orientation and mobility, activities of daily living, and overall well-being.

This visual information can translate in several ways into a patient's everyday life. On the functional side, it can help them perform simple visual tasks, such as locating doors and windows, avoiding obstacles, sorting light and dark clothes. Many patients can use the system to see the lines of a crosswalk, allowing them to stay within the designated area, and more readily locate key landmarks as they navigate (e.g., bus stop poles).

Equally important for many patients are the psychological, emotional and social benefits the partially restored vision can provide to them. The System can allow them to feel more connected with people in their surroundings, because, for example, they can see when people were moving in front of them, and can tell when someone was approaching them or had moved away. Subjects can also gain enjoyment from being "visual" again. Some ways in which pleasure can be derived from use of the System include, locating the moon, seeing the changing light levels on a TV (providing a rudimentary form of "watching" TV), tracking groups of players as they move around the field at an athletic event, seeing the movement of waves at the ocean, detecting the moving streams of lights from fireworks, and being able to locate important landmarks while on vacation.

For patients with bare or no light perception (the indicated patient population), the vision provided by the Argus II System can provide clear clinical benefits.

2.5 IMPLANTATION PROCEDURE

The implant procedure consists primarily of scleral buckling and three port pars plana vitrectomy, which are standard techniques in vitreo-retinal surgery. The implant procedure and concomitant medications used in the clinical trial are described below.

At the start of the implant procedure, 8 mg of dexamethasone and 1 g cefazolin (or equivalents) were administered by intravenous injection. After careful sterile preparation of the eye, for phakic subjects, the lens was removed via clear cornea phacoemulsification and patients were left aphakic. The eye was then prepared for a pars plana approach to the vitreous cavity and a 360-degree

limbal conjunctival peritomy was performed. The rectus muscles were then isolated.

The implant coil was inserted temporally on the globe and 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 a Watzke® silicone 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. If an epiretinal membrane or well-adhered posterior hyaloid was observed in the area where the surgeon intended to tack the array, this was carefully peeled. The array was then inserted through a temporal sclerotomy (approximately 5 mm in width). The electrode array was placed onto the retina in the macular region and then tacked using a retinal tack. The extraocular portion of the cable was sutured to the sclera and all sclerotomies were closed.

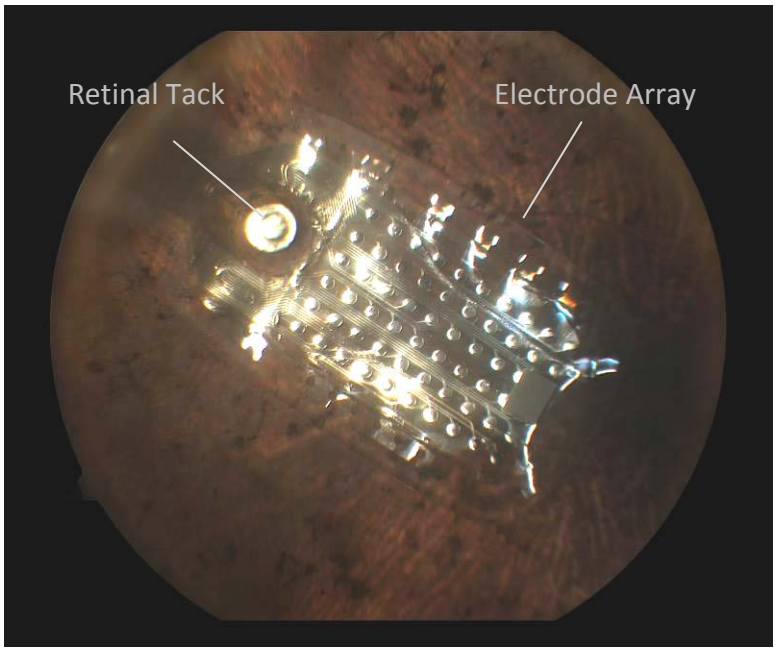
An allograft or suitable alternative was fixed over the device to reduce the likelihood of conjunctival irritation. Finally, the Tenon's capsule and the conjunctiva were closed.

At the end of the surgery, 100 mg of cefazolin, 2 mg of dexamethasone, and 2 ml of lidocaine (or equivalents) were injected under the conjunctiva. Beginning in early 2009, intravitreal injections of antibiotics (0.1cc intravitreal vancomycin [1 mg/0.1cc] and ceftazidime [2.25 mg/0.1 cc]) were administered prior to close as an extra preventative measure to reduce the likelihood of infection.

Post-operatively the following medications were administered: 500 mg pills of Ciprofloxacin twice a day for 14 days, 1 drop of Gatifloxacin four times a day for at least 14 days, 60mg pill daily of Prednisolone for 2 weeks, immediately followed by a Methylprednisolone (Medrol) taper pack (8mg per tablet starting with 6 tablets) until the pack was completed (or equivalent taper of Prednisolone), 1 drop four times a day Pred Forte 1% for 2 weeks, and 1 drop daily Atropine 1% for 2 weeks.

Figure 6 provides a fundus photo from an implanted subject.

Figure 6: Argus II Implant, Implanted on a Right Eye



2.6 EXPLANTATION PROCEDURE

Several explants were successfully conducted during pre-clinical studies. During the clinical trial, a single device explant was successfully performed without further incident.

Under general anesthesia, the eye was prepared for a pars plana approach to the vitreous cavity and a 360-degree limbal peritomy was performed. With an infusion line in place, scleral ports permitting access to the posterior chamber were created in locations that were different from those employed in the implant procedure. Fibrotic capsular material was removed from around the extra-ocular portion of the device. If deemed necessary, a core vitrectomy was performed.

The intra-ocular portion of the device was inspected for the presence of fibrotic strands or membranes and these were carefully dissected away from the implant to remove sources of traction on the retina. With an infusion pressure of at least 60 mmHg, the tack was extracted from the posterior coats using the retinal tack forceps, and then isolated from the array in mid-vitreous prior to being withdrawn from the eye. The sclerotomy through which the array was originally inserted was reopened to about 5 mm prior to withdrawing the array from the eye. At the surgeon's option, laser was employed around the wound created by the tack extraction to prevent bleeding.

All sutures fixing the extra-ocular portion of the device to the sclera were removed and the Watzke sleeve used to hold the scleral band in place was removed to facilitate extraction of the entire device from the orbit. All remaining scleral incisions were closed and the tenon's capsule and conjunctiva were reattached at the limbus. Appropriate medications were administered.

3 SUMMARY OF NON-CLINICAL TESTING

3.1 BIOCOMPATIBILITY TESTING

Biological testing and evaluation were performed on the Argus II implant and the patient-contacting external system components in accordance with ISO 10993 (Biological Evaluation of Medical Devices) as shown in Table 1. All tests passed. Testing was conducted in compliance with Good Laboratory Practice (GLP) regulations.

Table 1: Biological Testing and Evaluation

Argus II Implant		
Test	**Standard**	**Test Method**
Cytotoxicity	ISO 10993-5	ISO Cytotoxicity Study (Elution Method) in mice
Irritation	ISO 10993-10	ISO Intracutaneous Study in rabbits
Acute systemic toxicity	ISO 10993-11	ISO Systemic Toxicity Study in mice
Sensitization	ISO 10993-10	ISO Maximization Sensitization Study in guinea pigs
Pyrogen (material mediated)	ISO 10993-11	Rabbit pyrogen test (USP XXII, NF XVII <151>)
Subchronic toxicity	ISO 10993-11	ISO subcutaneous test in rats (13 weeks) – both local and systemic effects
Implantation	ISO 10993-6	ISO Subcutaneous implantation Study in rabbits: 4 sites, 3 rabbits each for 2 and 6 week duration. 12 week cohort satisfied by 13 week subchronic study
Genotoxicity	ISO 10993-3	• Bacterial Reverse Mutation Study • Mouse Lymphoma Assay • Mouse peripheral Blood Micronucleus Study
Carcinogenicity	ISO 10993-3	In accordance with ISO 10993-1 and FDA G95-1 guidelines, documentation provided from published sources and genotoxicity was used to assess the carcinogenicity of the implant.
Chronic toxicity	ISO 10993-11	In accordance with ISO 10993-1 and FDA G95-1 guidelines, a systemic approach based on the body of evidence (subchronic toxicity test, implantation test, supporting documentation) was used to assess the chronic toxicity of the implant.
External Components (Patient Contacting)		
Cytotoxicity	ISO 10993-5	ISO Cytotoxicity Study (Elution Method) in mice.
Irritation	ISO 10993-10	ISO Intracutaneous Study in rabbits.
Sensitization	ISO 10993-10	ISO Maximization Sensitization Study in guinea pigs

3.2 STERILITY TESTING

The implant is sterilized with ethylene oxide. The sterilization process has been validated according to ANSI/AAMI/ISO 11135:1994 and EN 556 requirements for terminally-sterilized medical devices. Ethylene oxide (EtO) residual testing has demonstrated that the sterilization process will not leave residual toxin levels inappropriate for use of the implant in the eye.

3.3 BENCH TESTING

A series of bench tests was performed which demonstrated that the Argus II System intended for approval under the HDE, and its constituent parts, meets the intended performance, safety and reliability specifications. This testing included the following:

Implant

- Mechanical Testing
  - Ability to withstand flexure and tear forces
  - Maintaining shape and curvature following exposure to heat, sterilization and surgical implantation.
  - Ability to withstand repeated eye movements
- Environmental Testing: Temperature, vibration, atmospheric pressure
- Corrosion Resistance Testing: Testing of the electronics package and implant
- Particulate Testing
- Dynamic Lifetime Test: Ability to function long-term while undergoing constant simulated saccadic eye movements.
- Shipping, Packaging and Shelf Life
- Magnetic Resonance Imaging (MRI) (1.5T and 3T) and Diagnostic Ultrasound Compatibility

System

- Electromagnetic Compatibility: Compliance to IEC 60601-1-2 and EN 300330-1
- Basic Safety and Essential Performance: Compliance to IEC 60601-1
- Reliability/Environmental Testing: Temperature, humidity, pressure and vibration
- Specific Absorption Rate and Current Densities
- Functional Testing: Ability to meet System functional requirements

3.4 ANIMAL TESTING

Extensive chronic animal testing in a canine model has been conducted to aid the development of the Argus II implant and to verify the design prior to clinical use. The majority of this testing was performed with mechanical models (i.e., non-active devices) of the Argus II implant to evaluate the mechanical design of the implant and the surgical implantation technique. The remainder of the testing was performed with active implants to test the functionality of the device.

Summaries of the animal studies conducted during the design development and design verification process for the Argus II System are provided below.

Mechanical Model Studies

The following studies were performed with mechanical models of the implant (i.e., non-functional devices).

- *Design Verification Series:*
    - Three canines were implanted with the final design configuration mechanical models of the Argus II. The number of days implanted ranged from 60 to 182. The study demonstrated the mechanical design was suitable and safe for use in humans.

    - Midway through the human clinical trial, the implant design was modified to incorporate feedback obtained during the first 15 subjects implanted in the clinical trial. The primary modifications were as follows:
        - Changed the silicone application process for the array from a manual process to a molding process to provide greater control and consistency in the array shape.
        - Made the width of the cable narrower to increase flexibility

      A complete description of these changes can be found in Section 6.11.1.1 (refer to "Dual Metal Implant Design").

      This upgraded design was re-verified in six canines using non-functional mechanical models. The number of days implanted ranged from 183 to 211. The design proved to be surgically feasible to implant.

Active Implant Studies

The following studies were distinct from the Mechanical Model Studies and were performed with fully-functional implants.

- *Validation Study for Temperature Rise*: A temperature study conducted in canines verified that the outer surface temperature of the implant does not rise more than 2°C above the normal surrounding body temperature.

- *Verification Study for Device Functionality*:

    - Three canines were implanted with fully active Argus II devices to verify the functionality of the device design following implantation. The implanted devices underwent monthly testing for up to 6 months. This testing demonstrated that the design met the acceptance criteria for device functionality. This design of the Argus II Retinal Prosthesis (referred to as the "Single Metal Implant Design") was implanted in the first 15 subjects in the clinical trial (refer to Section 6.11.1.1).

- Following modification of the implant design midway through the clinical trial as described above, verification of device functionality was repeated in two additional canines that were implanted with devices that incorporated the modified implant design. Functionality testing was performed at 2 and 4 weeks. The devices met the acceptance criteria for functionality. This design of the Argus II Retinal Prosthesis (referred to as the "Dual Metal Implant Design") was implanted in the last 15 subjects in the clinical trial (refer to Section 6.11.1.1).

Safety of Explantation Study

Three canines that had been implanted with mechanical models of the Argus II were selected to have their device explanted to evaluate and refine the explantation procedure. The study found that the device could be safely explanted without damage to tissue.

4 REGULATORY HISTORY

4.1 UNITED STATES

A prospective study was conducted under IDE G050001 (original application submitted December 2005) to evaluate the safety and probable benefit of the Argus II Retinal Prosthesis System in providing visual function to blind subjects with severe to profound retinitis pigmentosa (RP). This was a non-randomized, single-arm study. In the US, a total of 14 subjects were enrolled at 6 centers. This US trial was run concurrently with a clinical investigational study in Europe. Enrollment in the study in the US and Europe took place between June 6,2007 – August 11, 2009.

The Argus II System received a HUD designation (application number #09-0216) from the Office of Orphan Product Development on May 28, 2009 for use in blind patients with severe to profound RP.

The HDE Application (H110002) for the Argus II Retinal Prosthesis System was submitted by Second Sight Medical Products to the FDA on May 3, 2011. The application was accepted for filing by the FDA on May 27, 2011.

Second Sight's manufacturing facility was subject to a HDE pre-approval inspection by the FDA in October of 2011. The focus of the audit was process validation, design control, corrective and preventative actions, and management controls. The inspection resulted in no FDA-483 observations.

4.2 STATUS OUTSIDE THE UNITED STATES

Clinical Trial

The Argus II clinical trial was also conducted at 4 centers in 3 countries in Europe. A total of 16 subjects were enrolled in the trial in Europe. The appropriate approvals were obtained from the European Competent Authorities and Ethics Committees (i.e., Institutional Review Boards or IRBs) to conduct this study.

CE Mark Approval

The Argus II Retinal Prosthesis System is approved for use in the European Economic Area (EEA) for the treatment of severe to profound outer retinal degeneration. The CE Mark approval was obtained in February 2011 and Second Sight began commercially selling the System in select countries in Europe in October 2011.

As of July 15, 2012, 9 patients have been implanted with the commercialized Argus II device at 4 new centers in Italy and Germany (none of these centers or surgeons participated in the Argus II clinical trial). The mean length of implant is 4.7 ± 2.5 months (range 1.9 – 8.6 months). There have been no serious adverse events and no device recalls.

5 PRIOR CLINICAL INVESTIGATIONS

The Argus II Retinal Prosthesis System is a novel device intended for a rare patient population for whom there are currently no other *commercially* available therapies. The Argus II System represents the culmination of over 20 years of research and development to design a retinal prosthesis that partially restores vision to individuals who have severe to profound retinitis pigmentosa.

Acute Clinical Tests

This research began in the early 1990s when researchers tested the feasibility of directly stimulating the retina or RP subjects to elicit a visual percept in a series of acute tests. In these experiments, performed in the operating room under local anesthesia, the blind patients reported seeing percepts that corresponded in time and location to the electrical stimulus.[15,16]

[15] Humayun, M. S., de Juan, E., Jr., Dagnelie, G., Greenberg, R. J., Propst, R. H., & Phillips, D. H. (1996). Visual perception elicited by electrical stimulation of retina in blind humans. Archives of Ophthalmology, 114(1), 40–46.

[16] Humayun, M. S., de Juan, E., Jr., Weiland, J. D., Dagnelie, G., Katona, S., Greenberg, R. J., et al. (1999).

Argus I Clinical Trial

Following the success of these acute feasibility studies, Second Sight was founded in 1998 to create a retinal prosthesis that could be chronically implanted to partially restore vision to blind individuals. Second Sight's first generation retinal prosthesis was called the Argus I (also referred to as the Argus 16). The Argus I was developed as a "proof of concept" device intended to evaluate whether a fully-implantable, chronic epiretinal prosthesis could be safely implanted and elicit light percepts in implanted patients. The Argus I utilized a commercially available implantable pulse generator (from a cochlear implant), which was implanted behind the ear in a recessed well created in the temporal skull as is done for cochlear implants. This generator was attached to a Second Sight-designed cable that terminated in an array of 16 electrodes. This device was originally intended for use only in the clinic. The device was later refined so that subjects could take the Argus I System home for use in their daily lives.

Six subjects were enrolled in an FDA-approved Investigational Device Exemption (IDE) trial (G010099) of the Argus I device between February 2002 and June 2004. These subjects were implanted for an average of 5.2 years (range 0.9 to 7.8 years) as of March 15, 2012. All subjects were able to see visual percepts when the System was ON. Three of these subjects died due to causes unrelated to the Argus I System. One subject was partially explanted at approximately 1 year post-implant due to recurrent conjunctival erosion (she was one of the 3 subjects who later died), and one subject was explanted 6.4 years post-implant at her request. Two of these subjects remain implanted and are still using their devices.[17,18,19]

Clinical Trial of an Early Version of the Argus II Implant

Based on the success of the Argus I device, Second Sight began to develop the Argus II Retinal Prosthesis System (Argus II System), which is the subject of this HDE application. The Argus II System was designed to be a commercial device and incorporated several improvements over the Argus I device, including:

- Increased the number of electrodes from 16 to 60.

Pattern electrical stimulation of the human retina. Vision Research, 39, 2569–2576.

[17] Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J, Mech B, Cimmarusti V, Van Boemel G, Dagnelie G, de Juan E. Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. Vision Res. 2003 Nov; 43(24):2573-81.

[18] Yanai D, Weiland JD, Mahadevappa M, Greenberg RJ, Fine I, Humayun MS. Visual performance using a retinal prosthesis in three subjects with retinitis pigmentosa. Am Jour of Opthal. 2007 May; 143(5): 821-827.

[19] Caspi A, Dorn JD, McClure KH, Humayun MS, Greenberg RJ, McMahon MJ. Feasibility study of a retinal prosthesis: spatial vision with a 16-electrode implant. Arch Ophthalmol. 2009 Apr; 127(4):398-401.

- Eliminated the cable that wrapped around the eye in the Argus I device, to reduce the incidence of conjunctival erosion that was observed in the Argus I trial.
- Relocated the electronics package and telemetry coil to the outside of the globe of the eye. This eliminated the need to implant the pulse generator in the skull and tunnel the cable along the side of the head. In doing so, this reduced the number of specialized surgeons required for the implant procedure and reduced the surgical time required to implant the device dramatically (from approximately 8 hours to approximately 4 hours).

An early version of the Argus II implant was evaluated at Puerta de Hierro Centro Medico (Guadalajara, Mexico) by Arturo Santos, MD, who served as both the surgeon and principal investigator. Two subjects were enrolled in this trial and were implanted in September 2006. During the implantation surgery for these subjects, it was determined that the intraocular portion of the implant was too short and that the angle at which the cable entered the eye needed to be adjusted. As a result, the implant fit poorly in these eyes (i.e., the array cable was taut and the array could not be located over the macula), which limited the performance the subjects could achieve with their devices. Both devices remained implanted for the 2 year duration of the study. At the end of the study, one subject kept the device implanted and the other subject had the extraocular portion of the device removed to resolve recurrent conjunctival erosion.

Following the clinical experience with the early version of the Argus II, modifications were made to the implant design to lengthen the cable and adjust the angle at which it enters the eye. In addition, minor adjustments were made to the implant procedure (recommending the use of running sutures to close the conjunctival wound and adjusting how the Tutoplast® allograft is placed over the device to reduce its bulk[20]). In addition, several adjustments were made to the protocol test procedures to better characterize subjects' residual vision at baseline.

After these changes had been implemented and FDA approved them as part of an IDE application amendment, Second Sight initiated a clinical trial of the Argus II System. This trial was conducted both in the United States and Europe. As described in Section 6, below, this 30-subject clinical trial demonstrated the safety and probable benefit of the system for the indicated patient population.

[20] Tutoplast® is an allograft commonly used in ophthalmic surgery such as glaucoma implant/valve surgery.

6 ARGUS II SYSTEM CLINICAL TRIAL

6.1 JUSTIFICATION FOR STUDY DESIGN

Designing a Trial for Rare Populations

The Argus II System is indicated for blind patients with severe to profound retinitis pigmentosa and bare light or no light perception in both eyes. As discussed earlier, this population meets the criteria of an orphan population, and the Argus II System was designed a Humanitarian Use Device by the FDA. Conducting a clinical study in an orphan population poses many challenges. While the FDA has not issued any guidance specific to this subject, the European Medicines Agency (EMEA) issued a guidance document titled "Guideline on Clinical Trials in Small Populations," in February 2007. Two topics discussed in this document are particularly relevant to this clinical study:

(1) When working with orphan populations, large randomized controlled trials are not possible; and
(2) The choice of the primary endpoint can be challenging due to the lack of commonly accepted, validated measures.

Sample Size

This clinical study was designed to evaluate the safety and probable benefit of the Argus II Retinal Prosthesis System. It was originally intended to enroll 10 subjects. The study was later amended to increase the sample size to 30 subjects. This sample size was chosen because it would (a) provide a reasonable cohort of subjects in which this evaluation could be performed, and (b) it was feasible to enroll this number of subjects in a reasonable amount of time if the study were conducted at several centers of excellence in the field of retinal degeneration in Europe and the United States. Despite having 10 enrolling sites, the study took approximately 2 years to enroll 30 subjects, which demonstrates the challenge of finding individuals who met the subject selection criteria.

Scientific Advisory Meeting to Select Study Endpoints

At the time this study was designed, the basic framework for the study endpoints was understood based on trial designs for other ophthalmic devices. It was agreed that the study should be designed to evaluate the safety and probable benefit of the device, and that probable benefit should be measured both in terms of visual function (i.e., how the eye, as an organ works [e.g., visual acuity]), functional vision (i.e., how the patient performs in vision-related

activities of daily living), and quality of life. The goal was to select quantitative and qualitative endpoints that could be objectively measured. However, choosing the endpoints proved to be extremely challenging since there were no measurement tools that were designed and validated for use in this particular subject population (i.e., subjects with severe to profound vision loss).

Therefore, while developing the study protocol in 2006, Second Sight convened a meeting of scientific advisors who are experts in the field of low vision and low vision assessment tools to help choose the most appropriate endpoints for the study. The following scientific experts attended this meeting: Aries Arditi, PhD (Lighthouse International, New York, NY), Judith Babcock-Parziale, PhD (Tucson Veterans Administration, Tucson, AZ), Gislin Dagnelie, PhD (Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD), Greg Goodrich, PhD (Palo Alto Veterans Administration, Palo Alto, CA), Robert Massof, PhD (Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD), and Ron Schuchard, PhD (Atlanta Veterans Administration, Atlanta, GA).

For endpoint assessments (e.g., visual acuity, orientation and mobility, etc.), currently available tests designed for better-sighted individuals were adapted with assistance from these experts to meet the needs of subjects with severe vision loss. Some of these tests, such as orientation and mobility tests, also needed to be adapted for use across multiple sites (which often did not have the facilities to set up a permanent, sophisticated orientation and mobility course). These experts also helped identify two established questionnaires for use in the study, one for activities of daily living and one for vision-related quality of life. During the course of the study, some additional tests were added to better quantify visual function in the very-low-vision range (i.e., between no light perception and hand motion) and the orientation and mobility test methods were adjusted so that they would better characterize subjects' performances using the Argus II System versus not using the System.

In 2010, in collaboration with the FDA and another term of experts, Second Sight developed a new observer-rated assessment (the Functional Low-Vision Observer Rated Assessment or "FLORA") to evaluate functional vision and well-being (see Section 6.2.7.7). This team of experts was led by Duane Geruschat, Ph.D., COMS, CLVT (Johns Hopkins University and Salus University, Baltimore, MD), and included Michelle Bianchi, OTR/L, CLVT, James Deremeik, CLVT, CVRT, Marshall Flax, CLVT, COMS, Audrey Smith, Ph.D., CLVT, COMS, and Nilima Tanna, OT, CLVT.[21]

[21] OTR/L = occupational therapist, registered, licensed; CLVT = certified low vision therapist; CVRT = Certified Vision Rehabilitation Therapist; COMS = certified orientation and mobility specialist; OT = occupational therapist

Summary

Despite the challenges associated with designing a study in a rare disease population with few commonly accepted endpoint measurements, the resulting study protocol allowed for a robust analysis of the safety and probable benefit of the Argus II System. In addition, direct, controlled comparisons were achieved in this study by measuring many outcomes with the Argus II System turned ON and OFF.

6.2 PROTOCOL SUMMARY

6.2.1 STUDY OBJECTIVES

The objective of this study was to evaluate the safety and probable benefit of the Argus II Retinal Prosthesis System in providing visual function to blind subjects with retinitis pigmentosa.

Safety was assessed by collecting and analyzing rates of adverse events.

The Argus II System was intended to provide a basic level of artificial vision to the study subjects and, in doing so, improve their ability to perform activities of daily living and provide improvements in their quality of life. Both quantitative and qualitative assessments, as well as self-report questionnaires were used to objectively assess the probable benefit of the System.

6.2.2 STUDY DESIGN

This study was a prospective, single-arm, non-randomized, controlled, feasibility study. Due to the limited subject population and lack of other treatment options for the subject population, a large, randomized control trial was not feasible; however, subjects served as their own control at each time point for several endpoint measures where the System could be turned on and off. Performing tests in both conditions allowed the evaluation of performance with the System compared to performance with the subject's native residual vision.

Prior to initiating the study at any investigational site, approval from the Institutional Review Board (IRB) or Ethics Committee (EC) was obtained. FDA/Competent Authority approval was also obtained for the study in each of the countries (US, France, Switzerland, and UK) where the study was conducted. Changes made to the device or protocol were also pre-approved by the FDA/Competent Authorities and IRBs/ECs, as required.

Informed consent was obtained from all subjects.

6.2.3 SUBJECT INCLUSION/EXCLUSION CRITERIA

Subject Inclusion Criteria

Each subject was required to meet all of the following criteria to be enrolled in the study:

1. Have a confirmed history of retinitis pigmentosa with remaining visual acuity of bare light perception or worse in both eyes (i.e., worse than 2.9 logMAR).[22]
2. Have functional ganglion cells and optic nerve in the implanted eye as determined by documented light perception or a measurable electrically evoked response.
3. Have a history of useful form vision in the worse-seeing eye.
4. Be a minimum of 50 years old to enroll in the study. This age limit was conservatively chosen at the beginning of the study to minimize the risk to the subject. However, midway through the study, regulators approved a loosening of this age criterion to a minimum of 25 years old in the US and Switzerland and 18 years old in France and the UK.
5. Reside within two hours distance (by ground transportation) of the investigational site. Midway through the study, this criterion was expanded to 3 hours from the investigational sites in France and Switzerland to facilitate recruitment.
6. Be willing and able to comply with the protocol testing and follow-up requirements.

Subject Exclusion Criteria

Subjects meeting any of the following criteria were excluded from the study:

1. Optic Nerve disease
    a. History of glaucoma
    b. Optic neuropathy or other confirmed damage to optic nerve or visual cortex

[22] Midway through the study, this inclusion criterion was changed slightly (in Europe only) to a confirmed history of outer retinal degeneration and a grating visual acuity of 2.3 logMAR or worse in both eyes. This change was made in an effort to facilitate enrollment, which still proved challenging. Second Sight did not implement this change in the US since the FDA did not approve these changes. It should be noted that despite making these changes, they did not have an effect on the subjects actually enrolled in the trial. After the changes were implemented in Europe, only one subject was enrolled with a diagnosis other than RP (i.e., choroideremia) and no subjects were enrolled with a baseline vision better than 2.9 logMAR.

2. Diseases or conditions that affect retinal function including but not limited to:
    a. Central retinal artery/vein occlusion (CRAO or CRVO)
    b. End-stage diabetic retinopathy
    c. Retinal detachment or history of retinal detachment
    d. Trauma
    e. Infectious or inflammatory retinal diseases
3. Diseases or conditions that prevent adequate visualization of the retina including, but not limited to, cataract or corneal degeneration that could not be resolved before baseline testing. Cataracts that permitted visualization of the retina were not excluded but were removed at the time of implant surgery.
4. Diseases or conditions of the anterior segment that prevented the ability to adequately perform the physical examination including, but not limited to, trauma or lid malpositions.
5. Diseases of the ocular surface including, but not limited to, keratitis sicca and corneal ulcers.
6. An ocular condition that predisposed the subject to eye rubbing.
7. Any disease or condition that prevented understanding or communication of informed consent, study demands, and testing protocols, including:
    a. Cognitive decline including diagnosed forms of dementia and/or progressive neurological disease
    b. Psychiatric disease including diagnosed forms of depression
    c. Inability to speak a principal language associated with the region
    d. Deafness. Midway through the study, selective frequency hearing loss that prevented hearing device alarms and alerts was also added as an exclusion criterion.
8. Pregnancy.
9. Any metallic or active implantable device (e.g., cochlear implant) in the head.
10. Conjunctival thinning, which may predispose the subject to conjunctival erosion in the area where the implant will be installed extra-ocularly.
11. Participation in another investigational drug or device study that may conflict with the objectives, follow-up or testing of this study.
12. Any health concern that made general anesthesia inadvisable.
13. Unrealistic expectations of the System.
14. Known allergy or contraindication to anticipated pre-operative, intra-operative and post-operative medications. (Added midway through the study.)
15. Conditions likely to limit life to less than 1 year from the time of screening. (Added midway through the study.)

16. Diseases or conditions that, in the judgment of the surgeon, would impede the ability to implant the device or would prevent the System from functioning for the duration of the study (e.g., strabismus). (Added midway through the study.)
17. An axial eye length <21.5 mm or >26.0 mm in the implanted eye as measured by ultrasound. This change was only implemented in the U.S. (Added midway through the study.)

6.2.4 SAMPLE SIZE

The study was initially designed as a 10-person study. The study was then expanded to 30 subjects, which was determined to be both reasonably achievable and of sufficient power to measure safety and probable benefit, and has previously been accepted by FDA as sufficient for other orphan products[23] and HDE-approved products. Furthermore, in correspondence with the FDA regarding a pre-HDE meeting, the FDA recommended a sample size of 30-40 subjects to support the HDE application and indicated that even fewer subjects may be acceptable if most subjects could demonstrate some ability to distinguish spatial patterns within the area of the array.[24]

Although no formal statistical hypothesis was established for the larger 30-person sample size (and thus no formal sample-size calculation was prepared), the improvements observed in nearly all subjects using low-vision measures indicated that a group of 30 was sufficiently large to establish probable benefit.

6.2.5 DURATION OF FOLLOW-UP

The study was designed to have subjects participate for 3 years (36 months) so that extensive long-term follow-up data could be obtained on all subjects implanted with the device. Second Sight met with the FDA in February 2010 and obtained agreement that an HDE application could be submitted when a minimum of 1 year follow-up data had been collected on all subjects.

It should be noted that Second Sight elected in 2010 to extend the study for an additional 2 years/subject (i.e., a total of 5 years follow-up/subject) to allow subjects to continue to use the Argus II System at the end of the original 3 year study and to collect long-term follow-up data in expectation of FDA's desire for this information. For similar reasons, Second Sight recently extended the study in the U.S. an additional 2 years/subject to collect follow-up data through 7 years post-implant.

[23] Buckley BM. Clinical trials of orphan medicines. Lancet 2008; 371:2051-55.
[24] FDA Memorandum dated January 22, 2010 regarding I090874.

6.2.6 STUDY SCHEDULE

All subjects underwent standardized screening to ensure that they met the subject selection criteria defined in Section 6.2.3. This screening included: a medical evaluation, a complete eye exam, an ultrasound A-scan to measure the axial length of the eye, visual acuity testing, and a psychological evaluation.

All subjects enrolled in the study were implanted with an Argus II Retinal Prosthesis. The device was implanted in the subjects' worse-seeing eye; each subject was only implanted in one eye. The surgical implantation procedure and associated medication regimen were described earlier in Section 2.5.

Routine clinical follow-up and endpoint testing occurred throughout the follow-up period. Table 2 below provides the study schedule for the first 3 years. Table 3 provides the schedule for the 2 study extension periods (years 4-5 and years 6-7). There were minor variations in this schedule between the U.S. and Europe due to approvals granted by the Competent Authorities. These variations are noted and discussed in the footnotes. It is important to note that the processes for capturing and reporting safety data were the same at all sites in the U.S. and Europe. In addition, the case report forms used during the study were the same at all sites in the U.S. and Europe.

Following implantation, subjects came to the clinic weekly for several visits so that the System could be custom-programmed for their use at home and to conduct other research testing. This process of custom-programming is referred to as "System Fitting." Subjects underwent training in how to use the System and, once adequately trained, were provided the System to take home. Subjects started using the System at home between 1-3 months post-implant.

Subjects also participated in routine psychophysical research experiments to explore the effect of different stimulation parameters on their perception with the System. Subjects initially came in weekly for psychophysical research experiments and/or system fitting. As time went on, some subjects elected to reduce the frequency of these visits to 1-2 times per month.

Table 2: Protocol Study Schedule: Initial 3 Years

Evaluation or Test	Screening (-60 days – BL)	Baseline (BL) (-60 days – day 0)	Implant (Day 0)	1 Day (12-36 hours)	1 Week (5-9 days)	2 Weeks (12 – 16 days)	4 Weeks (24- 32 days)	3 Months (80-100 days)	6 Months (170-200 days)	9 Months[25] (250 – 290 days)	12 Months (340-380 days)	18 Months (525-565 days)	24 Months (700-740 days)	30 Months[25] (890 – 930 days)	36 Months (1070-1120 days)
Informed Consent	x	x													
Medical Evaluation	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Psychological Evaluation	x														
Complete Eye Exam	x			x	x	x	x	x	x	x	x	x	x	x	x
Visual Field		x							x		x		x		x
Retinal Photography, Fluorescein Angiogram, Optical Coherence Tomography		x			x		x	x	x	x	x	x	x	x	x
Ultrasound A-scan and B-scan[26]	x						x								
CT Scan[27]					x										
Document Fixation Position and Eye Movement Range		x			Performed on an as-needed basis.										
Visual Acuity, including Grating Acuity, Full Field Stimulus Threshold, and Electrically Evoked Response (EER)[28]	X							x	x		x	x	x		x
Orientation and Mobility Tasks, Massof Activity Inventory, VisQOL		x						x	x		x	x	x		x
Functional Low-Vision Observer Rated Assessment (FLORA)[29]											x				x
Square Localization & Direction of Motion[30]		x						x	x		x	x	x		x
Perceptual Thresholds for Electrical Stimulation							x	x	x		x	x	x		x
System Fitting and Psychophysical Testing					Ongoing. Typically 1-2 times per week.										
Home Use					Ongoing after subjects meets home use criteria.										

[25] Midway through the trial (in late 2008/early 2009), the 9 and 30 month follow-up visits were eliminated from the protocols in the UK, France and Switzerland. The FDA requested that these visits remain in the protocol for the US subjects.
[26] The ultrasound B-scan was added to the protocol in late 2010 and was not implemented as of the data cut-off for this report. At 4 weeks post-implant, only a B-scan is performed.
[27] This test was added midway through the trial (beginning in late 2007) but was not included in the UK protocol.
[28] EER was only performed at screening and only if the subject had no light perception.
[29] The FLORA was added to the protocol in late 2010. Since it was added to the protocol late, in order to collect data specifically requested by the FDA for the HDE application, it was performed as soon as possible after the subject signed the consent form, even if the subject was not in a study visit window.
[30] These tests began in 2009.

Table 3: Protocol Extended Follow-Up Schedule: Years 5-7

NOTE: In Europe, the study has only been extended to 5 years.

Evaluation or Test	**Enrollment in Years 4-5 Extended Follow-up** (After 36 Month follow-up)	**3.5 Years (40.5 – 43.5 Months)**	**4 Years (46.5 – 49.5 Months)**	**4.5 Years (52.5 – 55.5 Months)**	**5 Years (58.5 – 61.5 Months)**	**Enrollment in Years 6-7 Extended Follow-up** (After 5 Year follow-up)	**5.5 Years (64.5 – 67.5 Months)**	**6 Years (70.5 – 73.5 Months)**	**5.5 Years (76.5 – 79.5 Months)**	**7 Years (82.5 – 85.5 Months)**
Informed Consent	x					x				
Medical Follow-Up, including: Complete Eye Exam Current Medical Status Adverse Events		x	x	x	x		x	x	x	x
Retinal Photography			x		x					
Optical Coherence Tomography			x		x					
Visual Function Full-Field Stimulus Threshold (FST)* Photographic flash test Grating Visual Acuity Square Localization Direction of Motion			x		x					
Orientation and Mobility Tasks			x		x					
Massof Activity Inventory			x		x					
Functional Low-Vision Observer Rate Assessment (FLORA)		If not performed in years 1-3, perform as soon as practical following subject consenting to this additional assessment. This assessment will serve at the 3 year FLORA.								
Perceptual Thresholds for Electrical Stimulation			x		x			x		X
System Fitting and Psychophysical Testing	Optional at the joint discretion of subject and investigator. May occur as frequently as 1x/week, but usually occurs no more than 1x/month.									
Home Use	Optional at the discretion of the subject. Ongoing.									

* FST is only required at those centers that have a Diagnosys Espion System

6.2.7 STUDY ENDPOINTS AND ENDPOINT TEST METHODS

This study was designed to evaluate the safety and probable benefit of the Argus II Retinal Prosthesis System. It was a single arm study, but for several performance measures the subjects served as their own control since the System could be turned on and off.

6.2.7.1 SAFETY AND PROBABLE BENEFIT STUDY ENDPOINTS

Safety Endpoints

The primary safety endpoint for the study was the number, seriousness, and relatedness of all adverse events reported through the cut-off date of March 15, 2012. All adverse events were reviewed and adjudicated by an Independent Medical Safety Monitor.

Probable Benefit Endpoints

Visual Function

The primary probable benefit endpoint was visual function, which was assessed using the following tests:

- **Grating Visual Acuity**: The Grating Visual Acuity test was designed to determine a subject's visual acuity using the principles of acuity charts such as the ETDRS[31], modified for extremely low vision subjects. It measured the ability of subjects to determine the orientation of black and white bars and used this information to calculate the subject's visual acuity between 1.6 and 2.9 logMAR (20/796 – 20/15887).

  The Grating Visual Acuity test was modeled after standard tests such as the grating visual acuity test used by Optobionics Corporation[32], the BaGA (a grating acuity test developed by Bach, et al.[33]) and the FrACT[34].

[31] Early Treatment Diabetic Retinopathy Study (ETDRS). Visual acuity measurement for this clinical trial was performed with a letter chart, which has become standardized. The acronym often is used to refer to the chart/visual acuity measurement method itself.

[32] Bittner AK, Bowie H, Chow AY, et al. Repeatability of the Grating Acuity Test in Advanced Retinitis Pigmentosa (RP). Invest Ophthalmol Vis Sci, 46, ARVO abstract #517 (2005).

[33] 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(2):1255-60.

[34] Schulze-Bonsel K, Feltgen N, Burau H, et al. Visual acuities "hand motion" and "counting fingers" can be quantified using the Freiburg Visual Acuity Test. Invest Ophthalmol Vis Sci 2006;47:1236–1240.

Since the FrACT has been shown to reliably estimate visual acuity for subjects with hand motion or above, it is likely that the Argus II subjects who were able to score on the test would also be clinically classified as hand motion, count fingers or above. In discussions with the FDA, the Grating Visual Acuity test was determined to be a more controlled and precise measure than the more commonly used clinical measures of hand motion or count fingers.

- **Direction of Motion**: The Direction of Motion test was intended to objectively measure the ability of subjects to determine the direction of an object moving in the visual field. It is similar to the Motion Module in the Basic Assessment of Light and Motion (BaLM) developed by Bach, et al. [35]

- **Square Localization**: The Square Localization test was developed to objectively measure a subject's ability to locate objects. It is similar to the Location Module in the Basic Assessment of Light and Motion [BaLM], developed by Bach, et al.

Initially, the protocol only included the grating visual acuity test. As the study progressed, the Square Localization and Direction of Motion tests were added to quantify vision below the lower bound of the grating visual acuity scale but above bare light perception. Because of the longitudinal nature of the testing regimen, all subjects, irrespective of implant date, were subjected to all benefit endpoints, including the assessments added later in the study. Since some measures were introduced midway through the study (beginning in February 2009), it was obviously not possible to obtain them at all follow-up time points for subjects enrolled prior to that date.

Functional Vision and Quality of Life

Secondary endpoints included assessments of functional vision and quality of life, including:

- **Orientation and Mobility Tests**: This was an objective, quantitative measure of the ability of a subject to locate a door and follow a line.
- **Functional Low-Vision Observer Rated Assessment [FLORA]**: This was an assessment performed by an independent, low-vision therapist to evaluate subjects' use of the Argus II System in their every-day lives. It included both an interview of the subjects and an assessment of the subjects using the Argus II System in their normal environment (e.g.,

[35] Bach M, Wilke M, Wilhelm B, et al. Basic Quantitative Assessment of Visual Performance in Subjects with Very Low Vision. Invest Ophthalmol Vis Sci. 2010;51:1255–1260.

home, outside, etc.). This assessment was added to the protocol in late 2010 at the request of the FDA.

- **Massof Activity Inventory**: This was an adaptive questionnaire that assesses subjects' difficulty in performing activities of daily living. An excerpt from the Massof Activity Inventory is provided in Appendix A.
- **VisQOL**: This 6-question questionnaire was designed to assess the impact of vision loss on quality of life. A copy of this questionnaire is provided in Appendix B.

The FDA has not issued any guidance specific to trials on small populations. However, the European Medicines Agency, in its "Guideline on Clinical Trials in Small Populations," acknowledged that in clinical studies in small populations, it is often challenging to identify an appropriate primary endpoint. They advised that in these studies it can be acceptable to collect data from all sensible endpoints and present the totality of the clinical experience in the final report.[36] This is the strategy that has been adopted in this study.

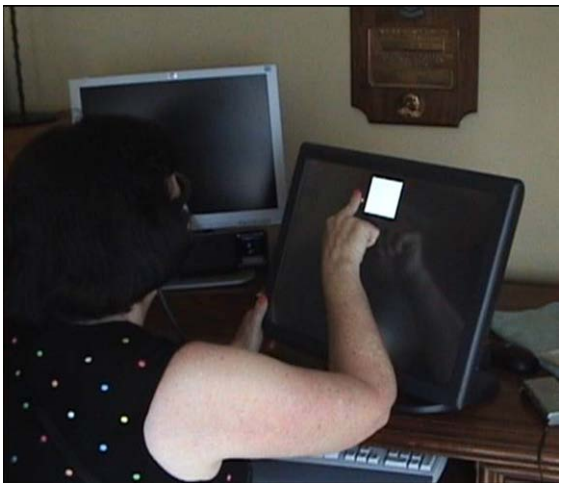
The methods for each of these tests are described below. The methods used in two additional research projects conducted during psychophysical research test sessions are described below as well.

6.2.7.2 SQUARE LOCALIZATION METHODS

Subjects were placed 12'' in front of a touch screen monitor. On each trial, a white 2.75" (7 cm) square was displayed at a random location on a black background and the subject was instructed to try to touch the square (Figure 7). Subjects were allowed to scan their head to locate the square. A test consisted of 40 trials. For each trial, the difference (in pixels) between the center of the target square and the subject's response was calculated; smaller values therefore indicate more accurate results. The test was repeated with the System ON and OFF for each subject at baseline and the designated follow-up visits. Subjects were tested binocularly – both eyes were open (unpatched) during all runs.

[36] "In some cases, the 'most appropriate' clinical endpoint may not be known or widely agreed or a validated clinical endpoint may not exist. In other cases, the mode of action of the test treatment may not be well enough known to predict which of several possible outcomes will be affected. In such circumstances, the usual approach of pre-specifying the primary endpoint may be too conservative and more knowledge may be gained from collecting all sensible/possible endpoints and then presenting all the data in the final trial report." Excerpted from "Guideline on Clinical Trials in Small Populations" issued by the European Medicines Agency. 27 July 2006. Page 6.

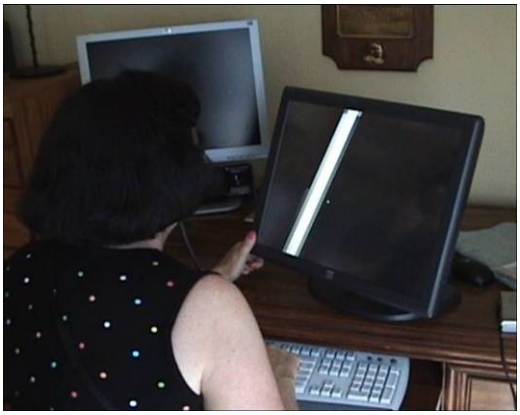
Figure 7: Subject Performing Square Localization Test



6.2.7.3 DIRECTION OF MOTION METHODS

Subjects were placed 12” in front of a touch screen monitor and were instructed to maintain head (camera) fixation on the center of the screen during the test. On each trial, after an audio prompt, a white line of fixed width (1.4’’, 3.6 cm) swept across the touch screen monitor at a random angle between 0 and 360° (Figure 8). After the stimulus presentation, subjects drew the direction of motion they perceived on the touch screen. A test consisted of 80 trials. For each trial, the difference between the stimulus angle and the response angle was calculated; smaller values therefore indicate a more accurate result. The test was repeated with the System ON and OFF for each subject. Subjects were tested binocularly – both eyes were open (unpatched) during all runs.

Figure 8: Subject performing the Direction of Motion Test



6.2.7.4 GRATING VISUAL ACUITY METHODS

The Grating Visual Acuity test was a four alternative forced-choice test in which black and white bars were presented in one of four orientations (horizontal, vertical, diagonal to the left or diagonal to the right), as shown in Figure 9. The bars were presented for 5 seconds; after 5 seconds, if the subject had not responded, the stimulus was replaced with a black screen and automated feedback informed them that the stimulus was off. Subjects were required to provide a response to each trial, even if they were just guessing. The widths of the bars were varied to evaluate different levels of visual acuity.

Figure 9: Example of Grating Visual Acuity (2.2 logMAR shown)

Subjects completed the test with the non-tested eye patched (i.e., monocularly). They completed the test 3 times: (1) Implanted eye, device ON; (2) Implanted eye, device OFF; and (3) Non-implanted eye, device OFF.

In the adaptive program, a total of 95 trials were presented and based on these results, a visual acuity score (ranging from >2.9 logMAR to 1.6 logMAR) and confidence interval for that score were determined (Refer to Table 4 for a conversion from logMAR to Snellen). Visual acuity results were considered valid if they had a 95% confidence interval (computed using the maximum performance estimated from a psychometric function fit of the data) that was fully contained within the tested scale (i.e., 2.9 – 1.6 logMAR)

Table 4: Grating Visual Acuity Scale and Conversion Chart

log MAR	Snellen
1.6	20/796
1.7	20/1002
1.8	20/1262
1.9	20/1589
2.0	20/2000
2.1	20/2518

log MAR	Snellen
2.2	20/3170
2.3	20/3991
2.4	20/5024
2.5	20/6325
2.6	20/7962
2.7	20/10024
2.8	20/12619
2.9	20/15887
N/A	Bare Light Perception (BLP)
N/A	No Light Perception (NLP)

6.2.7.5 ADDITIONAL RESEARCH - CHARACTER RECOGNITION AND READING WORDS

Between September 2009 and September 2010 all active Argus II subjects who were available for regular psychophysical testing were evaluated for their ability to recognize characters and read short words.[37]

A. Large character identification

For these tests, a standard size character (Century Gothic font, 600 pt, 8.9") was displayed on a computer monitor and the subject was asked to identify it. Subjects were seated 12" away from the monitor. All letters of the alphabet as well as numbers from 0 to 9 were included in the testing. The characters were split into four groups that were selected to represent increasing levels of typographical complexity. Testing was performed over multiple sessions.

Subjects were given unlimited time but were required to provide a response (by guessing if necessary). The subjects were aware of the character group being presented. A full test of a particular character group consisted of four trials of each letter (interleaved among trials for the other letters in the group). Full tests were run both with the System ON and OFF; testing was performed binocularly.

B. Word reading

The ability to read words was tested on four subjects who had, in prior research, demonstrated the ability to recognize smaller individual characters. Subjects were asked to identify various two-, three-, and four-letter words displayed in high contrast on a computer monitor. Subjects received no training in this task.

[37] During the year in which this research was conducted, some subjects were closer to 3 months follow-up while others were closer to 3 years.

All words included in the tests (10 words each of two-, three-, and four-letters) were selected using word lexical frequency and orthographic neighborhoods tables. English words were drawn from the public-access MRC Psycholinguistic Database created by Max Coltheart (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm) and French words from the public-access database Lexique (http://www.lexique.org/). The final words selected (10 of each length) were those with high lexical frequency and low orthographical neighbors, i.e., they were common words that are not easily confused with other words.

A time limit of 120, 180 and 240 seconds for two-, three- and four-letter words, respectively, was set with a warning 10 seconds from the end. Each word was presented once in each condition. The recorded outcome was the number of correct words.

6.2.7.6 ORIENTATION AND MOBILITY METHODS

To evaluate the clinical utility of the Argus II System for orientation and mobility, each subject completed two tests (walking to a high-contrast "door" on the wall and following a line on the floor).

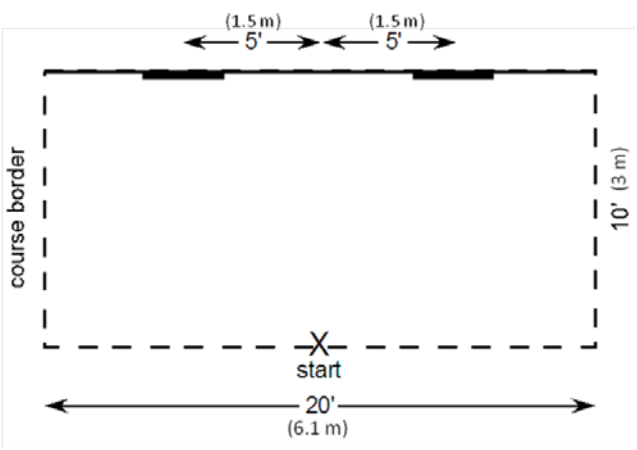
In the Door Task, a 3' X 7' black piece of felt was used to simulate a door and the subject was instructed to walk to the door and touch it (Figure 10). Trials where the subject's hand was touching the door were recorded as a "success."

In the Line Task, a 6" wide line was placed on the floor and the subject was instructed to follow the line to the end (Figure 11). Trials where the subject stopped within 6" of the end of the line were recorded as a "success."

For each task, subjects performed 6 trials with the device ON and 6 trials with the device OFF for a total of 12 trials. Repeating the tests with the System ON and OFF within each test session provided an important control for variability in the room, lighting, and configuration conditions. No other visual aids were used when the System was OFF.

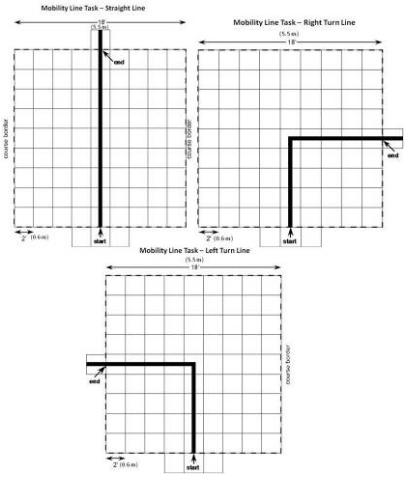
Some of the methods were modified for these tasks partway through the study (i.e., starting positions of the door and line configurations). A subgroup analysis was performed to demonstrate that the modification of these methods did not affect the study results. Refer to section 6.11.1.4 for a description of the modifications and a subgroup analysis.

Figure 10: Door Task



Note: While the figure above displays the 2 possible door positions (5' [1.5 m] to the left of center or 5' [1.5 m] to the right of center), only one door position was used at any one time for a particular "run" of the trial.

Figure 11: Line Task Diagram



6.2.7.7 FUNCTIONAL LOW-VISION OBSERVER RATED ASSESSMENT (FLORA) METHODS

Background—Assessment Development

In 2010, in response to a request from FDA, Second Sight developed a new observer-rated assessment to evaluate the functional vision of study participants.

In consultation with Duane Geruschat, Ph.D., COMS, CLVT[38] (Johns Hopkins University, Baltimore, MD; and Salus University, Elkins Park, PA) it was determined that there were no standardized functional vision assessments currently available that would be useful for this subject population, considering that these subjects were completely blind, had adjusted to life with no vision, and routinely used non-visual aids (canes, dogs, and/or human guides). Beyond even those difficulties, Dr. Geruschat believed that assessments normally used by low-vision therapists were aimed at patients with vision that exceeded Argus II subjects' theoretical vision.

A project was launched to develop the new assessment. The collaboration included O&M specialists, Occupational Therapists, Low Vision Therapists, and scientists, with input from FDA during the development process. The result was the Functional Low-vision Observer-Rated Assessment (FLORA), which was submitted to FDA and other regulatory agencies for inclusion in the clinical study protocol.

Assessment Tool and Conduct

The FLORA was added to the protocol in late 2010, to be performed at 1 year and 3 years post-implant. However, in order to collect data specifically requested by the FDA for the HDE application, it was performed as soon as possible after the subject signed the consent form, even if the subject was not in the 1 or 3 year study visit window.

The FLORA was administered to all currently-enrolled Argus II subjects between December 1, 2010 and April 8, 2011 by independent, certified low-vision rehabilitation experts who had been trained on the Argus II System and the FLORA tool itself. All assessors had an opportunity to interact with at least one Argus II subject prior to administering the assessment. In addition, they all participated in one of two conference calls in which they discussed their approaches to the administration of the tool (e.g., how they were planning on making judgments about ratings for the functional vision task performance). In many cases (depending on availability of subjects and therapists), assessors worked together in pairs. In the U.S. this often included one Orientation and Mobility Specialist and one Occupational Therapist. To perform the FLORA, assessors typically spent a half day with each subject at and/or near the subject's home.

The final FLORA tool consisted of three parts:

[38] COMS = Certified Orientation & Mobility Specialist; CLVT = Certified Low-Vision Therapist

Part 1: An in-depth interview of the subject by the assessors. Questions were provided to guide the discussion, such as: How do you use the [Argus II] system at home or work? What do you like about the system? What do you dislike?

Part 2: Observer-rated tasks, including Orientation and Mobility and Activities of Daily Living items, ranging from those expected to be possible (perhaps easy) for Argus II subjects (e.g., locate lights in the environment) and those likely to be difficult or impossible for many subjects (e.g., identify ordinary objects at various distances). Assessors were asked to rank each task (impossible, possible/difficult, possible/moderate, possible/easy) as well as identify how subjects performed it (vision only, some vision, no vision). Subjects performed tasks with the System ON and OFF. This assessment took place at or near the subjects' homes.

Part 3: A case-study narrative written by the assessors after the assessment. The case study served as the primary data for the assessment, as it represented the totality of the assessors' judgment and opinions about the effect of the Argus II System on the subject's everyday life.

In cases where assessors performed the assessments in pairs, they either wrote the case studies together, or each provided their opinions about the capabilities of the subject.

Data Analysis

Data analysis was performed by Dr. Geruschat, one of the independent assessors. Dr. Geruschat was masked to the assessors and subjects (except in the cases of the narratives he had produced as an assessor; n = 5). To perform the analysis, he was provided with Part 3 of each subject's FLORA, as reported verbatim from the assessors (forms from Geneva and Paris were translated from French to English), along with the suggested rating scale and instructions below. Dr. Geruschat reviewed these case reports and categorized each subject into one of the following groups:

- Positive effect: In general, a score of "positive effect" indicated that the subject self-reported an improvement in well-being and/or functional vision, which the assessor was able to confirm by observation. Feelings of satisfaction derived only from participation in a clinical study were not counted as positive effects.

- Mild positive effect: A score of "mild positive effect" indicated that the subject self-reported an improvement but the assessor was not able to confirm the report by observation.
- Prior positive effect: A score of "prior positive effect" indicated that the subject self-reported better function in the past than he or she was able to demonstrate on the assessment day.
- Neutral effect: A score of "neutral" generally indicated that neither the subject nor assessor believed the System had a net positive or negative effect on the subject's life.
- Negative effect. "Negative" indicated that the System had worsened the subject's life in some way.

Feelings of satisfaction derived only from participation in a clinical study (such as subjects feeling good that they were furthering research for future patients' benefit) were not counted as positive effects, as these would be unlikely to translate to benefits provided by the System outside of a clinical study.

6.2.7.8 MASSOF ACTIVITY INVENTORY METHODS

Changes in activities of daily living (ADLs) were measured using the subject self-reported Activity Inventory instrument developed by Robert Massof, Ph.D. (Johns Hopkins University, Baltimore, MD).[39, 40,41]

The Massof Activity Inventory (AI) is an adaptive functional vision questionnaire that consists of 457 Tasks nested under 50 Goals that in turn are nested under three objectives (daily living, social interactions and recreation). The tasks were grouped into subsets representing four visual function domains: reading, mobility, visual information (i.e., seeing) and visual motor (i.e., visually guided manipulation).

The questionnaire asked subjects to rate the importance of each Goal. For each Goal that has at least some importance, subjects rated the difficulty of the Goal and the difficulty of Tasks associated with that Goal. Consequently, each subject responded to an individually tailored set of questions that provided both a functional history and the data needed to estimate the subject's visual ability. The Activity Inventory data were scored and analyzed according to a method

[39] Refer to www.lowvisionproject.org

[40] Massof RW, Hsu CT, Baker FH, et.al. Visual Disability Variables I: The importance and difficulty of activity goals for a sample of low-vision patients. Arch Phys Med Rehab. 2005; 86: 946-53.

[41] Massof RW, Hsu CT, Baker FH, et.al. Visual Disability Variables II: The importance and difficulty of activity goals for a sample of low-vision patients. Arch Phys Med Rehab. 2005; 86: 954-67.

described by Dr. Massof.[42] For each follow-up time point, mean logit value and confidence interval (CI) for the overall population were calculated for Goals, Tasks and Domains by finding the maximum likelihood of difficulty for the population (using a Rasch distribution with an Andrich rating model). To evaluate changes over time between follow-up and baseline, a difference in logit values was calculated for the population using matched data (i.e., each subject had to have a score at both baseline and the follow-up time point being analyzed).[43] A positive change in the Goals or Tasks score was interpreted as an increase in functional ability. In other words, an increase in the overall score for Goals would mean that Goals were getting easier to achieve. Likewise, an increase in the overall score for Tasks would mean that for the population Tasks were easier to perform.

In personal communications with Second Sight, Dr. Massof provided more detailed guidance on how to determine if a change in logit scores was clinically significant and how to interpret the results based on his experience using the questionnaire in ophthalmology studies. Based on his research in more than 3,000 low vision subjects who were administered his Activity Inventory, Dr. Massof was able to provide the regression coefficient that allows one to benchmark the Massof Logit scores with visual acuity LogMAR values. Using this information, he advised that a clinically significant change of 0.2-0.3 logits is clinically significant. Thus, for this analysis, a clinically significant improvement was defined as a change ≥0.3 in the logit score between follow-up and baseline, while a clinically significant decline was a change ≤-0.3.

6.2.7.9 VISQOL QUESTIONNAIRE METHODS

The VisQOL questionnaire is a 6 question vision and quality of life-related utility measure that was intended to help perform economic evaluations of eye care and rehabilitation programs.[44] It was developed by a cooperative group of researchers at the University of Melbourne (East Melbourne, Australia) and Monash University (Clayton, Victoria, Australia).

The VisQOL is relatively recently developed survey that has not been used as an endpoint measure in any clinical studies to date. The scale focuses on broad quality of life issues related to vision and does not focus on specific visual tasks.

[42] Massof RW, Hsu CT, Baker FH, et.al. Visual Disability Variables II: The importance and difficulty of activity goals for a sample of low-vision patients. Arch Phys Med Rehab 2005; 86: 954-67.

[43] This was especially important for the domains such as reading, where a subject may not have found this important at baseline and thus would not have a score for that domain.

[44] Misajon R, Hawthorne G, Richardson J, et.al. Vision and Quality of Life: The Development of a Utility Measure. *Invest Ophthalmol Vis Sci.* 2005;46:4007-4015.

Nevertheless, a quality of life measure was considered to be a valuable assessment to include in this study.

The VisQOL was scored to produce a single dimension score also constrained to the range 0.00–1.00. For the VisQOL model, the lower scores (closer to 0) indicate a worse health state, while higher scores (closer to 1) indicate a better health state. The observed mean (and standard error) values across all subjects at each time point was calculated as well as the score at baseline and last visit completed.

6.2.7.10 ADDITIONAL RESEARCH – FUNCTIONAL VISION TASKS

To supplement the functional vision assessments in the protocol (the Orientation and Mobility tasks, Activity Inventory, and, later, the FLORA), three additional objectively-scored functional vision tasks were developed Second Sight in conjunction with investigators at the clinical sites. These tasks were performed by Argus II subjects with the System ON and OFF. These tasks were intended to mimic everyday activities that blind subjects may not be able to do without vision, and to measure – in uncontrolled, real-world environments – whether the Argus II System helped the subjects successfully perform them.

Between January 1, 2010 and November 30, 2010, all three Functional Vision tasks were performed by each enrolled subject during or close to each endpoint testing window. As Argus II subjects were implanted over the course of about two years, comparisons between subjects may be confounded by time post-implant. Therefore, results should be viewed as a snapshot of performance on these tasks rather than a metric through which performance of different subjects can be directly compared.

<u>Sock Sorting</u>

Subjects were presented with 30 socks jumbled together in a pile: 10 pure white socks, 10 pure black socks, and 10 of an intermediate gray color. The subjects' task was to sort the socks into three piles representing the three different colors. In order to meet the requirement of objective scoring, the articles to be sorted were socks of the same style, size and shape; all socks were bought from the same manufacturer and were intended to be indistinguishable by touch.

The task was performed in the clinic in lighting conditions that varied from site to site. Subjects sorted the socks four times: once each with the Argus II system ON and OFF and the surface of the table covered in a known-color of cloth (either black or white, as preferred by the subject), and once each with the system ON and OFF on a bare table.

Sidewalk Tracking

For this task, the tester identified three different 20-foot stretches of grass or low shrubbery bordered by concrete or asphalt such as a sidewalk, driveway, parking lot, etc. Some edges were straight; others were curved or angled. The subject was asked to walk along each of the three 20' paths on the concrete within three feet of the concrete/grass edge without stepping on the grass. The subject did not use any mobility aid such as a cane or a dog guide during the test. The test consisted of 3 trials with the system ON and three trials with the system OFF. The order of trials was varied by the tester.

Performance was measured by the number of times the subject moved out of bounds, that is, when they stepped on the grass or when they moved further than three feet away from the concrete/grass border. If subjects moved out of bounds during the trial, the tester corrected their direction accordingly, and subjects continued to complete the trial.

Direction of Walking

For this task the subject was seated, and markers were placed ten feet away. The test began with two testers positioned on the markers, on either side of the subject. Every fifteen seconds one of the testers crossed the subject's field of view by moving from one side to the other (an audible beep determined the start of each trial). A few seconds after the audio prompt, the subject identified in what direction the tester was moving. This was a two-alternative forced-choice test; if the subject did not see movement, he/she was asked to guess. The test consisted of 40 trials. Some care was taken to reduce the possibility of auditory cues – for example, testers may have removed their shoes. However, as the task was intended to represent real-world conditions, no masking noise or noise-cancelling headphones were used. The task was performed with the system ON and OFF.

Performance was measured by the number of correct answers, i.e., the trials in which the subject correctly identified the direction of the person walking in front of him/her.

6.2.8 ANALYSIS METHODS

Descriptive statistics (median/mean ± standard deviation for continuous variables and proportions for categorical variables) were used to analyze results in the study. Since statistical tests were not defined, *a priori*, in the clinical protocol, no p-values are presented below for endpoints, consistent with input from FDA.

6.3 ENROLLMENT AND LENGTH OF FOLLOW-UP

A total of 30 subjects were enrolled and implanted in this study. Table 5 on the next page lists the sites and investigators who enrolled the subjects.

Table 5: Enrollment by Site

Site ID	Site (City, State/Country)	Investigator(s)	# of Enrolled Subjects
[redacted]	University of Southern California, Doheny Eye Institute (Los Angeles, CA)	Dean Eliott, MD (PI) (Start of study to 12/10) Amani Fawzi, MD (PI) (12/10 to 12/11) Lisa Olmos, MD (PI) (12/11 to present) Mark Humayun, MD, PhD Rajat Agrawal, MD Eliot Sohn, MD	2
[redacted]	Johns Hopkins Hospital, Lions Vision Research and Rehab Center (Baltimore, MD)	Gislin Dagnelie, PhD (PI) Julia Haller, MD (Start of study through 1/08) James Handa, MD	5
[redacted][45]	Scheie Eye Institute (Philadelphia, PA)	Artur V. Cideciyan, PhD (PI) Samuel Jacobson, MD PhD	2
	Wills Eye Hospital (Philadelphia, PA)	Gary Brown, MD (PI) Allen Ho, MD Carl D. Regillo, MD Julia Haller, MD (6/09 to present)	
[redacted][46]	Columbia University, Edward S. Harkness Eye Institute (New York, NY)	Lucian del Priore, MD PhD (PI) (Start of study to 9/11) Stephen H. Tsang, MD PhD (PI starting in 9/11) Stanley Chang MD	1
	Lighthouse International (New York, NY)	Aries Arditi, PhD (PI)	
[redacted]	Retina Foundation of the Southwest (Dallas, TX)	David Birch, PhD (PI) Rand Spencer, MD	2
[redacted]	University of California, San Francisco (San Francisco, CA)	Jacque Duncan, MD (PI) Eugene de Juan, MD	2
[redacted]	Moorfields Eye Hospital (London, UK)	Lyndon da Cruz, MD (PI) Andrew Webster, MD	7
[redacted]	Manchester Royal Eye Hospital (Manchester, UK)	Paulo Stanga, MD (PI) Susmito Biswas, MD George Turner, MD	3
[redacted]	Le Centre Hospitalier National D'Ophtalmologie des Quinze-Vingts (Paris, France)	Jose Sahel, MD (PI) Pierre-Olivier Barale, MD Saddek-Mohand Said, MD Sarah Scheer, MD	4
[redacted]	Hôpitaux Universitaires de Genève, Clinique d'Ophtalmologie (Geneva, Switzerland)	Avinoam Safran, MD (PI) (Start of study to 9/10) Farhad Hafezi, MD (PI) (10/10 to present) Marco Pelizzone, PhD Joel Salzmann, MD	2

PI = principal investigator

[45] Surgery and clinical follow-up were performed by investigators at Wills Eye Hospital. Endpoint testing and psychophysical research were performed by investigators at Scheie Eye Insitute.

[46] Surgery and clinical follow-up were performed by investigators at Edward Harkness Eye Institute. Endpoint testing and psychophysical research were performed by the investigator at Lighthouse International.

Recruitment Challenges

Anticipating that it would be challenging to enroll subjects in this study due to the rarity of the disease, Second Sight elected to conduct the study at 10 sites, 6 in the US and 4 in Europe (in New York and Philadelphia, two centers in each city counted as one site because they ran the study jointly by splitting study responsibilities). These sites were selected based on the strong reputation of their vitreoretinal surgeon(s) and vision scientists. In addition, most were nationally recognized centers of excellence in retinal degeneration.

Since the European centers and investigators selected for the study have a similar high quality of care and clinical research as the US centers, the decision to include them in the study to facilitate recruitment was justified. Section 6.11.1.2 provides a sub-group analysis of data from the US subjects compared with that from the European subjects. This analysis supports the poolability of these data.

The first subject was enrolled on June 6, 2007 and the last subject was enrolled on August 5, 2009. Despite the fact that 10 internationally recognized eye hospitals were participating in the study, enrollment of the 30 subjects took a little over two years. This was partially due to the fact that enrollment was paused for approximately 7 months, but was mostly due to the fact that the Argus II System is intended for a rare patient population, many of whom had stopped going to their ophthalmologists.

The higher enrolling centers tended to either have a history of conducting clinical trials in RP patients and/or were the main hospital for retinal degeneration within their country. These centers typically had a database of patients that they initially screened for eligible study subjects. Once these centers had worked through this backlog of eligible, waiting patients, recruitment typically became more challenging for them.

Duration of Follow-Up

In early March 2012, the FDA requested that Second Sight provide an update of the clinical data. Therefore, the data cut-off for this report is March 15, 2012. All data received by Second Sight and entered in the clinical database as of that date were included in the report.

All subjects enrolled in the study are a minimum of 2.5 years post-implant (with the exception of subject XX-XXX who was explanted at 14 months). Approximately 50% of the subjects enrolled earlier in the study have completed 3 years follow-up and approximately 25% of subjects enrolled earliest in the study have completed 4 years follow-up. Refer to Table 6 below.

Table 6: Length of Follow-Up

Data cut-off date	March 15, 2012
Mean ± SD follow-up (years)	3.5 ± 0.9
Median follow-up (years)	3.1
Range follow-up (years)*	2.6 – 4.8
Total subject-years follow-up	104.7

* Minimum implant duration excludes the one subject explanted at 14 months post-implant.

6.4 SUBJECT ACCOUNTABILITY

No subjects withdrew from the study. During the 3 year study, two subjects did not complete all the assessments for the following reasons:

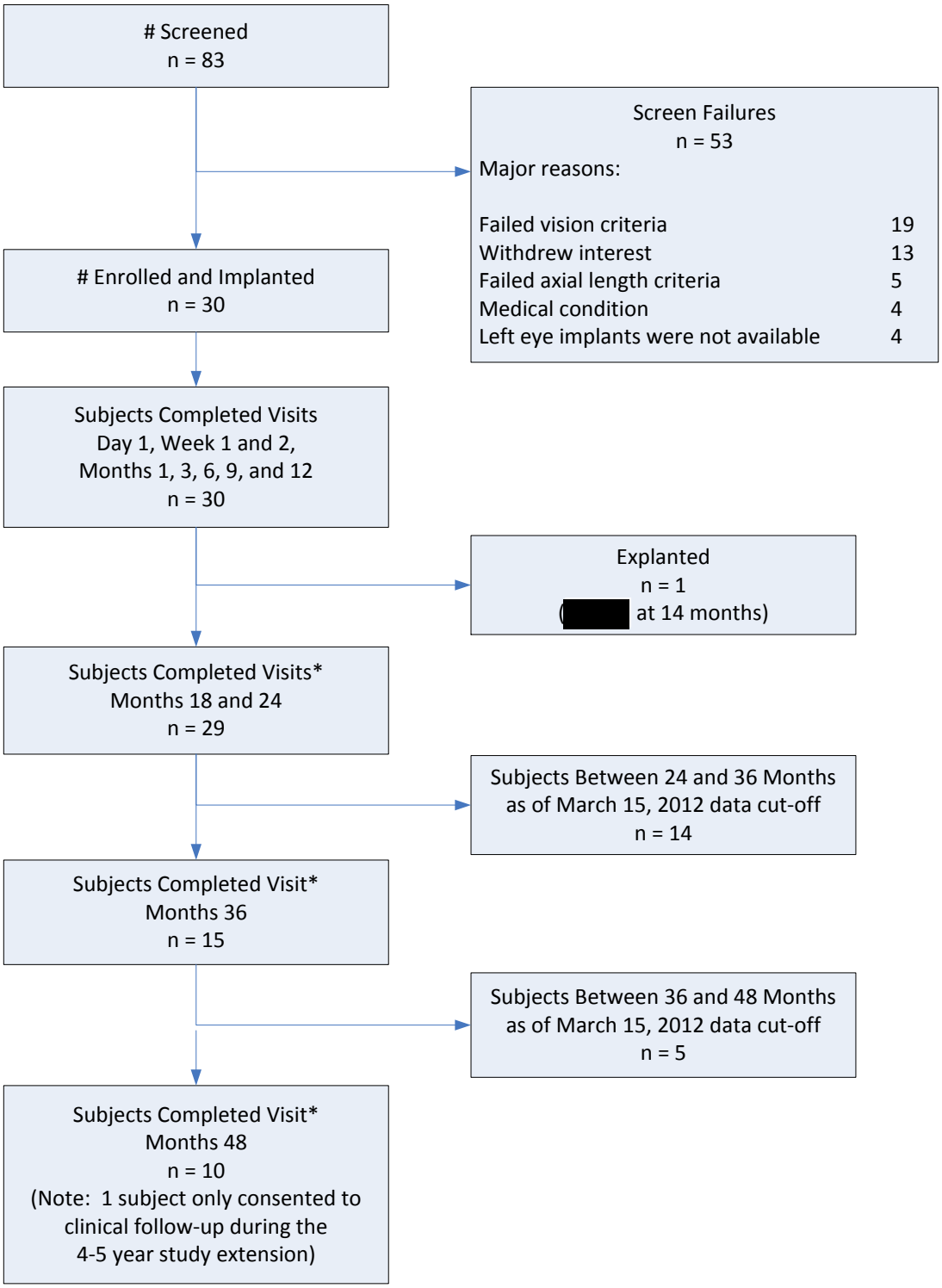
1. Subject XX-XXX was explanted 14 months post-implant due to recurrent conjunctival erosion (see Section 6.7.2). The subject has told the investigators that the subject would like to be re-implanted.
2. Subject XX-XXX's implant began experiencing a significant decline in the RF link at 10 months post-implant. This link is necessary for the implant to deliver stimulation. He continued to use the System, when possible, until the implant failed just prior to 3 years post-implant (Refer to Section 6.9). The subject still has the device implanted and would also like to receive a new implant.

Following completion of the initial 3 year study, subjects were offered the opportunity to extend their participation in the study for an additional 2 years (years 4-5). All subjects who had reached this time point elected to continue, but one subject (XX-XXX) consented only to clinical follow-up. He is still implanted, but he discontinued home use of the Argus II System.

Figure 12, below, provides an accountability of the subjects screened and enrolled in this trial.

Other than some data missing for XX-XXX and XX-XXX, there was very little data missing in the trial due to protocol deviations. Since there were few missing data points at any particular assessment time point, these missing data did not materially affect the assessment of safety or probable benefit of the Argus II System.

Figure 12: Subject Accountability



* For some subjects who completed the visit, their data were not yet collected and entered into the database as of the March 15, 2012 data cut-off.

6.5 DEMOGRAPHICS

Table 7 summarizes the key baseline demographics for the 30 subjects. The demographics highlight a couple of key aspects of the subjects enrolled in the study:

- Almost all subjects (97%) were bare light perception in both eyes at the time of implant. One subject was no light perception at implant.
- Subjects had been blind (i.e., bare light perception) for many years prior to receiving the Argus II implant, and were thus well-adapted to being blind. The average number of years at BLP at the time of implant was 16 years, with a range of 1 – 27 years.

Table 7: Subject Demographics

(n=30 subjects)

	Average	Median	Range
Age at Time of Implant (years)	58.3	57.9	27.8 - 77.4
Age at time of diagnosis (years)	23.1	22.5	2 - 54
Years since diagnosis of RP at time of implant	35.2	35.1	7.3 - 53.4
Age when vision declined to BLP*	39.1	38	20 - 69
Years of BLP at time of implant	15.9	17.5	1.5 - 26.9
# Years In School**	13.9	12.5	9.0 - 23.0
	n	**%**	
Gender			
Female	9	30.0%	
Male	21	70.0%	
Diagnosis			
Retinitis Pigmentosa	29†	96.7%	
Choroideremia††	1	3.3%	
Residual Vision at Baseline			
Implanted Eye			
Bare Light Perception	29	96.7%	
No Light Perception	1	3.3%	
Non-implanted Eye			
Bare Light Perception	30	100.0%	
Other Medical Conditions			
Diabetes	2	6.7%	
Depression	2	6.7%	
Migraines	2	6.7%	
Hearing loss	3	10.0%	
History of Smoking			
Never smoked	18	60.0%	
Past Smoker	6	20.0%	
Current smoker	6	20.0%	
Previous Eye Surgery (implanted eye only)			
Cataract	10	33.3%	
Other Ocular Surgery in the implanted eye	1‡	3.3%	

* BLP = Bare light perception. These data were not collected on the case report forms until midway through the trial and thus were only available on 15 subjects and only 4 in the US. No major differences were evident.

** These data were not available on 2 subjects.

† One subject (XX-XXX) had Leber Congenital Amaurosis.

†† The subject with choroideremia (XX-XXX) was enrolled in the UK, which allowed a slightly broader entry diagnosis of "outer retinal degeneration" than that used in the US (i.e., "retinitis pigmentosa").

‡ XX-XXX had prior pars plana vitrectomy to clear vitreous debris and experimental sub-conjunctival placental injections.

6.6 IMPLANTATION SURGERY RESULTS

Table 8 summarizes the implantation surgery details. All subjects were implanted in their worse seeing eye or, if the eyes were equivalent, the surgeon selected the eye to be implanted in consultation with the subject. Twenty-six subjects were implanted in their right eye, and four were implanted in their left eye. This disparity in the implant eye was due to the fact that until early 2009, only right eye implants were manufactured and available.

The median implant surgery time was 4 hours, 4 minutes (range 1:53 to 8:32 hours). The longest procedure was for subject XX-XXX. This implant procedure was complicated by the fact that the subject had several previous surgeries on his implanted eye (prior pars plana vitrectomy to clear vitreous debris and experimental sub-conjunctival placental injections), which left extensive scarring underneath the conjunctiva that required slow and careful dissection. In addition, this subject's lateral rectus muscle was fibrosed and disinserted and required re-insertion. The next longest procedure was 5 hours, 48 minutes.

All 30 subjects were successfully implanted with the Argus II Retinal Prosthesis by many surgeons, demonstrating the surgical procedure can be effectively learned by new surgeons who undergo training offered by Second Sight (Refer to Section 9, Clinician Training).

Table 8: Summary of Surgical Information

	Median (Range) Or % (n)
Eye implanted	
Left	13% (4)
Right	87% (26)
Implanted eye axial length (mm)	23.4 (20.5 – 25.6)
Lens removed	
Natural lens removed	67% (20)*
IOL removed	3% (1)
Sclerotomy width (mm)	5.0 ± 0.5 (4.5 – 6.0)
Well adhered posterior hyaloid that was peeled and/or epiretinal membrane that required peeling	57% (17)
Material used to cover extraocular portion of device	
Tutoplast® sclera	47% (14)
Tutoplast® pericardium	30% (9)
Aponeurosis	10% (3)
Banked sclera	10% (3)
PTFE patch	3% (1)
Duration surgery (Hours:Minutes)	4:04 ± 1:18 (1:53 – 8:32)

* All subjects were left aphakic, with the exception of one who had an IOL installed.

6.7 SAFETY RESULTS

6.7.1 INDEPENDENT MEDICAL SAFETY MONITOR

Second Sight's Independent Medical Safety Monitor is Suber Huang, MD. Dr. Huang is Professor of Ophthalmology and Vice Chairman of the Department of Ophthalmology at Case Western Reserve University (Cleveland, Ohio), Director of Vitreoretinal Diseases at University Hospitals Case Medical Center (Cleveland, Ohio), and Current President of American Society of Retina Specialists (ASRS).

During the study, all reported adverse events were subject to detailed review by Dr. Huang, both as individual events and collated data. For individual events, he reviewed and adjudicated the investigator's assessment of the event, which included the reportable terms, whether or not it met the definition of an adverse event (see Appendix C for anticipated adverse events and related definitions), the relatedness of the event (i.e., whether it was primarily device-, surgery-, or subject-related), and whether or not it met the regulatory definition of a serious adverse event (see definition below). In cases where the IMSM's findings differed from that reported by the investigator, notifications were sent to the investigators for their records. In no cases did the IMSM adjudicate an AE as

non-serious when the investigator had originally classified it as serious. In one case, the IMSM adjudicated an AE as serious, when the investigator had originally classified it as non-serious. The IMSM's decision was considered to be final; however, this process included active involvement of the Principal Investigators in determining which observations constituted adverse events and the reasons for considering such events as serious or not per the FDA and ISO standard definition described below. One of the IMSM's roles was to ensure consistency in reporting from different sites.

6.7.2 SERIOUS ADVERSE EVENTS RELATED TO THE DEVICE OR SURGERY

Serious adverse events (SAEs) were defined according to ISO 14155-1, 2003 (Clinical investigation of medical devices for human subjects – Part 1: General requirements), which is slightly broader than the FDA definition of a serious adverse event. SAEs were defined as medical occurrences that:

- Caused death,
- Were life threatening,
- Caused permanent impairment of a body function or permanent damage to body structure,
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage,
- Required hospitalization or prolonged hospitalization, or
- Caused fetal death or abnormality.

The majority of subjects (n=19 or 63%) did not experience any serious adverse events. Eleven subjects experienced a total of 23 SAEs. Ten of the 23 events were considered to be related to the Argus II device and the remaining 13 were considered to be related to a surgical procedure.

Table 9 presents a summary of SAEs by medical event and time of occurrence. Most SAEs were categorized as such because they required a surgical procedure to treat the event (e.g. re-suturing the conjunctiva or the sclerotomy). The majority of SAEs occurred in the immediate post-operative period (first 60 days) and all SAEs occurred within the first 2 years post-implant

Table 10 provides a listing of SAEs by subjects. This presentation of the data illustrates how events were clustered in certain subjects and how several events were inter-related. A detailed narrative of each subject is provided in Appendix D (Section 14.4).

Table 9: Serious Adverse Events (Device- or Surgery-Related)

	# of Events by Onset Time					Totals		
Reportable Term – Serious	**0-30 Days**	**1 - 2 Mo**	**2 – 6 Mo**	**6 Mo – 2 Yr**	**>2 Yr**	**# of Events**	**# of Subjects**	**% Subjects (n=30)**
Hypotony	-	1	1	2**	-	4	4	13.3%
Conjunctival erosion	-	1	-	3	-	4	3	10.0%
Intraocular inflammatory events:								
Presumed endophthalmitis - culture negative	1	2	-	-	-	3	3[†]	10.0%
Uveitis	-	1	-	-	-	1	1[†]	3.3%
Conjunctival dehiscence*	2	1	-	-	-	3	3	10.0%
Fibrotic events:								
Retinal detachment – rhegmatogenous	-	-	1	-	-	1	1	3.3%
Retinal detachment - tractional and serous	-	-	-	1	-	1	1	3.3%
Retinal tear	-	1	-	-	-	1	1	3.3%
Re-tack	2	-	-	-	-	2	2	6.7%
Corneal melt – infective	-	-	-	1	-	1	1	3.3%
Corneal opacity	-	-	-	1	-	1	1	3.3%
Keratitis – infective	-	-	-	1	-	1	1	3.3%

- No events at this time point.

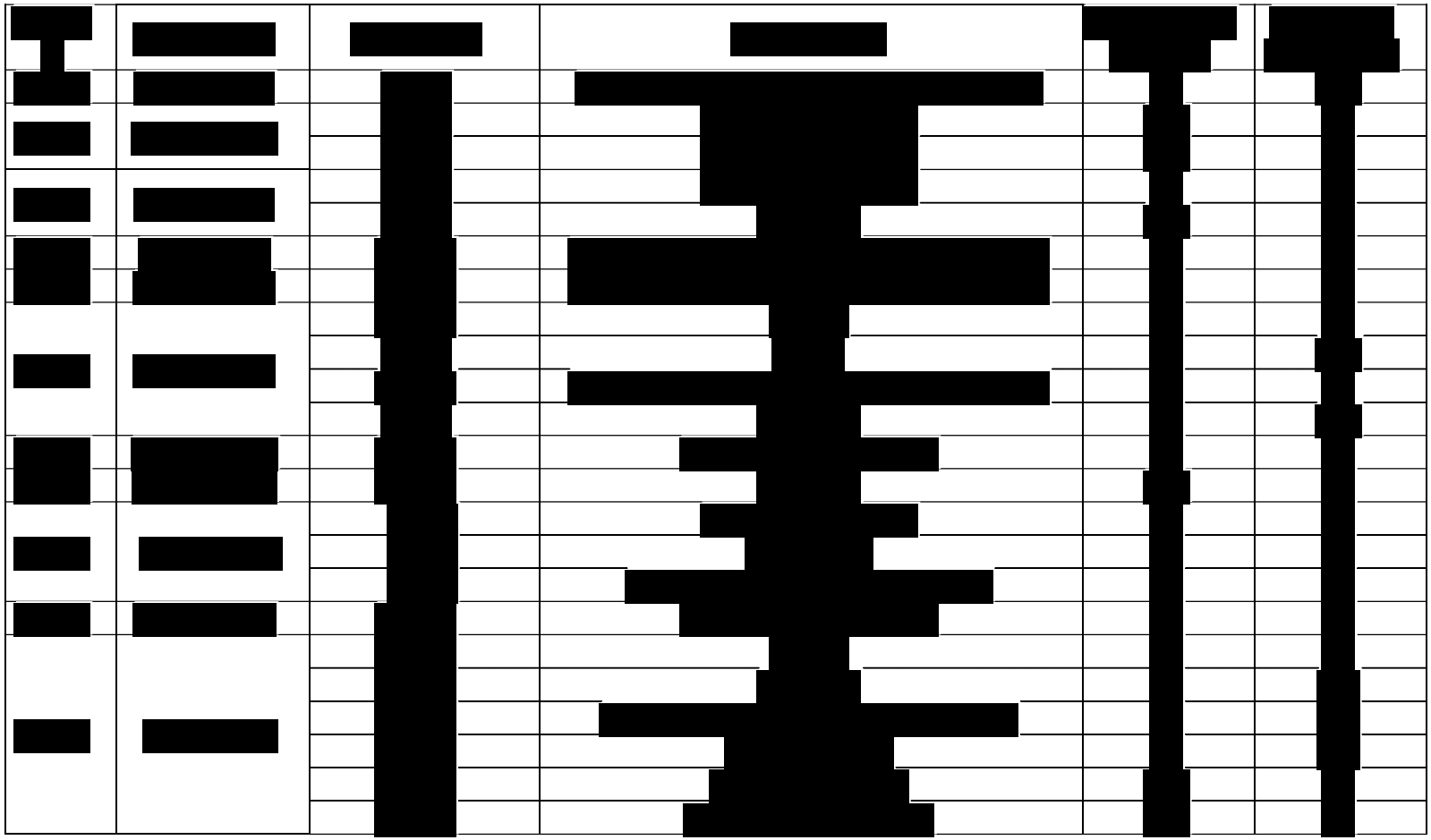
[†] One subject had uveitis followed by presumed endophthalmitis.

* Includes one incidence of conjunctival autograft dehiscence

** One of these events occurred at 2 years and 18 days.

Table 10: Serious Adverse Events by Subject

It became apparent that the majority of SAEs were clustered in a few subjects. A detailed narrative of each subject is provided in Appendix D (Section 14.4).



The majority of SAEs were resolved within 1-2 months through standard drug treatment and/or surgical intervention. Four SAEs resolved slowly (2-11 months), two were resolved by explanting the device, and 3 remained stable as of this report. There were no catastrophic events (e.g., loss of an eye).

A discussion and analysis of the SAEs is provided below in Section 6.7.5.1.

6.7.3 NON-SERIOUS ADVERSE EVENTS RELATED TO THE DEVICE OR SURGERY

Any adverse event that did not meet the definition of an SAE (as defined above in Section 6.7.2) was considered to be a non-serious adverse event. Table 10 summarizes the non-serious device and surgery-related adverse events. Once again, these events were all anticipated side effects associated with the implantation surgery and presence and/or use of the Argus II implant. These events normally resolved on their own or were treated with medical management (i.e., they did not require surgical intervention to treat).

A total of 140 non-serious (device or surgical procedure related) adverse events were reported, of which 78 were device-related and the remaining 62 were surgery-related. Of these 140 events, 39 (27%) occurred within the first post-operative month and 69 (49%) occurred within the first 6 months, and 83 (59%) occurred within the first 12 months.

A discussion and analysis of non-serious adverse events is provided below in Section 6.7.5.2.

Table 9: Non-Serious Device- and Surgery-Related Adverse Events

	# of Events by Onset Time				Totals		
Reportable Term – Non-Serious	0-30 Days	1-6 Mo	6 Mo - 2 Yr	>2 Yr	# Events	# Subjects	% Subjects (n=30)
Pain – ocular	3	1	8	5	17	9	30.0%
Fibrotic events:						13**	43.3%
Proliferative vitreoretinopathy (PVR)*	-	-	1	-	1	1	3.3%
Retinal detachment – tractional*	-	-	1	-	1	1	3.3%
360° Circumferential vitreous band traction*	-	1	-	-	1	1	3.3%
Epiretinal membrane	-	3	7	1	11	11	36.7%
Fibrosis around the tack	-	-	1	-	1	1	3.3%
Intraocular Inflammatory events:						10**	33.3%
Uveitis*	-	4	2	-	6	5	16.7%
Inflammation – ocular	1	2	1	-	4	4	13.3%
Ocular fibrin	-	-	-	1	1	1	3.3%
Keratic Precipitates	-	2	-	1	3	2	6.7%
Conjunctival congestion	8	3	-	-	11	10	33.3%
Elective revision surgery	-	-	7	-	7	7	23.3%
Hypotony*	6	-	1	-	7	7	23.3%

	# of Events by Onset Time				Totals		
Reportable Term – Non-Serious	0-30 Days	1-6 Mo	6 Mo - 2 Yr	>2 Yr	# Events	# Subjects	% Subjects (n=30)
Suture irritation	3	3	1	-	7	6	20.0%
Choroidal detachment	4	1	1	-	6	6	20.0%
Conjunctivitis – inflammatory	1	1	2	1	5	4	13.3%
Retinal thickening - cystoid macular edema (CME)	-	1	3	1	5	5	16.7%
Retinal thickening - without cystic changes	-	3	1	-	4	4	13.3%
Vitreous hemorrhage	1	1	1	1	4	4	13.3%
Headache	1	-	1	1	3	3	10.0%
High IOP	1	-	2	-	3	2	6.7%
Hyphema	1	-	2	-	3	3	10.0%
Corneal vascularization	-	-	2	-	2	2	6.7%
Epiphora	2	-	-	-	2	2	6.7%
Foreign body sensation	-	-	1	1	2	1	3.3%
Choroidal effusion	-	1	-	-	1	1	3.3%
Conjunctival cyst	-	-	1	-	1	1	3.3%
Conjunctival dehiscence*	1	-	-	-	1	1	3.3%
Conjunctival erosion*	-	-	-	1	1	1	3.3%
Corneal abrasion	1	-	-	-	1	1	3.3%
Corneal dryness	-	1	-	-	1	1	3.3%
Corneal epithelial defect	-	-	1	-	1	1	3.3%
Corneal filaments	-	-	1	-	1	1	3.3%
Corneal fold	-	-	-	1	1	1	3.3%
Corneal suture broken	-	-	-	1	1	1	3.3%
Decrease in light perception	1	-	-	-	1	1	3.3%
Filamentary keratitis	1	-	-	-	1	1	3.3%
Nausea	1	-	-	-	1	1	3.3%
Nystagmus increase	1	-	-	-	1	1	3.3%
Ptosis	-	-	1	-	1	1	3.3%
Retinal detachment - serous	-	-	-	1	1	1	3.3%
Retinal folds	-	-	-	1	1	1	3.3%
Retinoschisis	-	-	1	-	1	1	3.3%
Rubeosis	-	1	-	-	1	1	3.3%
Scleral patch displacement	-	-	-	1	1	1	3.3%
Scleritis	-	1	-	-	1	1	3.3%
Subconjunctival eyelashes	-	-	-	1	1	1	3.3%
Vertigo	1	-	-	-	1	1	3.3%

* These events did not require surgical intervention to treat (or if there were treated surgically, they were not the primary reason for the surgical intervention) therefore they were classified as non-serious events. Refer to the Section 6.7.5.1 for further discussion of these events.
** Some subjects had more than one fibrotic or intraocular inflammatory event.

6.7.4 SAFETY OF DEVICE EXPLANT

There was one case of device explant (XX-XXX) in which the tack and implant were completely removed to treat recurrent conjunctival erosion and hypotony. The explant surgery was uneventful and other than temporary high IOP and

corneal filaments in the immediate post-operative period, there were no other adverse events in the one year post-explant follow-up period. This subject has told the investigators at the site that she would like to be re-implanted with the Argus II implant.

In addition to the full device explant, the retinal tack was removed from the retina without incident in 5 subjects. In 3 elective revision surgeries, the retinal tack was removed from the retina and the device was re-tacked. There were also two cases where the retinal tack became dislodged between the time of implant and one week post-implant.

In none of these cases were there adverse sequelae associated with removal of the tack or the implant, indicating that the Argus II device has been safely explanted.

6.7.5 DISCUSSION AND ANALYSIS ADVERSE EVENTS

6.7.5.1 SERIOUS ADVERSE EVENTS

Conjunctival Dehiscence or Erosion

Five subjects experienced 7 SAEs of conjunctival dehiscence or erosion of the surgical wound which required surgical interventions to resolve. In addition, two events did not require surgical intervention and they were therefore categorized as non-serious: one case of early post-op conjunctival dehiscence and one late (2.5 years post-op) re-occurrence of conjunctival erosion.

All wound dehiscence cases occurred either in the first month (n=3) post-implant or within the second month post-implant (n=1, which occurred within two weeks following a repair of conjunctival erosion). All cases of wound dehiscence resolved and no re-occurrences were observed.

Conjunctival erosion occurred early (within 2 months) in the one case mentioned above) and between 9-12 months in 2 subjects. Both subjects with late conjunctival erosion (XX-XXX and XX-XXX) experienced multiple re-occurrences and one of these subjects (XX-XXX) required device explant to resolve the event.

In reviewing all cases, it appears that the initial implant surgery was the most significant factor in determining the risk of conjunctival breach at some point. In particular, the integrity and depth of the sutures was important. In one case (XX-XXX), the position of the suture tab may have contributed to the eventual erosion through the conjunctiva.

Conjunctival erosion and dehiscence are known risks when devices are implanted under the conjunctiva. One risk associated with conjunctival breach is endophthalmitis; however, there were no incidences of endophthalmitis associated with the conjunctival erosion/dehiscence in Argus II subjects. In addition, the erosions and wound dehiscences were all resolved surgically without further complications.

Beginning in 2009, midway through enrollment in the study, Second Sight implemented some minor adjustments to the surgical technique and the implant design to reduce the incidence of conjunctival erosion and dehiscence. Surgeons were instructed to suture the Tenons and conjunctiva to the limbus, in order to maximize the amount of tissue over the implant, and to use closely spaced sutures when closing the conjunctiva. To reduce the bulk underneath the conjunctiva, it was recommended that the surgeon use one layer of Tutoplast® pericardium (rather than two layers of Tutoplast sclera, which is thicker) to cover the junction of the implant electronics package and cable. Surgeons were instructed to make the relaxing incisions in the conjunctiva away from the electronics package/coil region of the implant to make it easier to re-closing the incisions at the end of the case. In addition, on the implant, the height of the electronics package was reduced slightly by 0.015" and, to allow the device to be more securely attached to the eye, the suture tabs were reinforced and an additional suture tab was added to the electronics package.

During surgeon training, Second Sight reviews the instructions from the Surgeon Manual intended to reduce the occurrence of conjunctival erosion or dehiscence and provides instruction in how to monitor for and treat one should it occur.

Presumed endophthalmitis - culture negative

Culture-negative, presumed endophthalmitis occurred in three (3) subjects, one in the immediate post-operative period and two cases approximately five and eight weeks post-operatively. All cases presented with ocular pain and varying levels of vitreous opacity and hypopyon. **No cases were associated with pre-existing conjunctival erosion or hypotony. All cases resolved completely with medical management and none required explantation.**

The first case (subject XX-XXX) presented on the third post-operative day and intravitreal antibiotics were initiated. All cultures were negative, the subject became asymptomatic, and the event was closed eleven days after its onset.

Both of the later presenting cases (XX-XXX and XX-XXX) were more severe and took longer to resolve but also resolved completely. These cases occurred in two subjects implanted on the same day in the same operating theater. Anti-inflammatory drugs were initiated, cultures were taken (all results came back

culture negative) and antibiotics were implemented. Subject XX-XXX had a single treatment of intra-vitreal antibiotics. Subject XX-XXX received one course of intravitreal antibiotics and an antifungal, followed up 3 days later with a second course of intravitreal injection of antibiotics. Both subjects responded to treatment.

As a result of these three cases, a rigorous and detailed investigation was conducted. The surgical procedure was reviewed and it was found that the implant surgery times were slightly longer for subject XX-XXX (5 hours) than normal, average for XX-XXX (4 hours), and slightly shorter for XX-XXX (3 hours) (mean implant time across all 30 subjects was 4 hours). The two subjects at site 51 were the first two implants performed at this center, which resulted in more personnel (i.e., observers) in the operating theatre than usual, and more personnel movement in and out of the room, and these factors may have accounted to some extent for the slightly longer surgical times. In addition, some of these individuals did not wear face masks in the operating theatre. A review of the implant surgery procedures did not reveal any common features unique to these three cases. However, Subject XX-XXX required a second procedure one week post-implant to re-tack the array to the retina (see section below regarding re-tacks). This occurred well before any evidence of endophthalmitis, but may have been a factor in this subject's ensuing infection.

Despite a thorough investigation of the device history records, surgical suite and surgical procedures, no root cause could be determined for these events. However, several potential contributing factors were identified and adjustments were instituted to the surgical guidelines beginning in January 2009. These included instructing the surgeons to cover the cable/array portion of the implant with a sleeve while the extraocular part of the implant was being installed. The company emphasized the need for strict rigor for prepping the subject's eye for surgery, ensuring that all personnel in the operating room cover their noses and mouths with masks, and limiting the flow of people in and out of the operating room. Surgeons were instructed to avoid injecting viscoelastic solutions into the eye as this may cause inflammation. Following implantation, subject testing with the device was delayed until at least 1 week post-implant to allow the conjunctiva to heal. Finally, as an extra precautionary measure, the antibiotic coverage for implanted subjects was increased by administering a treatment dose of intravitreal antibiotics at the conclusion of the surgery and increasing the length of post-operative oral and topical antibiotics from 7 to 14 days. Optional instructions were provided for soaking the implant in antibiotics after the implant sterile packaging was opened and before the start of the extra-ocular placement of the implant on the eye. After these measures were implemented, there were no further cases of presumed endophthalmitis.

In addition, during surgeon training, Second Sight reviews the instructions and warnings and precautions from the Surgeon Manual, and provides instruction in how to monitor for and treat endophthalmitis.

Uveitis

Uveitis was reported as SAE for subject XX-XXX approximately 6 weeks after surgery. The subject exhibited inflammation and, based on clinical suspicion of developing endophthalmitis, was commenced on oral antibiotics and topical steroids. [redacted]. After 24 hours of no response to topical steroids alone, treatment for endophthalmitis was initiated (as described before). Signs of inflammation persisted until 10 months post diagnosis.

Four other subjects also experienced uveitis early (2 to 4 months) postoperatively and were regarded to be surgery- (n=2) or device- (n=2) related non-serious events. They resolved with drug treatment within two weeks to three months, but one of the subjects (XX-XXX) had a re-occurrence at 18 months. There was also one late (13 months) occurrence of uveitis that was resolved with treatment within 3 months.

Intracameral inflammation is a common risk following any eye surgery, and particularly after implanting a device into the posterior chamber.

Retinal Detachment and Tear

One subject (XX-XXX) had an asymptomatic retinal defect ("retinal tear") repaired by laser shortly after implant surgery (and the intervention made it a serious adverse event). Two cases of retinal detachment, which eventually required surgical intervention to treat, occurred around the 5-6 month post-implant period (XX-XXX, XX-XXX). Both subjects had other retinal complications (360^{o} circumferential vitreous band traction and PVR, respectively) that were categorized as non-serious. These two subjects both also experienced fibrosis in the eye, which resulted in subsequent traction on the retina. In the case of Subject XX-XXX, the fibrosis was initiated by blunt trauma that resulted in vitreous hemorrhage. [redacted] Importantly, in both subjects, the retina under the electrode has remained attached following the repair procedures and they were able to continue to use their Argus II Systems.

One additional subject was diagnosed with a tractional retinal detachment, four months after a diagnosis of fibrosis around the retinal tack. This detachment is currently stable, has not required intervention, and was thus categorized as non-serious.

To address this issue, Second Sight now includes the following instructions in the Surgeon Manual:

> "Perform a complete vitrectomy, with removal of the posterior vitreous. To facilitate visualization of the vitreous and retinal surface, Triamcinolone approved for intraocular use (e.g., Triesence™) may be injected into the eye. Also, carefully remove peripheral vitreous at the nasal port and in the superior temporal quadrant by pressing on the sclera at those locations. Remove any epi-retinal membrane present in the region where the array is to be located."

In addition, during surgeon training, Second Sight emphasizes the steps listed above and provides instruction in how to monitor for and treat a retinal detachment in the post-implant setting.

Hypotony

In the study, hypotony was defined as intraocular pressure <5 mmHg that persisted for greater than two weeks, or was associated with kissing choroidals or with a flat anterior chamber. Four subjects had hypotony that was classified as serious because it required an intervention to treat. Two of these cases occurred within the first six months (2 and 5 months) of implant. The earlier case developed after the onset of uveitis with endophthalmitis, and the other case was attributed to tractional vitreous proliferation (due to insufficient removal of the retinal vitreous at the time of surgery) which resulted in traction on the ciliary body. One case of serious hypotony occurred at one year (in association with conjunctival erosion that ultimately resulted in the explanting of the device), and one occurred at 2 years post-implant in a subject with chronic, bilateral low IOP. Three of the four cases resolved. The fourth subject developed a rhegmatogenous retinal detachment in addition to hypotony, and both are unresolved, but stable.

In addition, seven cases of hypotony were categorized as non-serious as they resolved without invasive intervention. Six of these events occurred within 10 days of the implant surgery and resolved with IOP elevating treatment within a few days to six weeks. One case (XX-XXX) occurred 10 months post-operatively and was related to a retinal detachment; the pressure normalized after 8 months.

Hypotony is an accepted risk of any procedure requiring sclerotomy, and particularly so in cases where an intraocular device is placed across the sclera within the sclerotomy to connect intra- and extra-ocular parts of the device. To reduce the risk of hypotony, minor changes to the implant cable were instituted midway through the study to make it thinner and more flexible in the transcleral region (Refer to Section 6.11.1.1). These changes were introduced into the study in early 2009 and 15 subjects were implanted with the revised device. While there were still two new hypotony SAEs following implementation of these changes, neither of these cases of hypotony were attributed to leaks at the sclerotomy. Importantly, the rate of non-serious hypotony declined since the implementation of these changes (from 6 cases in the first 15 subjects enrolled in the study to 1 case in the last 15 subjects enrolled in the study).

During surgeon training, Second Sight provides instruction in how to monitor for and treat hypotony.

Re-tack

Two subjects (XX-XXX and XX-XXX) required the array to be re-tacked to the retina shortly after the implant surgery. In both cases it became apparent in the first few days post-operatively that the tack was not secure, either through imaging and/or measurements of the device function. In both cases the tack was successfully re-attached near the same site.

A number of implanting surgeons (including the two surgeons whose subjects had to be re-tacked) had no prior experience with retinal tacks and the technique of releasing the tack from the tack tool. There have been no reports to date of tacks dislodging late, rather both cases were a result of inadequate initial placement.

In response to these cases, Second Sight added the following instructions to the Surgeon Manual:

“The surgeon will know that the head to the tack is through the sclera when a ‘pop’ is felt. If no pop is felt, pull gently on the tack to ensure that it is secure.”

During surgeon training, these instructions are emphasized, and instructions are provided for how to monitor for and treat a dislodged tack in the post-operative setting.

Corneal Defects

Three consecutive, procedure-related SAEs and two non-serious complications affecting the cornea were reported for the same subject (XX-XXX). [redacted]

Four singular non-serious events of corneal complications were also reported in other subjects: corneal dryness, post-explant corneal filaments, corneal fold, and corneal vascularization. Overall, with exception of the single subject (XX-XXX) detailed above, corneal defects do not appear to be major complications related to implanting the device.

6.7.5.2 NON-SERIOUS ADVERSE EVENTS

During the first two years post-implant (the observation period that all subjects have surpassed at the time of data cut-off for this report), the most common non-serious adverse events were ocular pain (12 events), conjunctival congestion (n=11), epiretinal membrane (10), hypotony (7), suture irritation (7), elective revision surgery (7), choroidal detachment (6), and uveitis (6). Hypotony and uveitis were discussed in the previous section.

Ocular pain was mostly related to a physical insult to the eye (e.g., bumps to the head) or to electrical stimulation (i.e., during or after new settings were downloaded to the subject's Video Processing Unit). Pain related to physical insult was treated with non-prescription medications and typically lasted under 1 month. Pain related to electrical stimulation was resolved by adjusting the stimulation settings.

Conjunctival congestion typically resolved without intervention and lasted approximately 2 weeks to 3 months, although one case took 15 months to resolve and one event is still open.

Epiretinal membrane (or a well-adhered posterior hyaloid) was removed in 17 of the 30 subjects during surgery. Of these 17 subjects, epiretinal membranes reoccurred in six subjects in the first two years post-operatively, and it was also observed in four further subjects. The timepoint of (re-) occurrence did not correspond in any of the subjects to a vitreo-retinal adverse event and no systematic change in visual performance could be observed as a result of the development of an epiretinal membrane.

Suture irritation resolved with no intervention or was treated with topical medications and typically lasted under 1 month, although one case took 23 months to resolve.

Choroidal detachments resolved without any treatment and typically lasted 2 weeks to 3 months with one exception that took 8 months to resolve. Of the 5 cases of choroidal detachment, 3 occurred concurrent with hypotony.

During the study, the investigators observed several subjects whose array was either not well-positioned over the macula, or whose array was not in close contact with the retina. In consultation with the Second Sight, the investigators felt that some of these subjects may obtain better performance with the Argus II System if they underwent elective revision surgery to better position the array. A total of seven subjects underwent such an *elective* revision surgery (i.e., surgery was not performed to treat an adverse event). Four subjects had a second tack placed in the distal region of the array to attempt to improve the apposition of the array to the retina. One subject had his tack removed and the device was re-tacked in the same location using a shorter tack. For two subjects, the surgeons attempted to better position their array over the macula. All elective revision surgeries occurred at least 9 months after initial implant and they were performed without significant sequelae. The results of these revision surgeries were mixed, with some subjects experiencing an improvement in performance and others experiencing minimal or no improvement. Our current surgical guidance emphasizes the importance of placing the array over the macula.

6.7.5.3 OVERVIEW OF SAFETY EXPERIENCE

The majority of subjects (n = 19; 63%) in the Argus II study experienced no or only non-serious device- or surgery-related events. Non-serious events were treated routinely with medication or observation only.

An additional 23% of subjects (n=7) experienced serious adverse events that resolved with medical treatment or minor interventions.

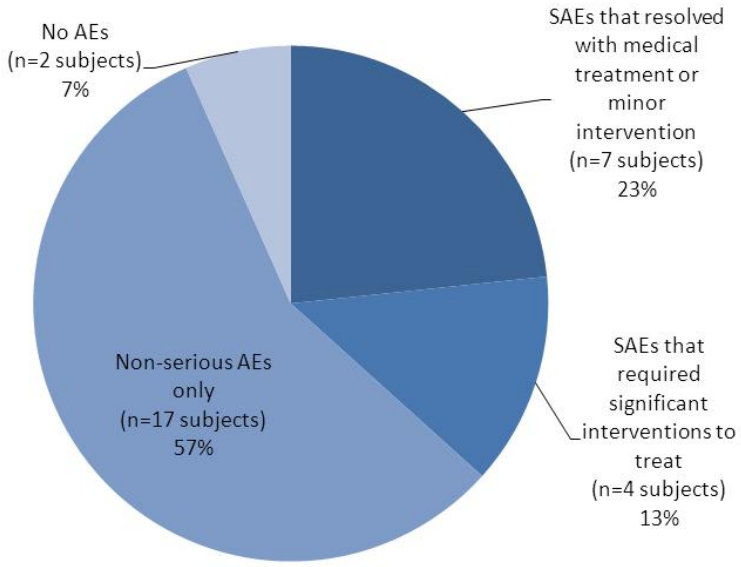
The remaining four subjects (XX-XXX, XX-XXX, XX-XXX, and XX-XXX) were distinct from the other 26 subjects in that they had multiple SAEs due to a cascade of related events. These 4 subjects accounted for 57% of all SAEs and 24% of all non-serious adverse events. Refer to Figure 13.

The majority of SAEs were resolved within 1-2 months through standard drug treatment and/or surgical intervention. Four SAEs resolved slowly (2-11

months), two were resolved by explanting the device, and 3 remained stable but unresolved as of this report. There were no catastrophic events (e.g., loss of an eye).

Figure 13: Overview of Safety Experience

NOTE: Device- or surgery-related events only (n=30 subjects)

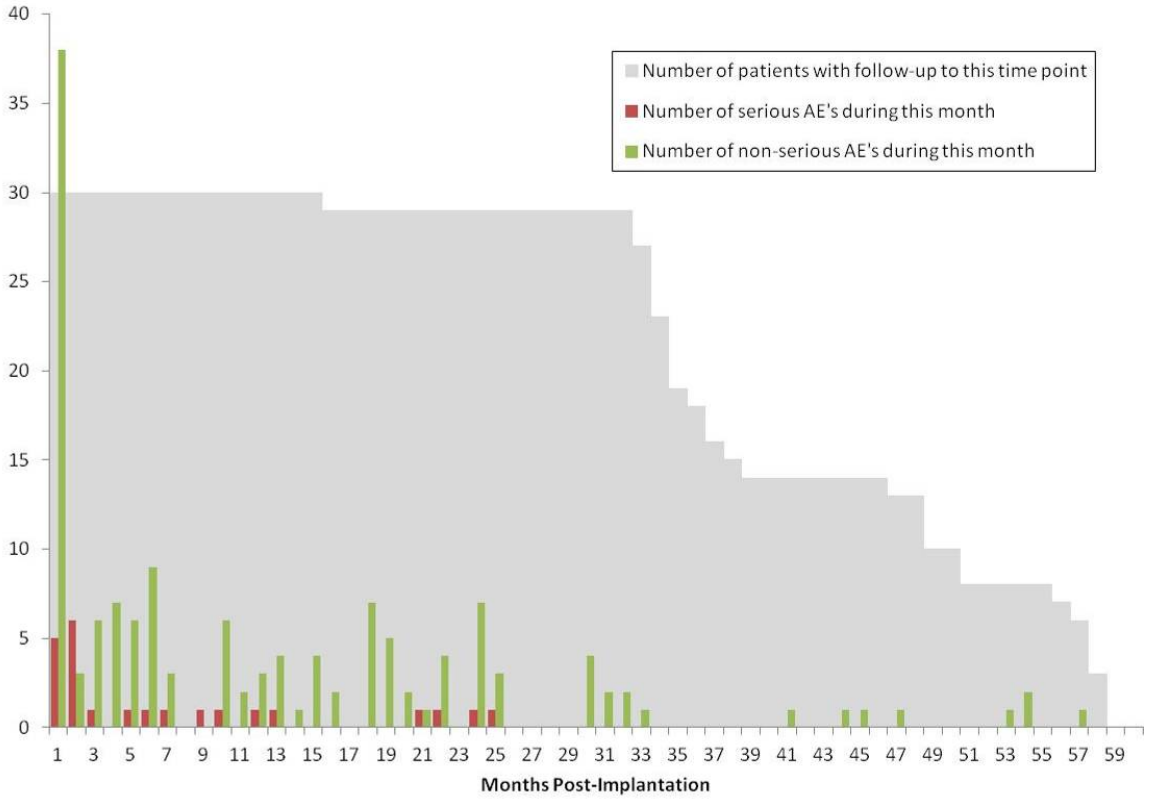


	No adverse events	Non-serious AEs only	SAEs that resolved with medical treatment or minor intervention	SAEs that required significant interventions to treat
# (%) Subjects	2 (7%)	17 (57%)	7 (23%)	4 (13%)
# SAEs	0	0	10	13
# Non-serious AEs	0	72	34	34

6.7.5.4 ONSET OF ADVERSE EVENTS

Figure 14 illustrates when events occurred with respect to the time implanted. As expected with a surgical procedure, most events occurred around the time of surgery. Half of the subjects have reached at least 4 years post-implant. **It is important to note that after 2 years post-implant, there have been no serious adverse events and very few non-serious events.**

Figure 14: Incidence of Device- or Surgery-Related Adverse Events over Time



6.7.6 CONCLUSIONS REGARDING SAFETY

This study has shown that the Argus II System has an acceptable safety profile for patients who are blind due to severe to profound RP. Extensive and detailed safety data have been generated from the long-term implantation of the Argus II retinal prosthesis, a first-of-its kind device, in an orphan population of 30 subjects suffering from severe to profound outer retinal degeneration. Mean follow-up per subject for safety data was 3.5 ± 0.9 years (median = 3.1 years, range 2.6 – 4.8 years[47]) with an overall implant duration of 104.7 subject-years. In no instance were any *unexpected* serious (or non-serious) adverse events reported in this study.

In summary:

1. **The majority of subjects (63%) experienced no or only non-serious adverse events**. An additional 23% experienced serious adverse events that resolved with medical treatment or minor interventions. The

[47] Minimum implant duration excludes the one subject explanted at 14 months post-implant.

remaining 13% of subjects (n=4) were distinct from the other 26 subjects in that they had a much higher rate of adverse events due to a cascade of related events.

2. **Most events occurred in the first 6 months post-implant.** In addition, after 2 years post-implant, there have been no serious adverse events and very few non-serious events.
3. **Most adverse events were managed without further complications and were successfully treated to resolution using standard techniques**. All adverse events that were observed in the study were anticipated events that ophthalmologists and vitreoretinal surgeons encounter in their normal practice. They could therefore be treated using standard medications or surgical techniques. There were only 3 permanent AEs, all of which were non-serious and did not have clinically relevant sequelae (e.g. epiretinal membrane). Only one subject, who experienced a cascade of AES, had stable but unresolved SAEs (i.e., hypotony, retinal detachment, and corneal opacity) at the time of this report.
4. **There were no catastrophic events.** (e.g., loss of an eye)
5. **The majority of SAEs were resolved within 1-2 months through drug treatment and/or surgical intervention.** Four SAEs resolved slowly (2-11 months), two were resolved by explanting the device, and 3 remained stable but unresolved as of this report.
6. **Adverse Events did not adversely affect performance with the Argus II System.** In no case did the Argus II implant stop working as a result of an adverse event. In addition, there was no clear trend observed of adverse events leading to a decline in performance.
7. **Lessons learned in the early part of the study led to some procedural and design changes that contributed to modest reduction in the occurrence of adverse events in the last 15 subjects enrolled in the study.** The procedural modifications and lessons learned during the clinical trial have been incorporated into the Surgeon Manual and surgeon training program. While there was a "collective learning" about how adverse events could be avoided, there did not appear to be a per-surgeon learning curve. The fact that 10 sites implanted subjects indicates that vitreoretinal surgeons can be successfully trained to perform the implant procedure.

6.8 ASSESSMENT OF CHANGE IN RESIDUAL LIGHT PERCEPTION DURING THE STUDY

All subjects were required to have bare light perception (BLP) or worse in both eyes before implantation. Subjects' residual native bare light perception (i.e., without the use of the Argus II System) was tested monocularly in both eyes using a Full-Field Stimulus Threshold (FST) test or a photographic flash test.

These results were monitored over the course of the study to evaluate changes in residual light detection (Table 11).

Table 11: Change in Native Residual Vision over Time

Residual Vision	Bare Light Perception n (%)	No light Perception n (%)
Pre-Implant		
Implanted Eye	29 (97%)	1 (3%)
Non-Implanted Eye	30 (100%)	0
As of Last Follow-Up		
Implanted Eye	29 (97%)	1 (3%)
Non-Implanted Eye	28 (93%)	2 (7%)

Almost all subjects had bare light perception (BLP) in both eyes prior to implant and at the latest follow-up visit (as indicated either by a light detection threshold value or a passing score on the photographic flash test). The exceptions were:

- XX-XXX was no light perception (NLP) in the implanted eye before implantation (intact ganglion cells confirmed by EER), but was BLP as of the latest follow up visit.
- XX-XXX was BLP in both eyes at the time of implant and NLP in both eyes as of the latest follow up visit.
- XX-XXX was BLP in both eyes at the time of implant and NLP in the fellow (non-implanted) eye during the latest follow up visit.

Since two subjects (XX-XXX and XX-XXX) both also declined to NLP in the fellow eye at the last follow-up exam, it appears that their decline may have been caused by a natural progression of the disease.

Taken together, assessments of residual vision throughout the study indicated that the Argus II implant has not led to a clinically significant decline in residual light perception when compared to fellow eyes.

6.9 IMPLANT FUNCTIONALITY

During final manufacturing of the implant, each unit was inspected and tested to determine which electrodes met all specifications. Electrodes that met all specifications were “enabled” and those that did not meet all specifications were “disabled.” The Video Processing Unit (VPU) prevented stimulation on disabled electrodes. During the clinical trial, the implant specification required that the fully assembled device have a minimum of 48 enabled electrodes. Subjects had

an average of 55.5 ± 3.6 (standard deviation) electrodes enabled at the time of implant.

The VPU firmware has a built-in safeguard system that monitors impedances of the electrodes each time the VPU is turned on to test for "open" electrodes. If an electrode's impedance measurement is too high, it is automatically disabled by the VPU to prevent any chance of stimulating on an "open" electrode. An average of 1.2 ± 1.8 electrodes per subject was automatically disabled by the VPU due to high impedance.

There was one implant failure during the clinical trial. One subject (XX-XXX) had extremely limited use of his device due to an intermittent RF link between December 2008 and January 2012. This implant eventually failed (in January 2012); however, the device remains implanted. An investigation indicated that this problem was most likely due to damage to the implant coil by pic forceps during the original implant procedure. It is important to note that this subject reported great benefit from the device prior to its failure and has requested to be implanted with a new device. To prevent this event from happening in future patients, the Surgeon Manual was revised to caution against using sharp instruments (especially pic forceps) when handling the implant.

6.10 PROBABLE BENEFIT RESULTS

6.10.1 VISUAL FUNCTION

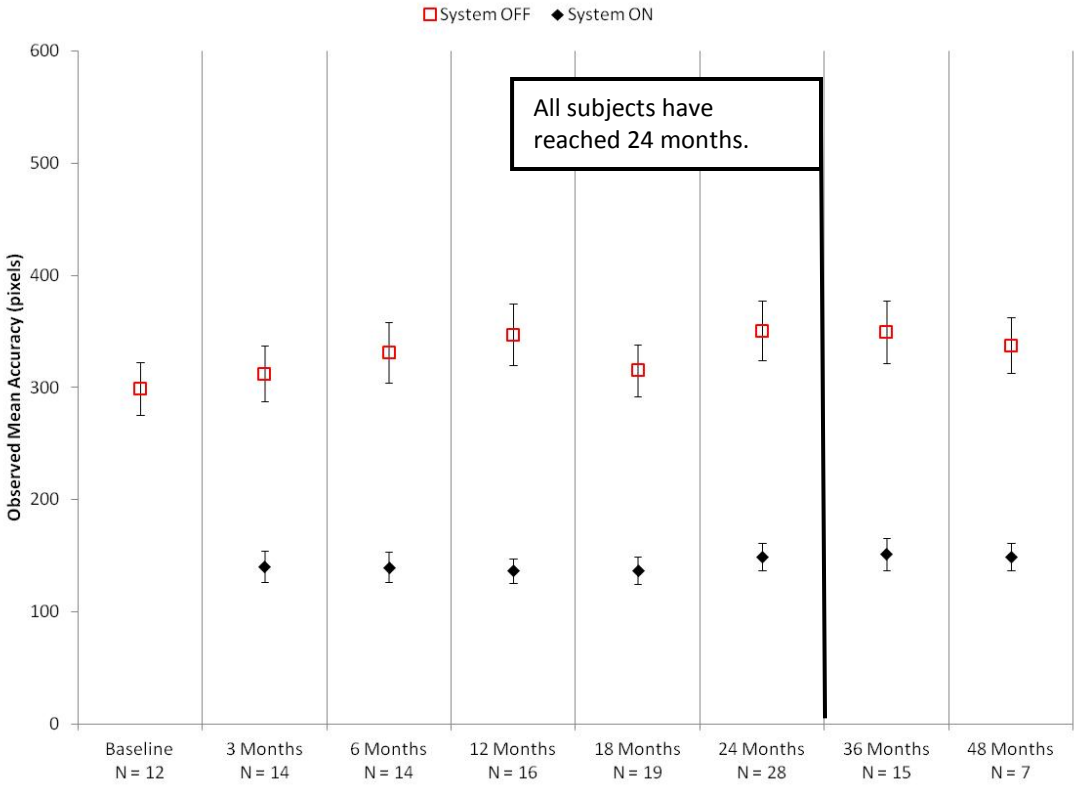
6.10.1.1 SQUARE LOCALIZATION

The Square Localization test was developed to test a subject's ability to locate objects using the Argus II System. See Section 6.2.7.2 for detailed methods.

Figure 15 displays the observed mean accuracy (distance from the center of the target) across all subjects for each follow-up visit. Error bars indicate mean of the standard error. The sample size at each follow-up visit differed since this test was added to the protocol in early 2009, after some subjects had already completed some of the follow-up visits.

Overall, subjects performed the square localization task better with the System ON than OFF at each time point. At the two-year time point, the mean System OFF error was 351 pixels, while the System ON error was 149 pixels, very close to the target square. These results indicate that the Argus II System improved the ability of subjects to visually locate small, high contrast objects.

Figure 15: Square Localization – Observed Mean Accuracy



Visit	n Subjects	System ON		System OFF	
		Mean Distance from Target Center* (pixels)	Mean of the SE	Mean Distance from Target Center (pixels)	Mean of the SE
Baseline	12	**N/A**	N/A	299.0	23.7
3 Months	14	**140.4**	13.9	312.1	24.9
6 Months	14	**139.9**	13.3	331.2	26.7
12 Months	16	**136.7**	10.8	347.2	27.3
18 Months	19	**137.0**	12.0	315.3	23.2
24 Months	28	**149.1**	12.4	350.8	26.3
36 Months	15	**151.3**	14.3	349.6	27.6
48 Months	7	**148.8**	12.1	337.8	25.0

SE = standard error

NOTE 1: Each square target measured 200 pixels across. So a distance less than approximately 100 pixels would have been within the target.

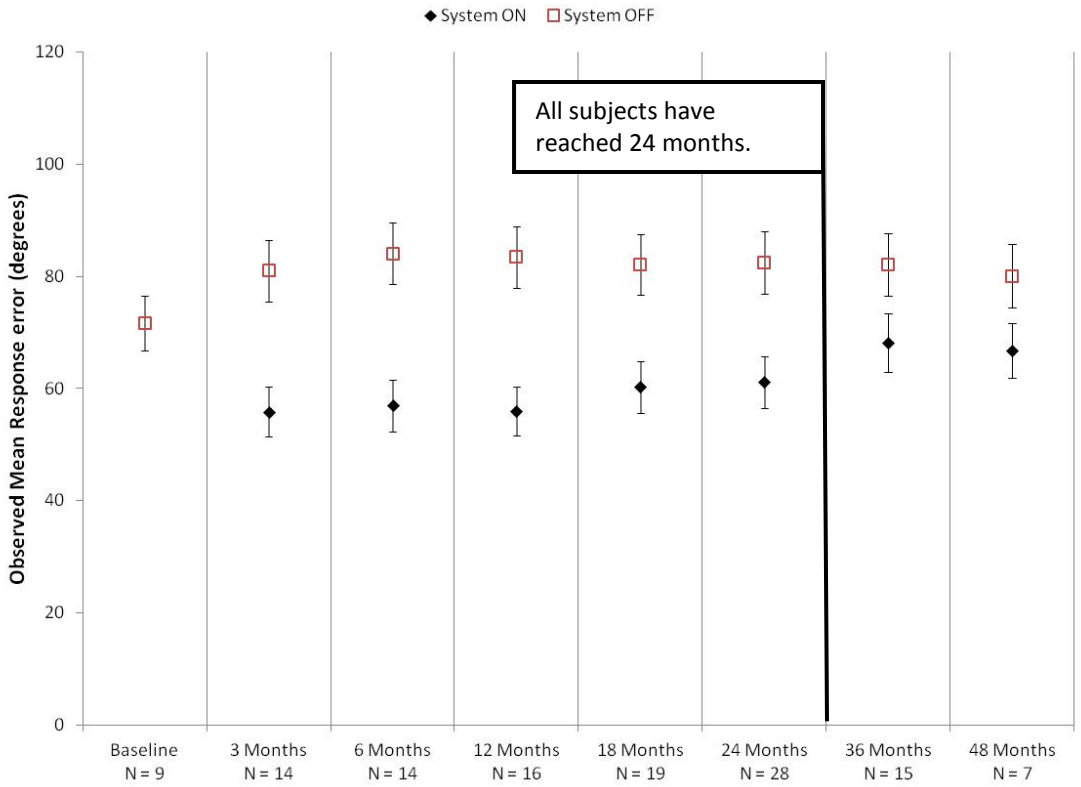
6.10.1.2 DIRECTION OF MOTION

The Direction of Motion assessment was intended to test whether the Argus II System improved the ability of subjects to determine the direction of an object moving in the visual field. See Section 6.2.7.3 for detailed methods.

Figure 16 displays the observed mean response error (the smaller the mean response error, the closer the subject's response was to the stimulus direction) across all subjects for each follow-up visit. Error bars indicate the mean of the standard error. The sample size at each follow-up visit differed since this test was added to the protocol in early 2009, after some subjects had already completed some of the follow-up visits.

These results indicate that, when averaged over all subjects, the Direction of Motion accuracy with the System ON was better than System OFF for all time points. At the two-year time point, the mean System OFF error (83˚) was close to that expected by chance (about 90˚), while mean System ON error was lower (61˚). Therefore, the Argus II System improved the ability of subjects to identify the direction of a moving object, a task that requires interpreting spatio-temporal information from multiple stimulating electrodes.

Figure 16: Direction of Motion – Observed Mean Response Error



Visit	n Subjects	System ON		System OFF	
		Mean Error* (degrees)	Mean of the SE	**Mean Error* (degrees)**	Mean of the SE
Baseline	9	**N/A**	N/A	71.6	4.9
3 Months	14	**55.8**	4.5	81.0	5.5
6 Months	14	**56.9**	4.6	84.1	5.5
12 Months	16	**56.0**	4.4	83.4	5.5
18 Months	19	**60.3**	4.6	82.1	5.5
24 Months	28	**61.1**	4.6	82.5	5.6
36 Months	15	**68.2**	5.2	82.1	5.5
48 Months	7	**66.8**	4.8	80.1	5.6

SE = standard error

NOTE 1: The possible error ranged from 0 to 180˚. If the subject was guessing on every trial, the mean error should be around 90˚. SE = standard error.

6.10.1.3 GRATING VISUAL ACUITY

The Grating Visual Acuity test was designed to determine a subject's visual acuity using the principles of acuity charts such as the ETDRS, modified for extremely low vision subjects. It measures the ability of subjects to determine the orientation of black and white bars. See Section 6.2.7.4 for method details.

Eight subjects (27%) had shown an improvement in measurable grating visual acuity with the System ON by the 24 month time point, while none had achieved improvement in their implanted or fellow eye with the system OFF, as indicated in Table 12. The best score achieved was 1.8 logMAR (20/1262).

Table 12: Grating Visual Acuity Results

	% of Subjects Whose Visual Acuity Improved to Better than 2.9 LogMAR
System ON	27% (n=8)
System OFF, Implanted Eye	0% (n=0)
System OFF, Fellow Eye	0% (n=0)

Table 13 shows the best Grating Visual Acuity measurement for each subject who scored at least once, along with the time point at which they achieved the score and the Snellen equivalent of the logMAR score.

Table 13: Best Grating Visual Acuity Scores (System ON, implanted eye)

Subject	1st Time point best score achieved	Best acuity score (logMAR)	95% confidence interval (logMAR)	Snellen equivalent of best score
XX-XXX	24 months	2.2	2.0 – 2.4	20/3170
XX-XXX	6 months	2.3	2.1 – 2.5	20/3991
XX-XXX	18 months	2.2	1.8 – 2.8	20/3170
XX-XXX	6 months	2.4	1.9 – 2.9	20/5024
XX-XXX	3 months	2.2	1.7 – 2.7	20/3170
XX-XXX	18 months	2.2	2.1 – 2.3	20/3170
XX-XXX	18 months	2.4	1.9 – 2.9	20/5024
XX-XXX	6 months	1.8	1.7 – 1.9	20/1262

6.10.1.4 ADDITIONAL RESEARCH – CHARACTER RECOGNITION AND READING WORDS

A. Large character identification

In the Large Character Identification task, subjects were tested for their ability to recognize large letters and numbers (in four character groups) displayed on a computer monitor. Data were analyzed both on a per-subject basis and for the population as a whole.

Since this test was designed as a forced-choice test with a closed set of letters (for each group), individual subjects' results could be evaluated for significant difference from chance according to the binomial distribution (assuming a chance rate of 1/N, where N is the number of letters in the group, and a significance criterion of two-tailed $p<0.05$). Table 14 shows the numbers of subjects whose percent correct was significantly better than would be expected by chance.

These tests demonstrated that a large majority of Argus II subjects could successfully identify large, high-contrast characters using the Argus II System.

Table 14: Percent of Subjects Who Can Recognize Characters

Group	N subjects	Chance rate	% of subjects better than chance	
			System ON	System OFF
A	21	0.125	95.2%	9.5%
B	19	0.1	78.9%	5.3%
C	20	0.125	80%	10%
D	16	0.1	87.5%	0%

Figure 17 shows whisker plots comparing ON and OFF performance for all subjects for each character group. The bottom and top of the boxes indicate the lower quartile and upper quartile values, while red lines indicate the median value. The whiskers extending from each end of the boxes show the range of the rest of the data. Outliers, shown as black dots, are data with values beyond the ends of the whiskers. (However, outliers were included in the mean and standard deviation calculations for Table 15, which shows the summary results in tabular form.)

These tests demonstrated that Argus II subjects, as a group, could successfully identify large, high-contrast characters using the Argus II System.

Figure 17: Character identification, all subjects

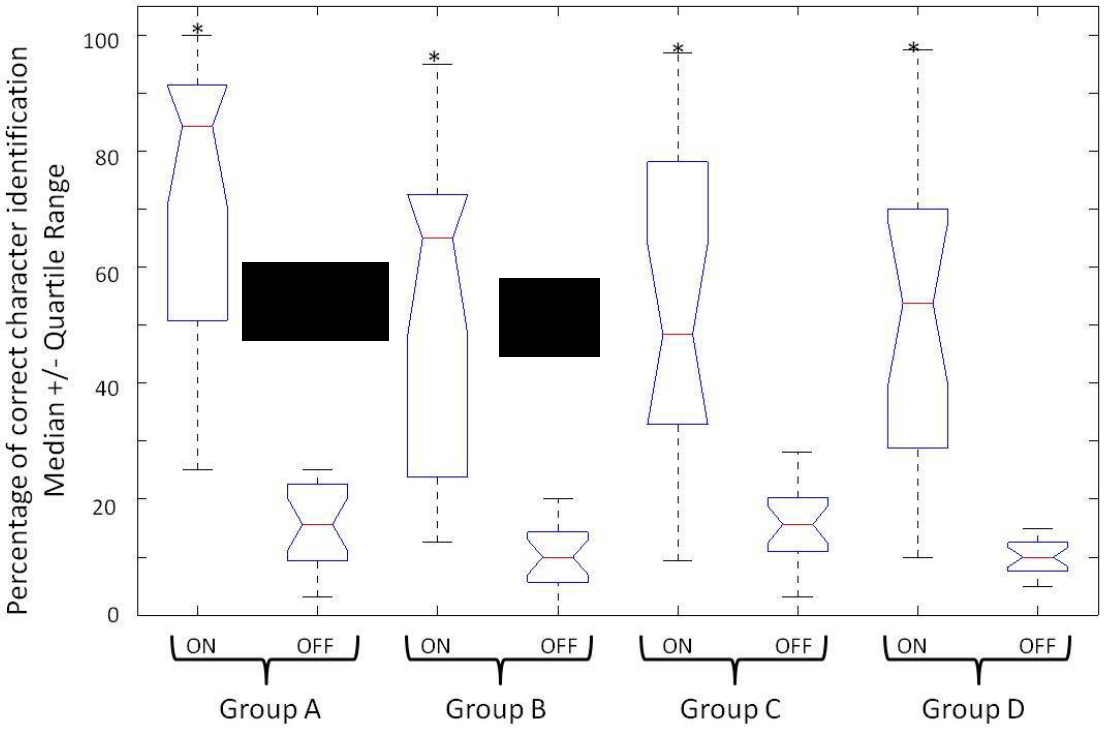


Table 15: Character identification summary results, percent correct

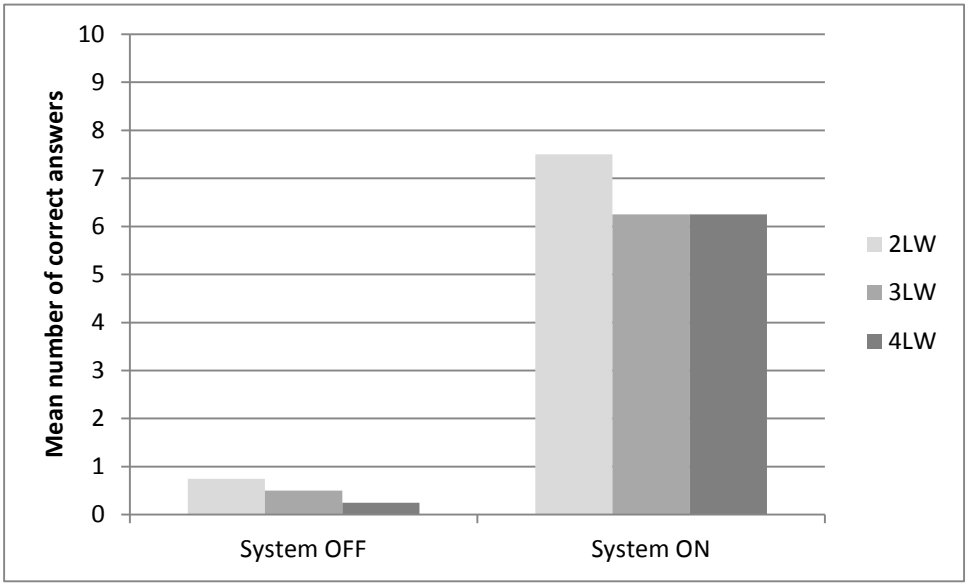
Group	Characters	N subjects*	Mean % Correct (± SD)		Wilcoxon signed rank test
			System ON	System OFF	Comparison ON vs. OFF
A	L,T,E,J,F,H,I,U	21	72.3 ±24.6	17.7 ± 12.9	p <0.001
B	A,Z,Q,V,N,W,O, C,D,M	19	55.0± 27.4	11.8 ± 10.7	p <0.001
C	K,R,G,X,B,Y,S,P	20	51.7± 28.9	15.3 ± 7.4	p <0.001
D	0, 1, 2, 3, 4, 5, 6, 7, 8, 9	16	51.9 ± 26.0	10.0 ± 3.4	p <0.001

*All subjects who were available for testing participated; some data were excluded due to inconsistencies in executing the test procedure. Some subjects who performed poorly on the earlier testing withdrew voluntarily from participating in later testing.

B. Word reading

In the Word Reading task, four subjects who had demonstrated the ability to recognize smaller individual characters were tested on their ability to read short words on a computer screen. Figure 18 shows the mean number of correct answers (over all four subjects) for two-, three-, and four-letter words (2LW, 3LW, and 4LW respectively). 10 words each of two-, three-, and four-letters were presented to each subject.

Figure 18: Phase III summary results



Conclusions

This research project yielded valuable information on Argus II subjects' abilities to perform a form-recognition task. It established that Argus II subjects, as a group, could identify large, high-contrast letters significantly better with their Systems ON than with their residual vision alone (i.e., System OFF). Median percent-correct values for each letter group were around 50% or higher using the Argus II System, which indicated that these results reflected good function across all subjects rather than a few good subjects.

Moreover, this project demonstrated that four Argus II subjects, as a group, performed much better at reading two-, three-, and four-letter words with the System ON than OFF. This demonstrated the ability to define separate letters with minimal spacing and not to confuse multiple letters, providing proof of principle that the Argus II System allowed word reading.

6.10.2 FUNCTIONAL VISION AND QUALITY OF LIFE

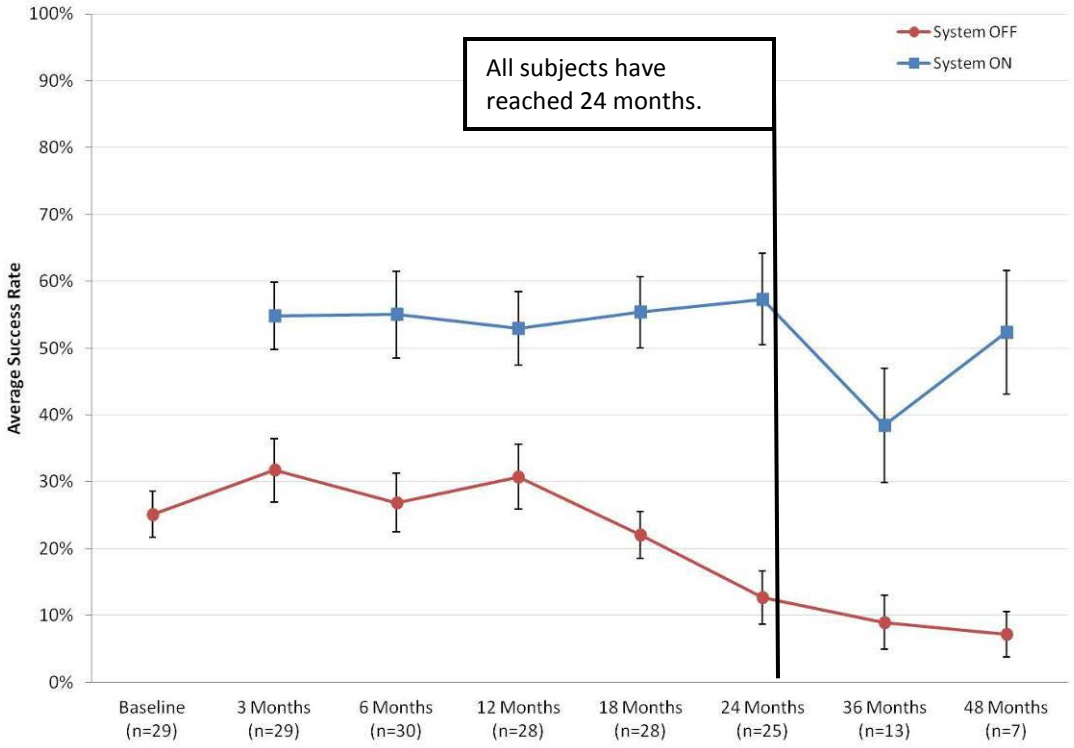
6.10.2.1 ORIENTATION AND MOBILITY

To evaluate the clinical utility of the Argus II System for orientation and mobility, each subject completed two tests (walking to a high-contrast "door" on the wall and following a line on the floor). These tasks were designed to mimic two important real-world activities that are challenging for blind individuals: locating a door in an unfamiliar room and crossing the street at a crosswalk. Performing these two tasks in simulated settings in the clinic allowed for more repeatable assessments over time, across multiple sites, and between multiple subjects than could be obtained if they were performed in actual real world settings.

Subjects' performances on the orientation and mobility tasks were better when using the Argus II System than without using the System. At the two-year time point, the large difference between ON and OFF performance was clear for both tasks: an average of 57% success with the System ON compared to 13% success with the System OFF for the Door Task, and 57% vs. 12% for the Line Task.

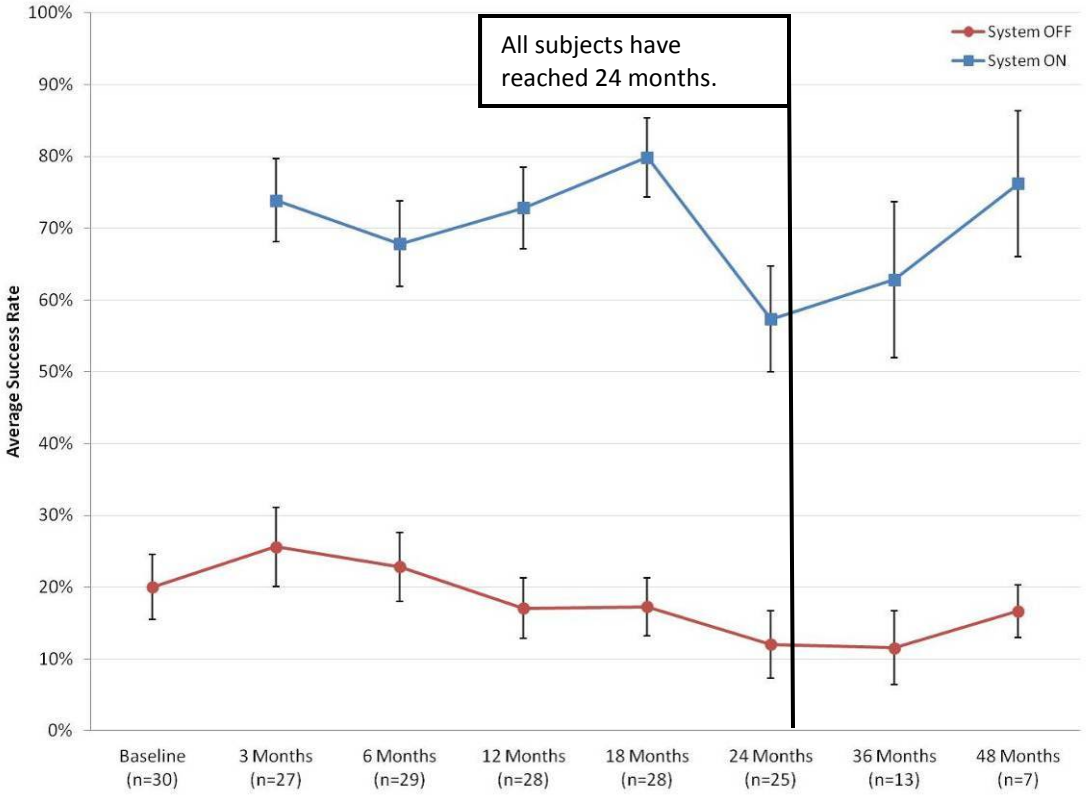
These results demonstrated that subjects were gaining significant benefit and clinical utility from the Argus II System for orientation and mobility tasks. Refer to Figure 19 (Door Task) and Figure 20 (Line Task).

Figure 19: Door Task -- Overall Results



Task	Visit	Number of Subjects	Success Rate System ON			Success Rate System OFF		
			Mean	Standard Error (plotted)	Standard Deviation	Mean	Standard Error (plotted)	Standard Deviation
Door – Overall	Baseline	29	**N/A**	N/A	N/A	**25%**	3%	0.19
	3 Month	29	**55%**	5%	0.27	**32%**	5%	0.26
	6 Month	30	**55%**	7%	0.36	**27%**	4%	0.24
	12 Month	28	**53%**	5%	0.29	**31%**	5%	0.26
	18 Month	28	**55%**	5%	0.28	**22%**	4%	0.19
	24 Month	25	**57%**	7%	0.34	**13%**	4%	0.20
	36 Month	13	**38%**	9%	0.31	**9%**	4%	0.15
	48 Month	7	**52%**	9%	0.24	**7%**	3%	0.09

Figure 20: Line Task -- Overall Results



Task	Visit	Number of Subjects	Success Rate System ON			Success Rate System OFF		
			Mean	Standard Error (plotted)	Standard Deviation	Mean	Standard Error (plotted)	Standard Deviation
Line – Overall	Baseline	30	**N/A**	N/A	N/A	**20%**	5%	0.25
	3 Month	27	**74%**	6%	0.30	**26%**	6%	0.29
	6 Month	29	**68%**	6%	0.32	**23%**	5%	0.26
	12 Month	28	**73%**	6%	0.30	**17%**	4%	0.22
	18 Month	28	**80%**	6%	0.29	**17%**	4%	0.22
	24 Month	25	**57%**	7%	0.37	**12%**	5%	0.23
	36 Month	13	**63%**	11%	0.39	**12%**	5%	0.18
	48 Month	7	**76%**	10%	0.27	**17%**	4%	0.10

6.10.2.2 FUNCTIONAL LOW-VISION OBSERVER RATED ASSESSMENT (FLORA)

The FLORA, a subjective assessment performed by trained observers to evaluate the effect of the Argus II System on subjects' lives, was developed by Second Sight in collaboration with Duane Geruschat, Ph.D., several other low-vision and blind rehabilitation experts, and Dr. Bernie Lepri and others at FDA. It was added to the protocol in late 2010 and all assessments were conducted as soon as possible thereafter (between December 2010 and April 2011).

The FLORA was completed on 26 Argus II subjects; four subjects did not participate (one subject was explanted before the assessment commenced, and three subjects did not consent to the assessment). At the time the FLORA assessments were conducted, approximately ½ the subjects were at 3.3 ± 0.4 years follow-up and the other ½ were at 1.7 ± 0.2 years follow-up.

As a reminder, five categories of responses were operationally defined and used by Dr. Geruschat to score the narratives. The categories were:

- Positive effect: In general, a score of "positive effect" indicated that the subject self-reported an improvement in well-being and/or functional vision, which the assessor was able to confirm by observation. Feelings of satisfaction derived only from participation in a clinical study were not counted as positive effects.
- Mild positive effect: A score of "mild positive effect" indicated that the subject self-reported an improvement but the assessor was not able to confirm the report by observation.
- Prior positive effect: A score of "prior positive effect" indicated that the subject self-reported better function in the past than he or she was able to demonstrate on the assessment day.
- Neutral effect: A score of "neutral" generally indicated that neither the subject nor assessor believed the System had a net positive or negative effect on the subject's life.
- Negative effect. "Negative" indicated that the System had worsened the subject's life in some way.

As judged by independent low vision rehabilitation experts, the Argus II System had a positive effect on the lives of 77% of Argus II subjects (at some point during the study) by improving their functional vision and/or their well-being. Twenty-three percent (23%) were rated as "neutral" effect; the System did not negatively affect any of the assessed subjects.

Table 16: Summary of FLORA results (n = 26 subjects)

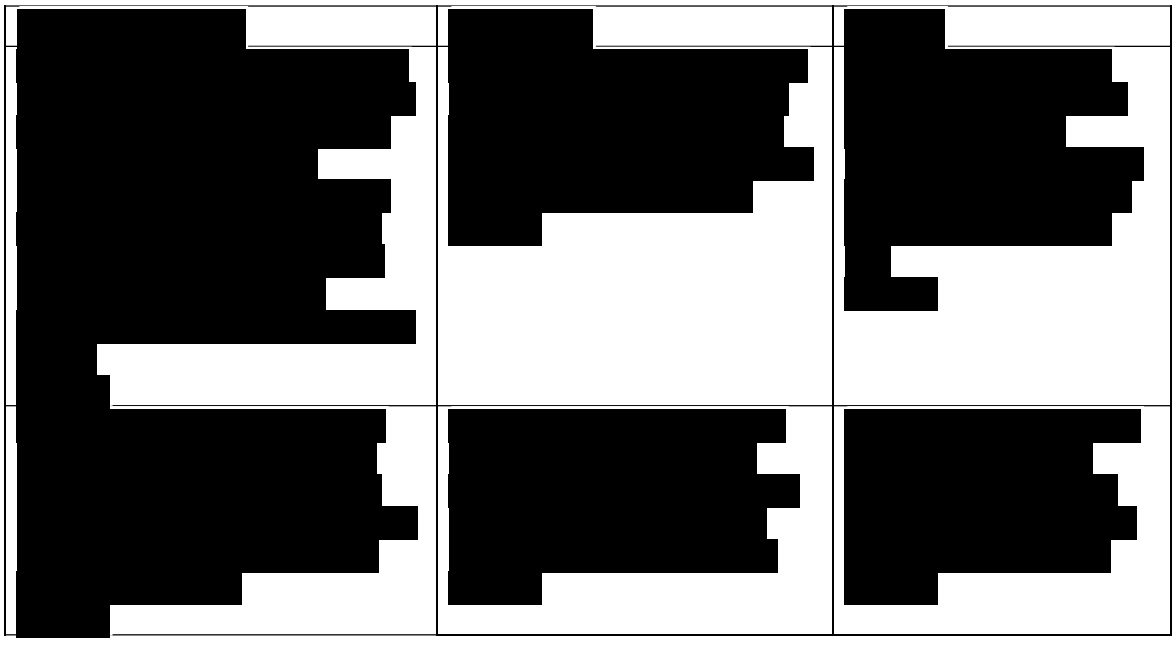
Positive effect N (%)	**Mild positive effect** N (%)	**Prior positive effect** N (%)	**Neutral effect** N (%)	**Negative effect** N (%)
9 (34.6%)	7 (26.9%)	4 (15.4%)	6 (23.1%)	0

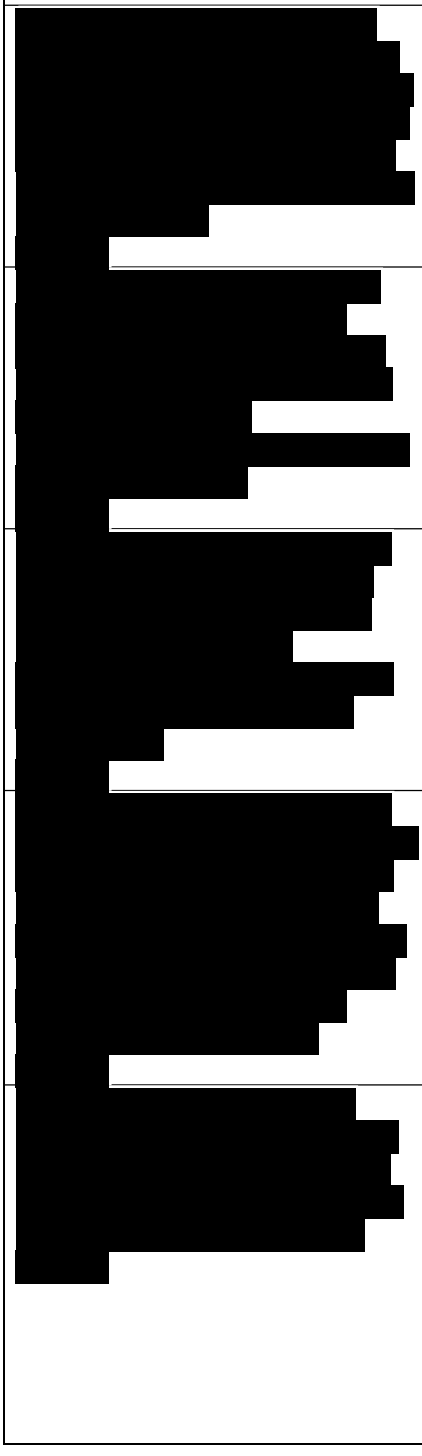
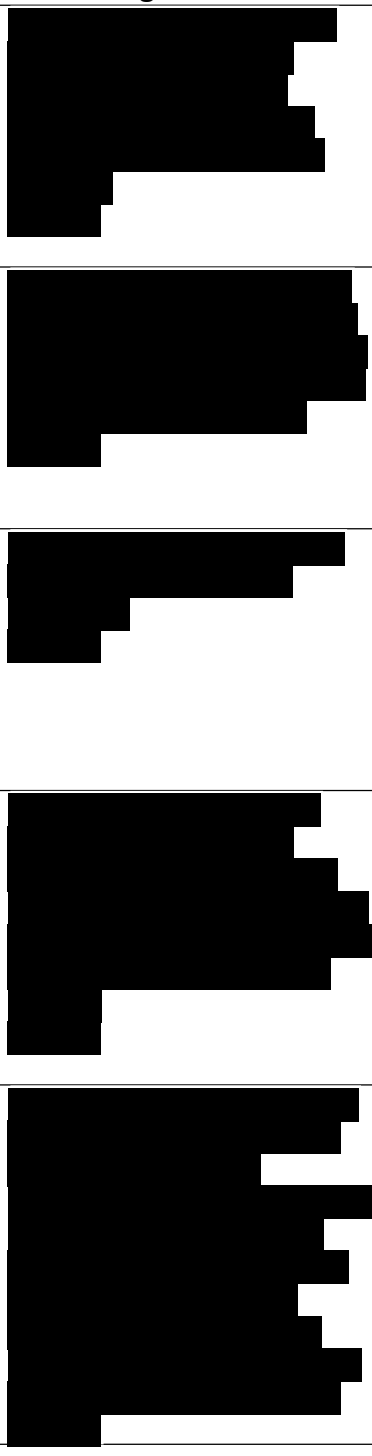
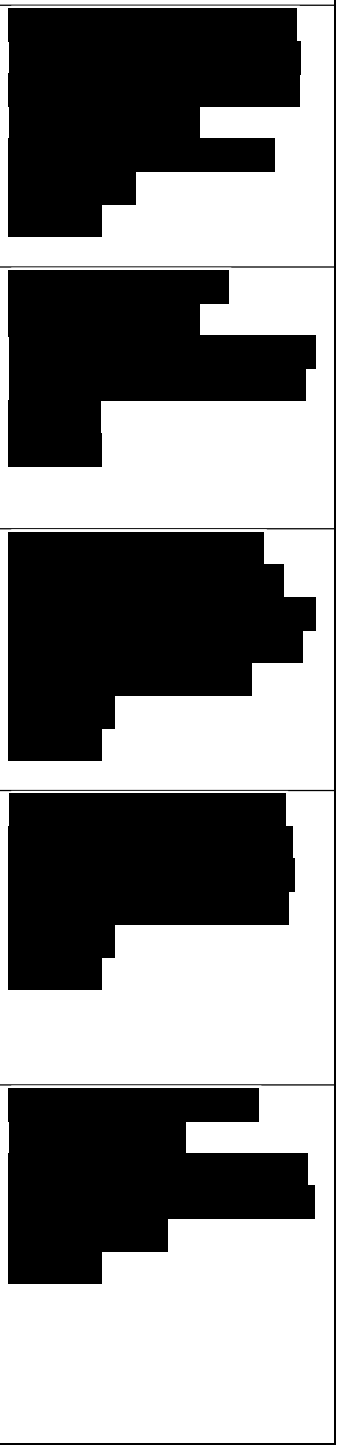
Positive effect	**No positive effect**
20 (76.9%)	6 (23.1%)

While the single scores provide a useful overview of the FLORA data, the nuances of the diverse effects of the Argus II System on subjects' lives can be better appreciated through the therapists' and subjects' own words. Selected quotations (one for each subject who participated in the FLORA) from the Part 3 reports appear in Table 17 below. These quotes illustrate different effects of the System reported by subjects and observed by therapists in both functional vision and well-being.

NOTE: These are single examples from each subject's narrative – they do not represent the entire data set, nor did they serve as the basis for the overall score for that subject.

Table 17: Examples of Reported Effects from use of the Argus II System (from FLORA Case Study Narratives)



Functional Vision	Well-being	Neutral
		

Functional Vision	Well-being	Neutral
[redacted]	[redacted]	
[redacted]		
[redacted]		
[redacted]		

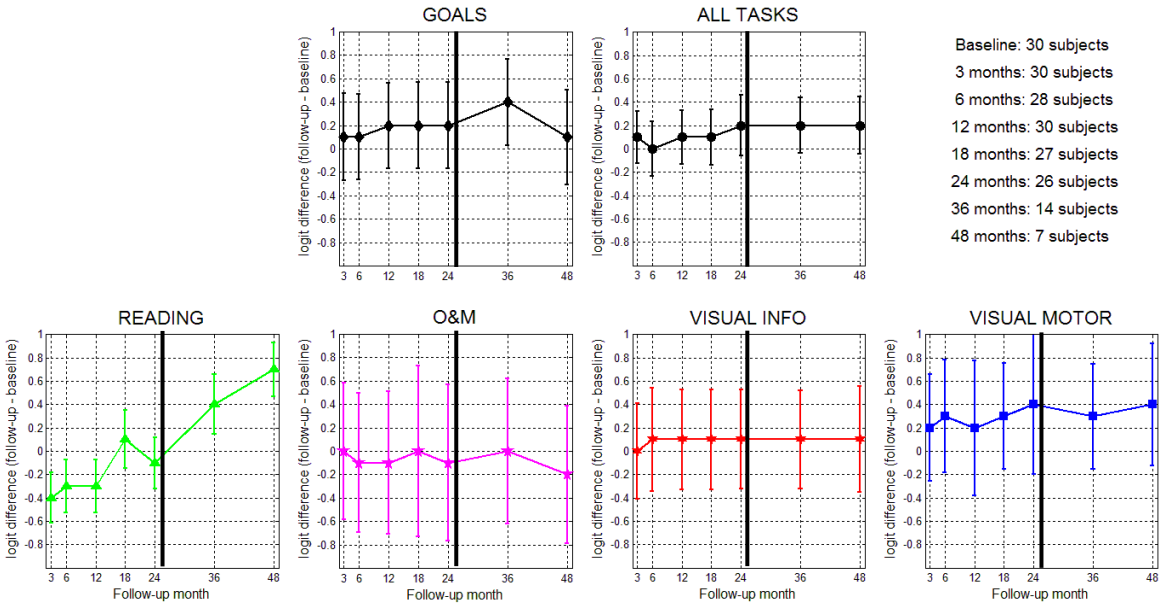
6.10.2.3 MASSOF ACTIVITY INVENTORY

Changes in activities of daily living (ADLs) were measured using the subject self-reported Activity Inventory instrument developed by Robert Massof, Ph.D. (Johns Hopkins University, Baltimore, MD).

Results from the Massof Activity Inventory showed that as a group, subjects reported functional vision goals and tasks became easier after starting to use the Argus II Retinal Prosthesis System. The visual motor domain showed a clinically significant improvement at most follow-up time points (i.e., 6, 18, 24, 36 and 48 months.

These data indicate that at the two-year time point, all goals and tasks were reported to have become easier, compared to baseline, though these changes did not reach clinical significance. However, a clinically significant improvement in the visual motor domain was observed.

Figure 21: Activity Inventory -- Mean Changes between Baseline and Follow-up



NOTE: Thick lines indicate the 24-month follow-up time point, which all subjects had reached as of this report.
Markers indicate the mean logit difference computed between baseline, considered having a reference "zero" value, and 3, 6, 12, 18, 24, 36 months post implant follow up for all subjects who had matched follow-up and baseline data. Error bars display the 95% confidence interval of the mean logit value. The number of subjects who completed the questionnaire at each follow-up time point is indicated in the legend.

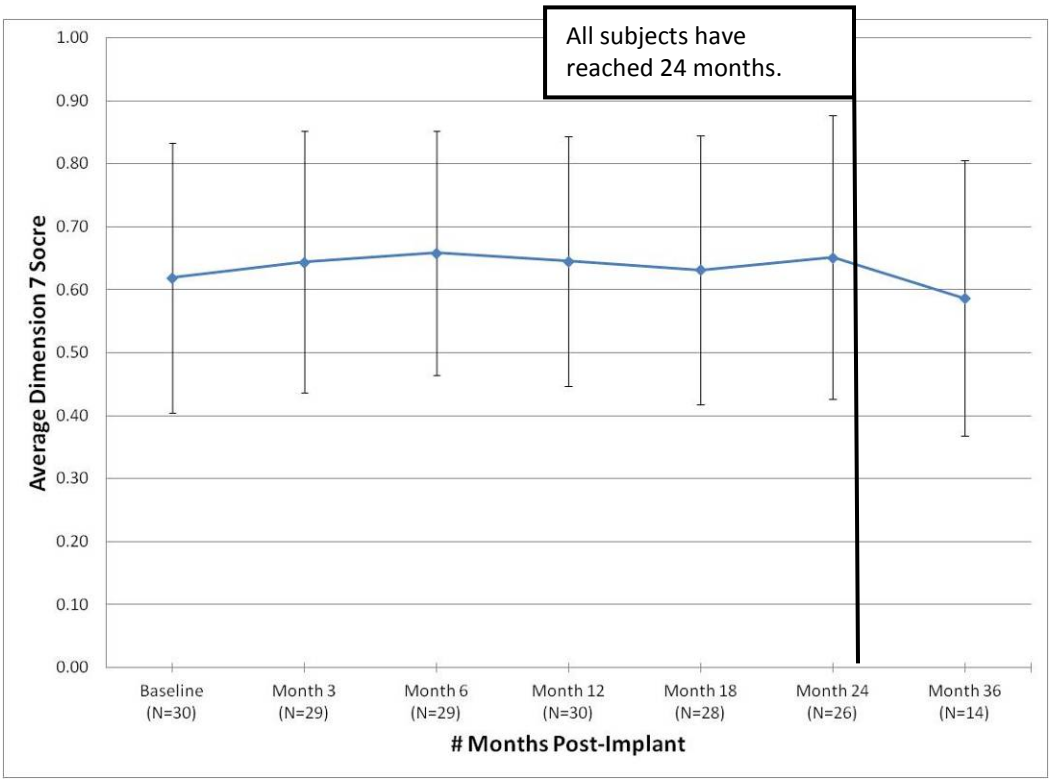
	Mean Change in Logit Values between Baseline and Follow-up						
	3	**6**	**12**	**18**	**24**	**36**	**48**
n Subjects	30	28	30	27	26	14	7
Goals	0.1	0.1	0.2	0.2	0.2	0.4	0.1
All Tasks	0.1	0	0.1	0.1	0.2	0.2	0.2
Reading	-0.4	-0.3	-0.3	0.1	-0.1	0.4	0.7
O&M	0	-0.1	-0.1	0	-0.1	0	-0.2
Visual Information	0	0.1	0.1	0.1	0.1	0.1	0.1
Visual Motor	0.2	0.3	0.2	0.3	0.4	0.3	0.4

6.10.2.4 VisQOL Questionnaire

The VisQOL questionnaire is a 6 question vision and quality of life-related utility measure that was intended to help perform economic evaluations of eye care and rehabilitation programs.

Across all subjects, no significant change (in comparison to baseline) could be measured with the VisQOL instrument. It is possible that this instrument is not sensitive enough to detect the effect of the Argus II System since it deals with on broad quality of life issues related to vision and did not focus on the ability to perform visual tasks.

Figure 22: Observed Mean VisQOL Scores



6.10.2.5 ADDITIONAL RESEARCH – FUNCTIONAL VISION TASKS

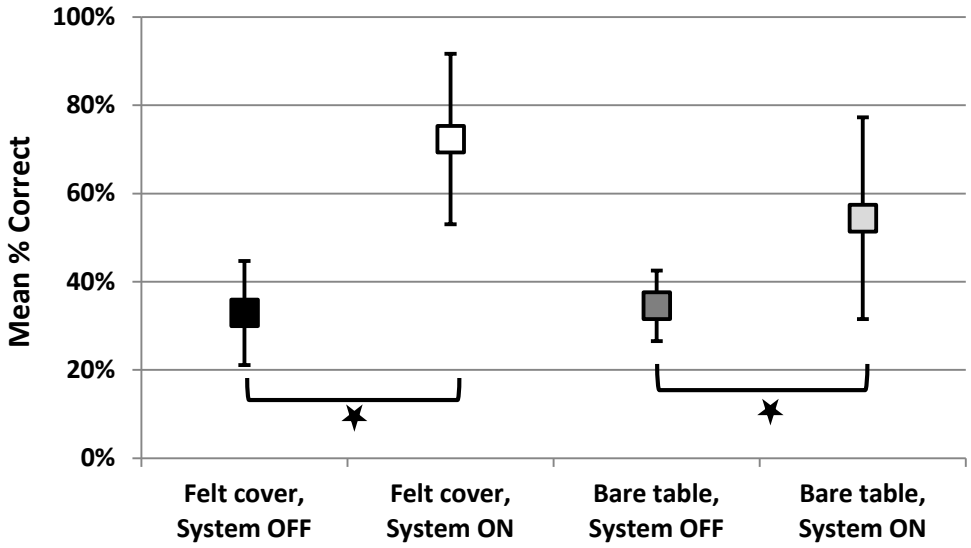
To supplement the functional vision assessments in the protocol (the Orientation and Mobility tasks, Activity Inventory, and, later, the FLORA), three additional objectively-scored functional vision tasks were developed and performed by Argus II subjects with the System ON and OFF. These tasks were intended to mimic everyday activities that blind subjects may not be able to do without vision, and to measure – in uncontrolled, real-world environments – whether the Argus II System helped the subjects successfully perform them.

Task 1: Sock Sorting

The sock sorting task was designed to mimic the real-world scenario of sorting light and dark laundry. It was chosen because it represents a task that is difficult or impossible to do without vision (i.e., it cannot be done through tactile cues alone).

Twenty-eight (28) subjects participated in this evaluation. Figure 23 shows the mean percent correct and standard deviation over all 28 subjects for all four conditions (i.e., test performed with socks placed on table covered with either a black or white piece of felt, System ON vs. OFF; and test performed with sock placed on a bare table, System ON vs. OFF).

Figure 23: Mean percent correct, sock sorting



As indicated by the stars on Figure 23, subjects performed significantly better on this task with the System ON vs. OFF (t-test assuming unequal variances, $p<0.01$).

Task 2: Sidewalk Tracking

The Sidewalk Tracking task was developed to assess subjects' ability to accurately track an edge such as a sidewalk bordered by grass in a real-world outdoor environment setting. The ability to follow along such an edge and detect the transition between two surfaces of different brightness levels is useful to blind subjects for mobility and orientation purposes in their daily life.

Twenty-seven (27) subjects were included in this research project. The mean and standard deviation of the number of times the subject went out of bounds for System ON and System OFF testing are shown in Table 18 below.

Results indicate that subjects performed significantly better on this task with the System ON than they did with the System OFF (two-tailed t-test, $p<0.05$).

Table 18: Sidewalk Tracking Summary Results

Mean out of bounds ± std dev, System ON	Mean out of bounds ± std dev, System OFF	P-value (paired t-test)
4.93 ± 2.62	6.85 ± 3.03	P<0.05

Task 3: Direction of Walking

The Direction of Walking task was developed to assess subjects' ability to identify the direction of motion of a person walking in front of them. The ability to detect people moving nearby and identify their direction is useful to blind subjects in unfamiliar environments or in social situations.

Figure 24 shows a comparison between system ON and OFF performance for all the tested subjects. A dotted line indicates the significance level according to the binomial distribution (two-tailed); 27 or more correct answers out of 40 are significantly different from chance.

Figure 24: Direction of Walking Results

Twenty-five (25) of 27 subjects (93%) performed better with the system ON compared with system OFF. Fifteen (15) subjects performed above chance with the system ON, while four subjects performed above chance with the system OFF (one of these four performed significantly above chance only with the system OFF, while the other three performed significantly above chance in both conditions).

Conclusions

The results indicated that performance on these tasks varied across subjects, but that as a group, Argus II subjects performed better on all three tasks (Sock Sorting, Sidewalk Tracing, and Direction of Walking) with their systems ON than they did with their systems OFF. These tasks provide an indication of the real-world benefit of the Argus II System to subjects.

6.11 ADDITIONAL FDA-REQUESTED ANALYSES

During the review of the HDE application, the FDA has requested that Second Sight perform additional analyses of the data from the clinical trial. A subset of the analyses that were run to address these FDA questions is presented in this section.

6.11.1 POOLING OF DATA FROM THE CLINICAL TRIAL

Data from all 30 subjects were pooled in this report, despite minor modifications having been made to the device design and study protocol during the course of the study. Poolability of the data was justified because the following key elements were consistent throughout the study:

- All subjects met consistent inclusion/exclusion criteria. While the protocol was modified to slightly broaden the subject selection criteria to facilitate enrollment, the effect of this change was negligible as the subjects enrolled in the study were homogenous in terms of demographics, baseline visual acuity (all were bare light perception with worse than 2.9 logMAR visual acuity at baseline) and baseline diagnosis (all subjects had RP with the exception of one subject who had choroideremia).
- Data management, monitoring, and event adjudication procedures were consistent for all subjects.
- All subjects received the same standard of medical care. This study was conducted in the United States, France, Switzerland, and the UK. The surgeon skill level and standards of care were similar at all centers. In addition, all surgeons underwent a similar training program which consisted of didactic lectures and direct hands-on instruction.
- The recommended surgical procedure was consistent irrespective of time-of-enrollment or center location. Although minor refinements were made to the procedure over time, all relevant elements were the same (e.g., lensectomy, pars plana vitrectomy, scleral buckling, insertion of retinal tack, etc).
- Concomitant medications and post-surgical follow-up were the same for all subjects.

- All subjects received an Argus II System that functioned under the same principle of operation. None of the changes made to the implant or externals affected the principle of operation of the System.
- Most subjects, irrespective of device design, demonstrated similar benefit from the device with basic visual tasks as evidenced by square localization and orientation and mobility testing.
- All subjects used the same glasses and Video Processing Unit.
- All subjects had the implant installed in a similar place and manner on and in their eye.
- All subjects received an implant with the same basic design and components. The minor changes to the device did not substantially impact the performance of the device or affect the applicability of the data to all versions of the system evaluated.

The following sub-group analyses were performed to support the decision to pool the data from all 30 subjects enrolled in the study:

1. By enrollment cohort: Minor design and surgical procedure changes were made during the course of the clinical trial. Most of these changes were implemented midway through enrollment in the study after the first 15 subjects had been enrolled. Therefore the clinical data from the first 15 subjects enrolled in the study were compared with the data from the last 15 subjects.
2. By Gender: A sub-group analysis was performed to compare the results for males and females.
3. By Region: A sub-group analysis was performed to compare the results for subjects enrolled in the US vs. Europe.
4. Orientation & Mobility Results by Method: In June 2009, minor changes were made to the methods used to perform the orientation and mobility tests. A sub-group analysis was performed comparing the O&M data before and after these changes.

The results of these sub-group analyses (described below in Sections 6.11.1.1, 6.11.1.2, 6.11.1.3), provide further justification for the pooling of these data.

6.11.1.1 DESIGN CHANGES AND ASSOCIATED SUB-GROUP ANALYSIS

Due to the rare patient population for which this device is intended, enrollment in this study spanned over 2 years. During the course of the study, modifications were made to the device and surgical procedure in response to feedback obtained during the study. All changes were made following design control standard operating procedures and were verified or validated, as required, and submitted to FDA and European regulators for review prior to implementation in the study.

Changes to the Argus II Implant

The changes for the Argus II implant are summarized in the Table 19 below. Two rounds of changes were made to the implant and tack. The first ("Slotted" Implant) was a minor one intended to improve the manufacturing yield of the device; it did not affect safety or performance.

Following the implantation of the first 15 subjects, clinicians and Second Sight engineers provided feedback for how the implant design could be slightly adjusted; the result was the "dual metal" design. Such optimization of a technology during clinical studies is to be expected as resulting from the clinical study of this type of device. Most importantly, these modifications did not in any way constitute a significant change in the design or the principles of operation of the device. In addition, they did not result in any significant change in the performance attributes or safety of the System (see "Sub-Group Analysis by Design Cohort" below).

Table 19: Changes to the Argus II Implant

Date of First Implementation in the Study	Modification of implant	# of subjects with this implant version
June 2007	"Single-Metal" Implant Design -- Original Design	12
February 2008	"Single-Metal" Implant Design -- "Slotted" Design • Change was made to the cable (by creating a slot in the folded region) to prevent damage to the electrode traces during manufacturing	3
January 2009	"Dual-Metal" Implant Design • Width of the cable was reduced 0.059" by changing from a single layer of metal traces to two layers of metal traces stacked on top of each other ("dual metal design") • Array was changed to a molded design from a hand-made one • Tack length was shortened slightly by 0.009" and the tack spring was made slightly stiffer • The stiff, pre-formed bend in the transcleral region was eliminated • The angle in the intraocular portion of the device (where the cable meets the electrode array) was eliminated so that the cable, tack and array were all in line with one another • The height of the electronics package was reduced slightly by 0.015" • Suture tabs were reinforced, and an additional suture tab was added	15

Changes to the Argus II Externals

The changes for the externals of the Argus II System are summarized in Table 20 below. The majority of changes were made to improve the ease with which the clinician could program the device and run diagnostic tests, to improve the programming options available for download to the subject's video processing unit (e.g., adding a contrast filter), and to improve the usability of the programming system.

Again, these are the kinds of minor optimizing changes that one would expect as resulting from the clinical study of this type of device. It is critical to note that these changes do not constitute a significant change in the design or the principles of operation of the device. Importantly, the changes to the Argus II Externals do not in any way affect the safety or performance endpoints of the System. All subjects and sites were upgraded to the latest version of the external equipment with each new release of hardware, software or firmware.

Table 20: Changes to the Argus II Externals

Date of First Implementation in the Study	Main Modifications of the Externals
October 2007	Updated RF board of the glasses and OR coil to aid manufacturability and enhance RF link between glasses/OR coil and implant
November 2007	Modified the firmware/software in the VPU, CFS and PTS to improve the graphical user interface for performing diagnostic tests and programming the VPU
March 2008	Modified the firmware/software in the VPU, CFS and PTS to: • Enable clinicians to measure stimulation thresholds up to 1.0mC/cm2 (in the clinic only) and to measure the electrical waveform of individual electrodes (diagnostic test) • Enable easier programming of VPU • Remove overheating check when VPU is in OR mode
September 2008	Modified the firmware/software in the VPU and CFS to: • Allow clinician to program a contrast enhancement filter and brightness scaling filter into the patient's VPU • Improve graphical user interface for performing diagnostic tests and programming the VPU • Improve RF link with the implant • Enable adjustment of the settings for the RF link loss alarm
July 2009	Modified the firmware/software in the VPU, CFS and PTS to: • Enhance diagnostic tests • Enhance the usability of the CFS and PTS • Address software bugs that were encountered during use of the CFS/PTS

Date of First Implementation in the Study	Main Modifications of the Externals
March 2012	Modified the firmware/software in the VPU, CFS and PTS to: • Increase the number of programs that can be stored on the VPU from 1 to 3 • Prevent the VPU from being inadvertently left in a special mode intended for use only in the operating room • Allow subjects to mute the RF alarm buzzer • Improve the flexibility and ease with which clinicians perform diagnostic tests and programming of the VPU Modified the hardware in the VPU and Glasses to: • Improve their ergonomics and their compliance with international standards for electrical safety and electromagnetic compatibility • Replace obsolete video camera with current model (glasses)

VPU: Video Processing Unit; CFS: Clinician Fitting System; PTS: Psychophysical Test System

Sub-Group Analysis by Design Cohort

A sub-group analysis was performed to compare the results of the first 15 subjects enrolled in the study ("Cohort 1") and the last 15 subjects enrolled in the study ("Cohort 2"):

- Cohort 1: Implanted between June 2007 and June 2008. All subjects received the original ("single metal") implant configuration.
- Cohort 2: Implanted between January and August 2009. All subjects received a modified ("dual metal") implant configuration.

A subgroup analysis was not performed relating to the change in externals as these changes could not impact the safety or effectiveness of the device. Table 21 summarizes the findings of the sub-group analysis.

Table 21: Summary of Sub-Group Analysis By Enrollment Cohort

Variable	Comparison of Cohort 1 to 2
Demographics	• No statistically significant differences in demographics with the exception of Cohort 2 having more Europeans and more past smokers.
Implantation Surgery	• No significant differences in surgical variables with the exception that Cohort 2 had a wider sclerotomy width than Cohort 1 and the materials used to cover the implant in situ differed between the two groups.
Safety	When comparing AEs that occurred in the first 2 years (<25 months post-implant): • There were no significant difference in the proportion of subjects with an SAE or the total number of SAEs. • The total number of non-serious AEs was lower for Cohort 2 than Cohort 1 (48 vs. 75). Cohort 2 had a lower rate of conjunctival congestion and hypotony than Cohort 1. Cohort 2, compared with Cohort 1, had a higher rate of retinal thickening without cystic changes but a lower rate of retinal thickening with cystic changes. • Adverse events by cohort are detailed in Table 22 and Table 23, below.
Implant Functionality	• Cohort 2 subjects had a significantly higher average number of enabled electrodes than Cohort 1 at the time of implant, but by the time of last follow-up there was no significant difference between the two cohorts in this variable.
Stability of Implant	• No apparent difference between the two cohorts.
Square Localization	• No statistical comparison was possible due to lack of overlap in follow-up time between cohorts (the test was introduced partway through the study).
Direction of Motion	• No statistical comparison was possible due to lack of overlap in follow-up time between cohorts (the test was introduced partway through the study).
Grating Visual Acuity	• Trend toward better performance on this task by Cohort 2 subjects but Ns were too small for statistical comparison. • Grating Visual Acuity Results are detailed in Table 24, below.
Character Recognition	• No statistical comparison was possible since Cohort 1 and Cohort 2 subjects were implanted for different periods of time when this research was performed. However, Cohort 2 subjects tended to perform better than Cohort 1 subjects on these tests. • Character Recognition Results are detailed in Table 25 below.
Orientation & Mobility	• No apparent difference between the two cohorts.
FLORA	• No statistical comparison was possible since Cohort 1 and Cohort 2 subjects were implanted for different periods of time when this test was performed. However, Cohort 2 subjects tended to perform better than Cohort 1 subjects on this assessment.
Massof	• No apparent difference between the two cohorts.
VisQOL	• No significant differences between the two cohorts.

Table 22: Serious Adverse Events Through 2 Years Post-Implant: By Enrollment Cohort

The 2 year cut-off date (< 25 months post-implant) was chosen since follow-up data are available on all subjects through this time point. NOTE: The FDA has previously reviewed a comparison of all adverse events between Cohorts 1 and 2 reported as of February 2011; however, the updated analysis of these data presented below has only recently been provided to FDA.

	Cohort 1 (n=15 subjects)			Cohort 2 (n=15 subjects)		
Reportable Term	**# subjects**	**# Events**	**% subjects**	**# subjects**	**# Events**	**% subjects**
Conjunctival dehiscence	2	2	13.3%	1	1	6.7%
Conjunctival erosion	2	2	13.3%	1	2	6.7%
Corneal Melt	0	0	0.0%	1	1	6.7%
Corneal opacity	0	0	0.0%	1	1	6.7%
Presumed endophthalmitis	3	3	20.0%	0	0	0.0%
Hypotony	2	2	13.3%	2	2	13.3%
Keratitis – infective	0	0	0.0%	1	1	6.7%
Re-tack	1	1	6.7%	1	1	6.7%
Retinal detachment - rhegmatogenous	0	0	0.0%	1	1	6.7%
Retinal detachment - tractional and serous	1	1	6.7%	0	0	0.0%
Retinal Tear	1	1	6.7%	0	0	0.0%
Uveitis	1	1	6.7%	0	0	0.0%
Total # Events		13			10	

Table 23: Non-SAEs Through 2 Years Post-Implant: By Enrollment Cohort

Reportable Term	Cohort 1 (n=15 subjects) # subjects	# Events	% subjects	Cohort 2 (n=15 subjects) # subjects	# Events	% subjects
360 Circumferential Vitreous Band Traction	0	0	0.0%	1	1	6.7%
Choroidal detachment	4	4	26.7%	2	2	13.3%
Choroidal effusion	0	0	0.0%	1	1	6.7%
Conjunctival congestion	9	10	60.0%	1	1	6.7%
Conjunctival cyst	0	0	0.0%	1	1	6.7%
Conjunctival dehiscence	0	0	0.0%	1	1	6.7%
Conjunctivitis - inflammatory	3	4	20.0%	0	0	0.0%
Corneal abrasion	1	1	6.7%	0	0	0.0%
Corneal dryness	0	0	0.0%	1	1	6.7%
Corneal epithelial defect	0	0	0.0%	1	1	6.7%
Corneal filaments	1	1	6.7%	0	0	0.0%
Corneal fold	0	0	0.0%	1	1	6.7%
Corneal vascularization	1	1	6.7%	1	1	6.7%
Decrease in light perception	1	1	6.7%	0	0	0.0%
Elective revision surgery	5	5	33.3%	2	2	13.3%
Epiphora	2	2	13.3%	0	0	0.0%
Epiretinal membrane	5	5	33.3%	5	5	33.3%
Fibrosis Around Retinal Tack	1	1	6.7%	0	0	0.0%
Filamentary keratitis	1	1	6.7%	0	0	0.0%
Foreign body sensation	0	0	0.0%	1	2	6.7%
Headache	1	1	6.7%	1	1	6.7%
High IOP	2	3	13.3%	0	0	0.0%
Hyphema	3	3	20.0%	0	0	0.0%
Hypotony	6	6	40.0%	1	1	6.7%
Inflammation - ocular	4	4	26.7%	0	0	0.0%
Keratic Precipitates	1	1	6.7%	1	1	6.7%
Nausea	1	1	6.7%	0	0	0.0%
Nystagmus increase	1	1	6.7%	0	0	0.0%
Pain - ocular	4	6	26.7%	4	7	26.7%
Proliferative vitreoretinopathy (PVR)	1	1	6.7%	0	0	0.0%
Ptosis	0	0	0.0%	1	1	6.7%
Retinal detachment - tractional	1	1	6.7%	0	0	0.0%
Retinal Thickening - cystoid macular edema	3	3	20.0%	1	1	6.7%
Retinal Thickening - without cystic changes	0	0	0.0%	4	4	26.7%
Retinoschisis	0	0	0.0%	1	1	6.7%
Rubeosis	1	1	6.7%	0	0	0.0%
Scleritis	0	0	0.0%	1	1	6.7%

Reportable Term	Cohort 1 (n=15 subjects)			Cohort 2 (n=15 subjects)		
	# subjects	# Events	% subjects	# subjects	# Events	% subjects
Suture irritation	2	2	13.3%	4	5	26.7%
Uveitis	1	1	6.7%	4	5	26.7%
Vertigo	1	1	6.7%	0	0	0.0%
Vitreous hemorrhage	3	3	20.0%	0	0	0.0%
Total # Events		75			48	

Table 24: Best Grating Visual Acuity Results by Enrollment Cohort

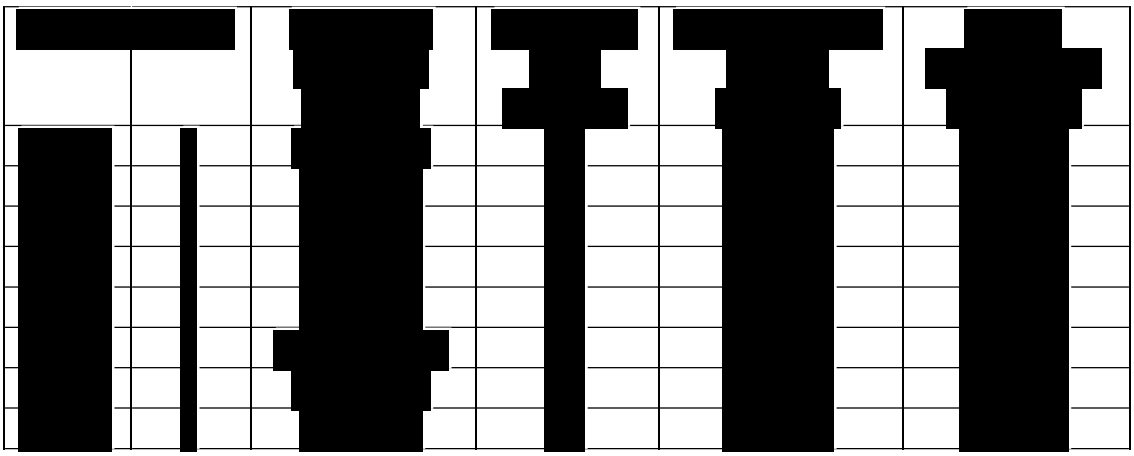


Table 25: Character Recognition Phase I Results by Enrollment Cohort

Group	N subjects, Cohort 1	N subjects, Cohort 2	Mean % Correct (± SD)			
			Cohort 1		Cohort 2	
			System ON	System OFF	System ON	System OFF
A	8	13	60.5 ± 29.1	21.5 ± 14.6	79.6 ± 19.1	15.4 ± 11.7
B	7	12	35.0 ± 25.0	12.1 ± 5.9	66.7 ± 22.1	11.7 ± 13.0
C	7	13	29.0 ± 16.8	16.5 ± 8.2	63.9 ± 26.9	14.7 ± 7.3
D	6	10	38.8 ± 14.9	12.5 ± 2.2	59.8 ± 28.6	8.5 ± 3.2
A,B,C,D	28	48	41.6 ± 25.0	16.0 ± 9.7	68.0 ± 24.6	12.8 ± 9.8

Overall, this analysis supports the fact that the two cohorts were comparable in terms of safety and probable benefit (i.e., both demonstrated the safety and probable benefit of the Argus II System) and that pooling of their data, to obtain an overall assessment of the Argus II Retinal Prosthesis System for the purposes of an HDE application, was warranted. Minor differences in the two cohorts were noted, but in all cases, were more favorable toward Cohort 2 whose minor differences are all incorporated in the implant design for which the HDE is being

requested. Thus, in the commercial setting, we expect the results will be closer to those for Cohort 2. Therefore, presenting data from the pooled 30 subjects provides a conservative assessment of the safety and probable benefit of the Argus II Retinal Prosthesis System.

6.11.1.2 SUB-GROUP ANALYSIS BY GENDER

FDA requested that Second Sight perform a sub-group analysis to compare results for the main outcome measures by gender. The results of these analyses are summarized in Table 26 below.

This analysis demonstrated that the outcomes with the Argus II System were comparable for men and women and that neither group performed substantially better or worse than the other on any of the main outcomes in the study. There were only 9 women enrolled in the study; therefore, some minor observed differences may have been due to the small sample size of women. Based on this analysis, there is no evidence of a gender effect or difference in outcomes with the Argus II System between men and women.

Table 26: Summary of Gender Sub-Group Analysis

Variable	Comparison of Female vs. Male
Safety	• Rates of SAEs were similar for men and women. • Twenty-two percent (22%) of women and 38% of men experienced an SAE; the number of events for women was largely influenced by one subject who experienced a cascade of adverse events (n=6 SAEs). • The rates of most non-serious AEs were, in general, comparable between the two genders with a few exceptions.
Square Localization	• Results on the square localization test were comparable between the genders. • The mean distance from the target center for male subjects (System ON) ranged from 122 – 173 pixels, while for female subjects the range was 115 – 194. • At all time points, both men and women performed better with the System ON vs. OFF.
Direction of Motion	• The range of mean error across follow-up time points was substantially the same for all groups. • At all time points, both men and women performed better with the System ON vs. OFF.
Grating Visual Acuity	• A similar proportion of men and women were able to score on the grating visual acuity test during the study (24 vs. 33%, respectively).
Orientation & Mobility	• The average success rates for men and women, on both the line and door tasks, were comparable across all time points. • At all time points, both men and women performed better with the System ON vs. OFF.
FLORA	• Overall, the proportion of subjects who were rated as having a positive effect from the Argus II System was similar between the genders.
Massof	• No differences were observed between the two cohorts with the exception of 36 month Tasks where the men showed an improvement and the women did not. However, the sample sizes were very small at 36 months.
VisQOL	• No significant differences between the two groups.

6.11.1.3 SUB-GROUP ANALYSIS BY REGION (US VS. EUROPE)

FDA requested that Second Sight perform a sub-group analysis to compare results for the main outcome measures by region (i.e., enrolled in the U.S. vs. Europe). The results of these analyses are summarized in Table 27 below.

The regional sub-group analysis demonstrated that the outcomes with the Argus II System were comparable for subjects enrolled in the U.S. versus Europe and

that neither group performed substantially better or worse than the other on any of main outcomes in the study. Based on this analysis, there is no evidence of a region effect or difference in outcomes between the United States and Europe.

Table 27: Summary of Regional Sub-Group Analysis

Variable	Comparison of U.S. vs. Europe
Safety	• Rates of serious adverse events were comparable overall between the two regions. • Two subjects in Europe accounted for 10 of the 16 SAEs experienced in Europe. Excluding these 2 subjects, the remaining 14 European subjects experienced 6 SAEs, which is very similar to the 14 US subjects who had 5 SAEs total. • Rates of most non-serious AEs were, in general, comparable between the two regions.
Square Localization	• Results on the square localization test were comparable between the two groups. • The mean distance from the target center for US subjects (System ON) ranged from 126 – 187 pixels (with one outlier at 219 pixels), while the range was 122 – 162 for subjects in Europe. • At all time points, both groups performed better with the System ON vs. OFF.
Direction of Motion	• The range of mean error across follow-up time points was substantially the same for both groups. • For subjects in the U.S., the mean error (System ON) ranged from 57 – 64 degrees (with one outlier at 81 degrees for a US subject at 18 months), while the range was 54 – 72 for subjects in Europe. • At all time points, both groups performed better with the System ON vs. OFF.
Grating Visual Acuity	• A similar proportion of subjects in the US and Europe were able to score on the grating visual acuity test during the study (29 vs. 25%, respectively).
Orientation & Mobility	• The average success rates for subjects from the US and Europe, on both the line and door tasks, were comparable across all time points. • At all time points, both groups performed better with the System ON vs. OFF.
FLORA	• Overall, the proportion of subjects who were rated as having a positive effect from the Argus II System was similar between the two regions.
Massof	• No difference between the two groups.
VisQOL	• No significant differences between the groups.

6.11.1.4 ANALYSIS OF ORIENTATION AND MOBILITY RESULTS BY METHOD

The analysis presented earlier in section 6.10.2.1 pooled all the data collected in the study for both orientation and mobility tasks (i.e., the Door Task and the Line Task). This form of analysis enabled the tracking of subjects' performance from the first follow-up visit up until the most recent visit. To examine whether the changes in test methodology that were initiated in June 2009 could have had an influence on the results, a sub-group analysis was performed.

Changes to the Door Task

For the first half of the study (until April 2009), subjects were placed at one of three possible start locations (left, center, or right), which were varied by the tester, and the "door" had one location (center). Subjects were started 20' from the door. Analysis of the results from this test configuration revealed that subjects were often able to successfully complete this task by chance, as evidenced by the rate of success with the System OFF.

Therefore, beginning in April 2009 the test configuration was modified slightly. Under the modified test condition, subjects were placed facing forward, at a fixed start location (center). The "door" was placed at one of the two target locations on the wall with the center of the door displaced either 5' (1.5 m) right or 5' (1.5 m) left from center. Subjects were positioned 10' from the door, a distance from which most subjects could detect the door with their Argus II System. Subjects were instructed to walk toward the "door" and place his/her hand on it. Trials where the subject's hand touched the "door" were recorded as a "success."

Changes to the Line Task

For the first half of the study, the Line Task course used a 6" (15 cm) wide, 20 foot (6.1 m) long straight line, which contrasted with the floor surface. For instance, black tape or paint was used to create the line on a white floor and white tape or paint was used to create the line on a dark floor. Subjects were positioned at the start of the line in one of the possible start positions (subjects were angled facing to the left, center, or right) and were instructed to follow the line to its end. During the study, investigators provided feedback to Second Sight that some subjects were likely using auditory or tactile feedback to follow the line. Therefore, the test set-up was modified to have sites use black interlocking floor tiles with the 6" white line painted on them to reduce the possibility of subjects using these cues to successfully complete the task.

In addition, analysis of the results from the line test revealed that subjects were

often able to successfully complete this task by chance, as evidenced by the rate of success with the System OFF. Therefore, beginning in April 2009, the test configuration was modified slightly. Under the modified test condition, there was one start location (with the subject facing straight ahead) but the course had three possible configurations: an 18' (5.5 m) straight line, a line with a left turn at 9' (2.7 m), and a line with a right turn at 9' (2.7 m). The trials were conducted by varying the course configurations for the 6 trials. Subjects were instructed to follow the line to the end. If they ended the trial on the same floor tile as the end of the line, the trial was recorded as a "success."

Results

In both the original and modified test methods, subjects as a group performed better (higher mean success rate) on the Door Task with the System ON than OFF. The difference between performance in the two conditions, however, was greater in the modified test method data, particularly at 12 months post-implant. Results of the Door Task are presented in Table 28.

As with the Door Task, in the Line Task, subjects as a group performed better (higher mean success rate) with the System ON than OFF in both the original and modified test methods. The difference between performance in the two conditions, however, was greater in the modified test method data, particularly at 6 and 12 months post-implant. Results of the Line Task are presented in Table 29.

The suspicion that subjects were successfully completing the Door and Line Tasks with the System OFF solely by chance prompted the change in the test methods (both tests were made more difficult). Results of the subgroup analysis suggest that this effort was successful; modified test method results show a larger difference between System ON and System OFF performance for both tasks, due to a lower success rate with the System OFF.

Table 28: Door Task by Method

Task	Visit	Number of Subjects	Success Rate System ON			Success Rate System OFF		
			Mean	Standard Error (plotted)	Standard Deviation	Mean	Standard Error (plotted)	Standard Deviation
Original Test Method	Baseline	22	**N/A**	N/A	N/A	**26%**	4%	0.17
	3 Month	16	**57%**	7%	0.27	**35%**	6%	0.25
	6 Month	15	**60%**	8%	0.32	**27%**	6%	0.25
	12 Month	11	**53%**	9%	0.30	**48%**	7%	0.23
	18 Month	8	**58%**	10%	0.28	**27%**	4%	0.12
Modified Test Method	Baseline	7	**N/A**	N/A	N/A	**24%**	10%	0.25
	3 Month	13	**53%**	8%	0.28	**28%**	7%	0.27
	6 Month	15	**50%**	10%	0.40	**27%**	6%	0.24
	12 Month	17	**53%**	7%	0.30	**20%**	5%	0.21
	18 Month	20	**54%**	6%	0.29	**20%**	5%	0.17
	24 Month	25	**54%**	6%	0.29	**20%**	5%	0.21
	36 Month	13	**38%**	9%	0.31	**9%**	4%	0.15
	48 Month	7	**52%**	9%	0.24	**7%**	3%	0.09

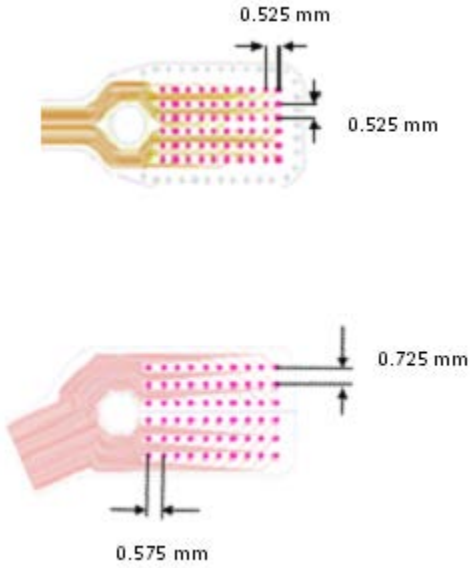
Table 29: Line Task by Method

Task	Visit	Number of Subjects	Success Rate System ON				Success Rate System OFF	
			Mean	Standard Error (plotted)	Standard Deviation	Mean	Standard Error (plotted)	Standard Deviation
Original Test Method	Baseline	23	**N/A**	N/A	N/A	**17%**	4%	0.21
	3 Month	14	**67%**	9%	0.35	**27%**	7%	0.25
	6 Month	14	**60%**	8%	0.31	**35%**	7%	0.27
	12 Month	11	**60%**	9%	0.30	**27%**	9%	0.30
	18 Month	8	**83%**	7%	0.20	**25%**	6%	0.18
Modified Test Method	Baseline	7	**N/A**	N/A	N/A	**29%**	14%	0.37
	3 Month	13	**81%**	6%	0.23	**24%**	9%	0.33
	6 Month	15	**76%**	8%	0.32	**11%**	5%	0.19
	12 Month	17	**81%**	7%	0.28	**11%**	3%	0.12
	18 Month	20	**78%**	7%	0.33	**14%**	5%	0.22
	24 Month	25	**57%**	7%	0.37	**12%**	5%	0.23
	36 Month	13	**63%**	11%	0.39	**12%**	5%	0.18
	48 Month	7	**76%**	10%	0.27	**17%**	4%	0.10

6.11.2 EFFECT OF DIFFERENCE IN ELECTRODE SPACING

The single metal devices implanted in the first 15 subjects (Cohort 1) and the dual metal devices implanted in the second 15 subjects (Cohort 2) differ slightly in the spacing between the stimulation electrodes. The horizontal spacing between electrodes in the original ("single-metal") array is 0.575 mm while the vertical spacing is 0.725 mm. Both the horizontal and vertical spacing between electrodes in the dual-metal array is 0.525 mm. The electrode size is identical in the two versions with each electrode having a diameter of 0.210 mm. These dimensions are illustrated in Figure 25.

Figure 25: Electrode Spacing in Dual Metal Array (Top) & Single Metal Array (Bottom)



As part of the poolability analysis, the FDA requested a comparative data analyses for any tests that could be affected by differences in electrode spacing. The minor difference in electrode configuration between Cohort 1 and Cohort 2 did not result in any major effect on performance on any of the assessments used in the clinical trial. The endpoint "Grating Visual Acuity" is the assessment most likely to be affected by electrode configuration since the spacing between the electrodes determines the array's theoretical visual acuity. The theoretical acuity limits are presented in Table 30. Please note that because the horizontal and vertical spacing is different in Cohort 1, it is difficult to calculate an exact theoretical maximum, so we have calculated the maxima for each spacing separately.[48]

[48] The calculation assumes the conversion factor of 1˚ of arclength = 293 µm on the retina.

Table 30: Calculated Theoretical Acuity Limit

Configuration	Spacing	Theoretical acuity limit
Cohort 1 (single metal), vertical	0.725 mm	2.17 logMAR
Cohort 1 (single metal), horizontal	0.575 mm	2.07 logMAR
Cohort 2 (dual metal)	0.525 mm	2.03 logMAR

There is just slightly greater than 0.1 logMAR difference in the theoretical maximum acuities of the different configurations. While a trend toward slightly better performance in Cohort 2 on Grating Visual Acuity was noted, the number of subjects was too small to perform statistical comparison. As one subject had scored 1.8 logMAR on the Grating Visual Acuity task (more than 0.2 logMAR better acuity than the theoretical maximum for Cohort 2), it seems that the additional information gathered through head scanning is more likely to affect performance on this task than small differences in electrode spacing.

For the Square Localization and Direction of Motion assessments, no statistical comparison of performance between the two cohorts could be performed since there was virtually no overlap in follow-up time between cohorts (as the tests were introduced partway through the study). Character Recognition also showed a trend toward better performance for Cohort 2. More real-world assessments such as Orientation and Mobility, the Massof, and the VisQOL did not show apparent differences between Cohorts; on the FLORA, Cohort 2 appeared to perform better than Cohort 1, but it was not possible to perform a statistical comparison.

6.11.3 STABILITY OF ELECTRODE FUNCTIONALITY

6.11.3.1 CHARACTERIZING THE STATUS OF AN ELECTRODE

Several terms are used to describe the status of an individual electrode:

Enabled vs. Disabled: These terms indicate whether the Argus II System allows stimulation to be delivered by this electrode. If stimulation can be delivered to an electrode, it is “enabled.” If the System does not allow stimulation to be delivered to the electrode, it is “disabled.”
Has a measurable stimulation threshold vs. Does not have a measurable stimulation threshold: These terms only apply to enabled electrodes. They indicate whether the electrode, when it delivers stimulation current (below some current and pulse duration limit) to the retina, is able to cause the subject to see a visual percept.

These terms are discussed in greater detail below.

Enabled vs. Disabled Electrodes

The Argus II implant is designed with 60 electrodes. During final manufacturing of the implant, each unit was inspected and tested to determine if all electrodes met specifications. Electrodes that met all specifications were enabled and those that did not were disabled. The VPU did not allow stimulation of disabled electrodes.

Once implanted, impedance measurements were used to monitor the status of the individual electrodes. If an electrode's measured impedance exceeded a pre-specified value set in the Video Processing Unit, the VPU would automatically disable the electrode. Electrodes with high impedance were disabled to prevent the possibility of stimulating on an open electrode. Once disabled, the VPU did not allow stimulation of that electrode.

In addition, some electrodes were damaged during a surgical procedure. These electrodes were then manually disabled by the person programming the subject's VPU.

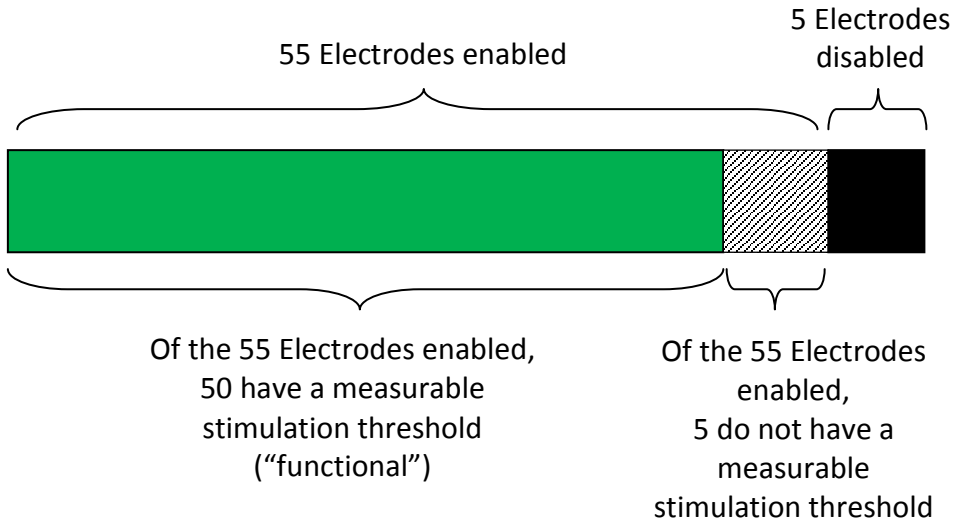
Electrodes with Measurable Stimulation Thresholds

Subjects were periodically tested to measure single electrode stimulation thresholds. The stimulation threshold is defined as the charge (current times pulse width) at which a single electrode produces a visual percept for the subject. Only enabled electrodes could be programmed to deliver electrical stimulation, so thresholds were only measured on enabled electrodes. Electrodes that produce a visual percept may also be called "functional" as they are typically included in the program downloaded to the subject's VPU.

Status of all 60 Electrodes

Ideally, all 60 electrodes would be enabled and all 60 electrodes would produce a visual percept when stimulated. Due to both technical and physiological reasons, however, this was not always the case. **Figure 26**, below, illustrates an example of what the status of all 60 electrodes may look like for a particular subject at a particular point in time. In this example, of the 60 electrodes, 55 are enabled, and of the 55 enabled electrodes, 50 have a measurable stimulation threshold below the current limit (i.e., "functional").

Figure 26: Theoretical Example of the Status of a Subject's Electrodes



The status of electrodes could change over time for a variety of reasons. These changes are discussed in the Sections 6.11.3.2 and 0, below.

6.11.3.2 DISABLED ELECTRODES AND EPOXY LOT ISSUE

As described in Section 6.11.1.1, modifications were made to the implant following the implantation of the first 15 subjects to incorporate feedback from clinicians. In assessing the poolability of the clinical data for the original design (single metal implant) and the modified design (dual metal implant), the FDA raised the question of whether there is a difference between the long-term functionality of these two designs in terms of the number of electrodes disabled over time. Specifically, the Agency was concerned that a particular lot of epoxy which was discovered to have high resistivity that was used in the manufacture of many of the dual metal devices, unduly compromised the functional performance of the device by resulting in a higher number of electrodes to be disabled post-operatively.

The system allows measurement of electrode voltage waveforms during stimulation. Evaluation of these waveforms can tell us whether the electrode is electrically "open" or is performing properly. As part of the investigation that led to the finding of high resistivity with the specific lot of epoxy, we realized that the majority of the electrodes that were automatically disabled by the VPU's electrode integrity algorithm (which was implemented to detect electrically "open" electrodes) were not, in fact, open, based on analysis of their waveforms. In other words, many of these electrodes were being disabled unnecessarily. The company re-evaluated the parameters being used to measure impedance,

and in late 2010, modified the electrode integrity algorithm's preset impedance limit value to prevent these electrodes from being incorrectly disabled. Electrodes that had previously been disabled could be safely re-enabled and used by the subjects. This adjustment was very effective in reducing the number of electrodes that were unnecessarily disabled in the dual metal implants. Table 31 provides the mean number of disabled electrodes over time for both the design Cohort 1 ("single metal implants") and Cohort 2 ("dual metal implants"). The "dual metal implants" had slightly more electrodes disabled due to high impedance as a result of the issue with the lot of epoxy. However, this difference in number of electrodes disabled between single and dual metal implants was reduced after adjustments were made to the impedance algorithm as described above. The mean value for the last time point (i.e., "last visit as of 1/31/12") takes into account the adjustment to the impedance algorithm.

In general, the number of disabled electrodes over time is small. Implant design Cohorts 1 and 2 were similar in terms of long-term stability.

Table 31: Mean Number of Disabled Electrodes over Time

Implant	Mean # Disabled Electrodes prior to implant	Mean Number of Electrodes Disabled by Impedance Algorithm at (# months post-implant):					
		3 Mo.	6 Mo.	12 Mo.	18 Mo.	24 Mo.	Last visit as of 1/31/12
Cohort 1	6.6	0.13	0.20	0.60	0.93	1.1	0.60
Cohort 2	2.5	1.1	2.3	3.3	4.0	3.3	1.6

6.11.3.3 STIMULATION THRESHOLDS BY COHORT

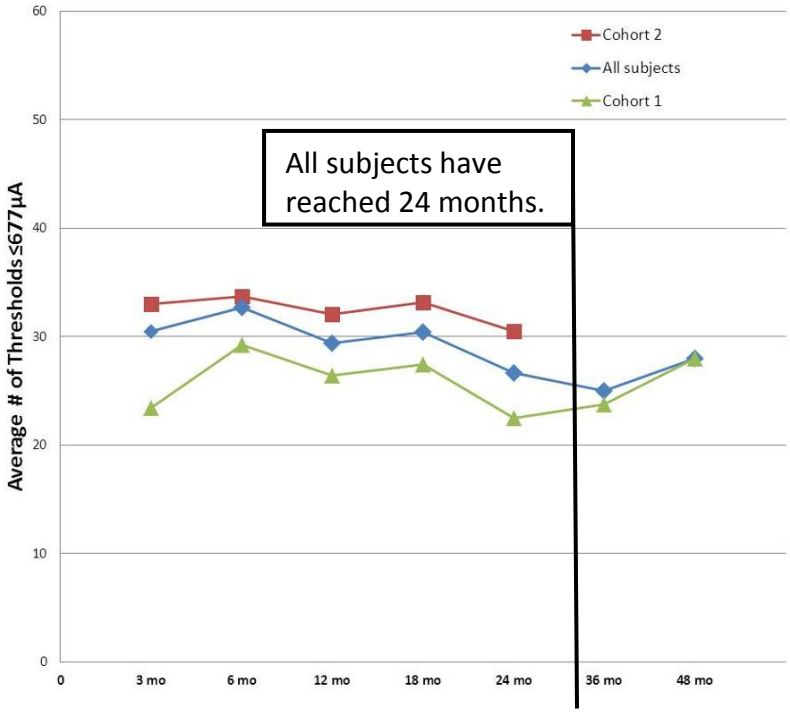
The single electrode stimulation threshold is the level of stimulation current (at a fixed pulse width) required for an individual electrode to consistently elicit a percept. These thresholds were measured for all enabled electrodes at routine time points throughout the clinical study.

The number of single electrode thresholds provides an indication of how many of the 60 electrodes provide visual perception to a subject below the current limit. In the study, there was a general trend that subjects who had more electrodes with lower thresholds did better on performance measures, particularly those most likely to depend on spatial vision, such as Direction of Motion.

The FDA asked Second Sight to perform an analysis of single electrode stimulation thresholds (up to 677µA at 0.45 ms pulsewidth) over time to assess

the long-term "functional stability" of the device. These graphs illustrate that the Argus II implant showed good functional stability in the average number of measurable thresholds over time (with data available on all subjects out to 2 years and out to 4 years on half of the single metal subjects). Subjects in Cohort 2 tended to have more electrodes with measurable thresholds than subjects in Cohort 1. This finding was expected since the array portion of the implant for Cohort 2 subjects was molded in silicone to provide a more consistent shape, whereas the array portion of the implant for Cohort 1 subjects was hand-made.

Figure 27: Average # of Electrodes with Measurable Thresholds Over Time
(Data collected through April 30, 2012)



		3 mo	6 mo	12 mo	18 mo	24 mo	36 mo	48 mo
Overall (n=30)	n	19*	18*	28	27	29	13	8
	Average	30.5	32.7	29.4	30.4	26.7	25.0	28.0
	Standard deviation	14.4	17.4	17.5	19.2	19.4	14.5	18.6
Cohort 1 (n=15)	n	5*	4*	13	13	14	12	8
	Average	23.4	29.3	26.4	27.5	22.5	23.8	28.0
	Standard deviation	14.3	4.2	14.8	15.8	14.8	16.5	18.6
Cohort 2 (n=15)	n	14	14	15	14	15		
	Average	33.0	33.7	32.1	33.1	30.5		
	Standard deviation	14.1	19.7	19.4	20.0	19.7		

Above figure is from HDE Amendment dated June 25, 2012 (Figure 12).
* NOTE: In the beginning of the study, stimulation thresholds were only measured up to 233µA.

Starting in March 2008, when approximately 10 of the Cohort 1 subjects had completed 3 and 6 months follow-up, thresholds were measured up to 677 µA (with a 0.45ms pulsewidth). To make a direct, meaningful comparison, threshold data were only included in the graphs below if they were measured up to 677 µA.

6.11.4 CORRELATION BETWEEN VISUAL FUNCTION AND FUNCTIONAL VISION

At the request of the FDA, a comparative analysis was performed to correlate subjects' performance on visual function tests with their performance on functional vision tests. The visual function tests that were used in the analysis were Square Localization, Direction of Motion, and Grating Visual Acuity. The functional vision tests were Direction of Walking, Sock Sorting, and Sidewalk Task. A positive correlation (at a 95% confidence level) was demonstrated for the following pairings:

- Direction of Walking and the Direction of Motion test
- Sock Sorting and Direction of Motion test
- Sock Sorting and Square Localization test

No significant correlations were found when comparing the Sidewalk Task to the visual function tests. Correlations with the Grating Visual Acuity data could not be obtained since a valid value cannot be assigned to a score of "worse than 2.9 logMAR."

Table 32 shows the correlation coefficient (r^2) for each comparison. If the slope of the regression line was significantly greater than zero ($p<0.05$), the coefficient is marked with an asterisk.

Table 32: Correlation Coefficient for Comparison of Functional Vision Tests vs. Visual Function Tests

		Visual Function Tests		
		Square Localization	**Direction of Motion**	**Grating Visual Acuity**
Functional Vision Tests	**Sock Sorting**	**0.26***	**0.17***	N/A
	Direction of Walking	0.04	**0.37***	N/A
	Sidewalk Task	<0.01	0.02	N/A

Since performance on Sock Sorting had a positive correlation with performance on both Square Localization (a light projection test) and Direction of Motion (a

spatial vision test), the real-world task of Sock Sorting may be a good general test of visual function and functional vision with the Argus II System. The functional vision task Direction of Walking is, not surprisingly, correlated with Direction of Motion performance since both of these tests aim to measure subjects' ability to determine the direction an object is moving, one using an artificial stimulus and one in a real-world context. The Sidewalk Task, on the other hand, did not correlate with any of these three visual function tests. This is not too surprising since this very complex real-world task, in which subjects must integrate information from their systems while walking in an outdoor setting, is a measure of multiple skills besides visual function.

6.11.5 STABILITY OF IMPLANT LOCATION IN THE EYE

The electrode array is tacked to the retina to secure it in position. However, slight rotation around the tack is possible, especially in the first couple of months post-implant. FDA requested that Second Sight analyze if the electrode array rotated over time and the effect this had on performance.

To perform this analysis, fundus photographs were compared from all time points after implantation at which a clear view of the retina could be obtained. Retinal landmarks (e.g., blood vessels and pigmentary changes) and array landmarks (e.g., individual electrodes and the silicone landmarks located on the back of the array) were used to determine if the position of the array had rotated. For subjects who underwent elective revision surgery, movement prior to and after the revision surgery was considered independently, since the array may have been moved during surgery. Table 33 summarizes these results.

Table 33: Stability of Implant Location in the Eye

(n=30 subjects)

Amount of Array Rotation	n Subjects	Comment
No rotation of the array	19	Note, for one subject data were only available through 6 months, after which time posterior capsule opacification prevented a clear view of the retina.
Array rotated approximately 0.1 – 0.2 mm	3	For 2 subjects, this rotation occurred during the first 3 months after implantation. For one subject, this rotation occurred during the first 6 months after implantation.
Array rotated approximately 0.3-0.4 mm	7	For 2 subjects, this movement occurred within the first 3 months after implantation. For 5 subjects, this rotation occurred within the first 6 months after implantation.
Array rotated approximately 0.8 mm	1	The rotation was gradual, beginning sometime after 2 months post-implantation and continuing up until the last available follow-up at 24 months after implantation.

The majority of subjects experienced no array rotations. Most rotations that did occur, occurred in the first 3-6 months post-implant, during which time the eye was healing. Minor events during the healing process (e.g., changes in intraocular pressure) could have led to an adjustment in how the array was positioned with respect to the retina. There were no instances where these minor rotations led to an adverse event. In addition, these array rotations did not result in any detectable changes in performance.

7 PATIENT VIDEOS

Five videos are included with the Panel Pack. Together, they allow a greater understanding of the Argus II System and the impact it has had on clinical trial subjects' lives.

Table 34: List of Panel Pack Videos

Filename	Description
Argus II Principle of Operation	A narrated animation that explains the basic principle of operation of the System.
Argus II Testimonials	A video in which two subjects explain, in their own words, the effect the System has had on their lives.
Reading Tasks	A video that shows several examples of Argus II subjects recognizing alphanumeric characters and reading short words with their Argus II Systems.
Real-World Tasks Indoors	A compilation of video clips from the FLORA assessments and training sessions showing Argus II subjects using the System to perform tasks inside their homes or clinics.
Real-World Tasks Outdoors	A compilation of video clips from the FLORA assessments and training sessions showing Argus II subjects using the System to perform tasks outside their homes or clinics.

8 POST-APPROVAL STUDY

It should be noted that the FDA has not reviewed the proposed post-approval studies described below.

8.1 POST-APPROVAL STUDY FOR NEW PATIENTS

It is anticipated that at the time of approval of the HDE application the Agency will request that a post-approval study be performed to document continued safety and probable benefit of the approved device. Following the FDA Advisory Panel Meeting, but prior to HDE approval, Second Sight will submit a full protocol for the post-approval study to FDA for review and approval.

After obtaining CE Mark for the Argus II System in Europe in 2011, Second Sight initiated a post-market study in Europe.[49] By design, it is a non-randomized, controlled, prospective, multi-center post-market study. It is planned to enroll subjects until a total of 45 subjects have been enrolled or 30 subjects have reached 1 year follow-up, whichever comes first. Subjects are being followed for 3 years each. The primary endpoint of the study is safety, as measured by adverse event rates. The secondary endpoints are visual function (as measured by the Square Localization, Direction of Motion and Grating Visual Acuity Tests) and Activities of Daily Living (as measured by the Massof Activity Inventory). The NEI-VFQ 25 quality of life questionnaire and the Landolt C[50] visual function test are also being administered to subjects in the study, although these measures are not study endpoints. The synopsis of this protocol is included in Appendix E (Section 14.5).

Second Sight intends to propose this protocol to the FDA to qualify as the US post-approval study. Second Sight will work with the FDA to determine if any protocol changes are necessary prior to commencing the post-approval study in the US. All US sites that are trained to implant the device will be offered participation in the post-approval study with the goal to enroll all subjects into this protocol until enrollment is complete.

8.2 POST-APPROVAL STUDY FOR EXISTING STUDY SUBJECTS

Post-approval, Second Sight intends to continue to obtain long-term follow-up

[49] Protocol number NCT01490827 on the NIH www.clinicaltrials.gov website

[50] A test in which the subject must determine the direction of the opening in the C optotype in a four-alternative forced-choice test.

on the subjects enrolled in the pre-market (IDE) clinical trial. In the US, the study has been extended to follow-up subjects through 7 years post-implant. In Europe, the study has been extended to follow-up subjects through 5 years post-implant.

9 CLINICIAN TRAINING

A *Surgeon Manual*, a video describing the surgical procedure and implantation of the Argus II Implant, and hands-on training are provided by Second Sight to all surgeons prior to them performing an implantation procedure. The Surgeon Manual also provides instructions on how to screen potential patients for eligibility for the Argus II System and provides a recommended clinical follow-up schedule. Surgeons must undergo training in order to implant the Argus II Implant. Additionally, Second Sight strongly recommends that for the first implantation procedure conducted at each site, a vitreoretinal surgeon experienced in implanting the Argus II Implant is present during the surgery to guide the new implanting surgeon through the procedure.

A *Device Fitting Manual* is also provided to all clinical centers and is included with the Argus II Clinician Fitting System. The Device Fitting Manual provides instructions for use of all components of the Argus II System. Clinicians and/or technicians must be knowledgeable about state-of-the-art Argus II System fitting procedures. These personnel must be fully trained and qualified by Second Sight in the fitting of the Argus II System.

In addition, a *Visual Rehabilitation Guide* and hands-on training is provided to low-vision therapists who will provide visual rehabilitation to Argus II patients post-implant.

10 PATIENT TRAINING AND VISION REHABILITATION

Patients receive a copy of the Patient Manual in print and audio formats. The Patient Manual describes how to use the external equipment of the Argus II System that is provided to the patient. Argus II System patients receive training on all aspects covered in the Patient Manual prior to taking the Argus II external equipment home for everyday use.

In addition to the System training provided to the patient by hospital clinicians, in-home visual rehabilitation sessions will be provided by certified low-vision therapists and/or orientation and mobility specialists who have been trained by Second Sight to perform rehabilitation with Argus II patients. The rehabilitation

process for Argus II patients follows the traditional approach of assessment, establishment of rehabilitation goals, and vision rehabilitation intervention. It was developed by independent, certified orientation and mobility experts and low-vision therapists in collaboration with Second Sight; it is based on well-established and effective low-vision and blind therapy approaches, but customized for the unique population of Argus II patients. Note, at the time of the data cutoff of this report, no subjects in the Argus II trial had received vision rehabilitation as part of the trial.

In the recommended schedule, rehabilitation sessions at the patient's home will begin four weeks post-implant and continue biweekly through week 10, with an optional follow-up in month 3. This schedule was based on the recommendations of Duane Geruschat, Ph.D., and other low-vision rehabilitation specialists, who felt it was important to begin rehabilitation very soon after the patient starts using the Argus II System at home. However, the actual schedule, including the total number of sessions, will be determined by the therapist in order to meet the needs of the individual patient.

The rehabilitation consists of three main components: a functional vision assessment (the Functional Low-vision Observer-Rated Assessment, or FLORA); modification of the patient's home environment; and visual rehabilitation, during which trained low-vision therapists will work with the patient to develop his or her functional vision (reinforcing and building on the skills learned during in-clinic training) and integrate the use of the Argus II System into his or her daily life. An Instructional Kit, consisting of objects developed by rehab specialists for use with Argus II patients, has been developed by Second Sight and will be provided to each therapist working with commercial patients to help develop the patients' functional vision and visual-motor skills. A subset of materials in this Instructional Kit will also be provided to the patients to practice the skills they've been taught.

A Rehabilitation Guide has been developed to help therapists plan their rehabilitation sessions with the patient. As each patient's goals, system performance, and motivation will be different, therapists also customize their sessions to the needs of the patient. After the in-clinic training, most Argus II patients should be proficient with the basic skills required to use the device, but therapists will assess their skills and address their system use in a real-world (home) environment. Most of the rehabilitation sessions will be spent reinforcing proper techniques with the device, as well as providing assistance with problem solving and integrating the Argus II System into their everyday life.

11 RISK-BENEFIT ANALYSIS

The following risk-benefit analysis is prepared in accordance with the FDA guidance document, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications" which was issued March 28, 2012.

11.1 PROBABLE BENEFIT

The study protocol contained several endpoints designed to evaluate the probable benefit of the device in terms of visual function, functional vision and quality of life. Together, these measures provided a robust assessment of the probable benefit of the Argus II System.

Visual Function

The Visual Function tests were objectively scored, employed high-contrast stimuli, and were administered on a computer. Subjects served as their own controls, performing all tests with the System ON and OFF (with only their residual vision, if any).

The Square Localization test was essentially a measure of light projection, and was clinically relevant because it equates to important orientation tasks such as locating objects like windows, lights, etc. When data from this test were averaged over all subjects, performance with the System ON was better than System OFF for all time points. These results were consistently maintained through at least 2 years post-implant, at which (on average) subjects missed the target by about 50 pixels with System ON vs. about 250 pixels with the System.

The Direction of Motion Test is a more complex task that requires interpreting spatio-temporal information from multiple stimulating electrodes. It provides an indication of a person's ability to detect the direction of moving objects which, in the real world, could include such events as cars passing by on the street or people walking in front of them. When data were averaged over all subjects, accuracy with the System ON was better than System OFF for all time points; these results were also maintained through at least two years post-implant, at which subjects' average error with the System ON was about 60˚, compared to almost chance with the System OFF.

The Grating Visual Acuity test was the most complex task, and it was modeled after the principles of the ETDRS chart, which has been validated for visual acuity to 20/1000 (Snellen) or 1.70 logMAR. The Grating Visual Acuity test extended

the ability to evaluate subjects from 1.6 logMAR down to 2.9 logMAR. Twenty-seven percent (27%) of subjects were able to score on the Grating Acuity scale (between 1.6 and 2.9 logMAR) with the System ON during the course of the study, while none of the Argus II subjects were ever able to score on the scale with the System OFF in either eye. The best performing subject was able to achieve 1.8 logMAR (20/1262).

As discussed in Section 6.2.4, the Argus II subjects who were able to score on the test would likely be clinically classified as being able to detect hand motion (HM), count fingers (CF), or better. The Grating Visual Acuity results, in short, were a dramatic achievement since all subjects previously had bare light perception or worse.

To characterize performance on a test that is more similar to the traditional ETDRS chart, the Character Recognition and Reading Words research project was initiated. Over half of the subjects (between 71% and 95% depending on the character group) identified large letters better than chance with the System ON while only 0-10% performed better than chance with the System OFF. The four subjects best able to identify the large characters further demonstrated the ability to read short words later in the project. Again, this represented a dramatic improvement for subjects who were previously bare light perception.

Taken as a whole, the suite of visual function tests demonstrated that the Argus II System improved subjects' ability to localize light, recognize large characters, identify the direction of motion of an object, and score on a Grating Visual Acuity test. **This is the first example of a device – or any therapy – that has objectively demonstrated improved visual function in this population.**

Functional Vision and Quality of Life

The significant improvements in visual function in Argus II subjects corresponded to similar achievements in functional vision and quality of life, as measured by several protocol tests and research projects. These assessments represented a variety of methods including self-reporting, objective scoring of tasks, and subjective rating of tasks by a trained observer. By examining the totality of the data, one can gain insight into the effect the Argus II System had on subjects' lives.

Objectively-scored tasks were performed by patients with the System either ON or OFF, providing an internal baseline control. Tasks included Orientation and Mobility (i.e. finding a door; following a line on the floor of a room) and Functional Vision tasks (e.g. sorting white, black, and grey socks; following an outdoor sidewalk; determining the direction of a person walking by). All of these

tasks were developed to be representative of real-world activities that Argus II subjects could not do with their native residual vision. All subjects performed better on these tasks with the System ON than with it OFF. The Orientation and Mobility test, which was conducted on all subjects at routine follow-up time points throughout the study, demonstrated that these results with the Argus II System were maintained out to at least two years post-implant.

The Functional Low-vision Observer Rated Assessment (FLORA) was recently developed with input from the FDA to meet the need for an assessment of real-world functional vision and quality of life in ultra-low-vision subjects. The FLORA results indicated the Argus II System provided improvements in functional vision and/or well-being for over three quarters (77%) of the subjects. The assessors reported the Argus II System was not detrimental to any subjects in terms of their functional vision and/or well-being.

Additionally, the two self-report questionnaires (Massof Activity Inventory and VisQOL) indicated mild improvement in subjects' overall goals and some tasks (Massof Activity Inventory) or no significant change (VisQOL). In retrospect, these tools were not sensitive enough to measure changes in functional vision for retinal prosthesis subjects, who before the study, had minimal to no sight (bare light perception or worse in both eyes).

Overall, the results of the different functional vision and quality of life assessments indicated that the Argus II System provided benefit to the majority of Argus II subjects in both clinical settings and real-world activities. It gave them the ability to perform tasks that they could not do without the System (e.g., locating people, orienting in unfamiliar environments, avoiding obstacles, etc.) and provided psychological benefits that can be difficult to measure but are extremely important for these profoundly blind subjects who have no other treatment alternatives. Some subjects described their enjoyment of the System in vivid detail to the rehabilitation experts conducting the FLORA. For example: "She stated really liking using the device for fun things, especially seeing movement outside, as a passenger in the car or seeing the moon or Christmas lights", "…he has gained pleasure from 'seeing' light after years of blackness", "…[the subject] describes the experience of seeing light sources and the sun as 'marvelous'". These kinds of benefits are not likely to be captured by most standard assessment tools, but cannot be discounted for the satisfaction they bring to people learning to live with an incurable, degenerative disorder that has slowly robbed them of their sight.

11.2 RISK

The Argus II device is implanted in the worse-seeing eye. Typically with an ophthalmic implant, the main risk is loss of residual vision. With the Argus II implant, this risk is limited since the patients have minimal to no residual vision in either eye. The Argus II device is safely explantable, further limiting the risk. Finally, if permanent damage were to happen to the implanted eye, the fellow eye (with comparable or better residual vision) is unaffected, preserving it for future potential treatments or alternative therapies. The external software and hardware are also upgradeable providing a way for the patient to benefit from future retinal prosthesis research. These factors combine to make the baseline risk of the Argus II implant low.

The clinical study has shown that the Argus II System has an acceptable safety profile for blind patients with severe to profound RP. Safety was monitored throughout the study by an Independent Medical Safety Monitor (Suber Huang, MD, Director, Center for Retina and Macular Disease, Professor and Vice Chairman, Dept. of Ophthalmology & Visual Sciences, University Hospitals, Cleveland, OH).

Adverse events observed in the study were manageable and were successfully treated using standard techniques. No catastrophic adverse events (e.g., lost eyes) occurred.

As one would expect with a surgical intervention, the majority of adverse events (51%) occurred in the first 6 months post-implant. The majority of subjects (n=19 or 63%) in the Argus II study experienced no or only non-serious device- or surgery-related events. Non-serious events were treated routinely with medication or observation only. There were only 3 permanent AEs, all of which were non-serious and they did not have clinically relevant sequelae (e.g. epiretinal membrane).

An additional seven subjects experienced serious adverse events that resolved with medical treatment or minor interventions. The remaining four subjects were distinct from the other 26 subjects in that they required significant interventions to treat what was often a cascade of related SAEs. In total, these 4 subjects accounted for 57% of all SAEs and 24% of all non-serious adverse events. SAEs were resolved in all but one subject who had 3 stable, but unresolved events (i.e., hypotony, retinal detachment, and corneal opacity) as of the cut-off date of this report. Only one subject required device explant to resolve recurrent conjunctival erosion and hypotony.

Modifications made to the surgical procedure and implant design midway

through the study contributed to a modest decline in the rate of adverse events in subjects enrolled in the latter half of the trial. This trend of event rates improving over time as more experience is gained with a device is common in the field of implants and new surgical procedures. The trend suggests that adverse event rates will continue to improve in the commercial setting.

There were no systemic injuries or permanent impairments associated with the implantation or use of the Argus II System. In fact, all subjects continued to be able to perceive light with the Argus II System, despite any SAEs (with the exception of the one subject who was explanted). These adverse events did not have any detrimental effect on patient's residual vision, nor did they change the benefit patients received from the System.

Safety of Device Explant

The Argus II Implant was successfully explanted in one subject and the retinal tack was successfully removed and replaced in an additional three subjects. There were no adverse sequelae following any of these cases. These cases, along with 3 animal explants during the pre-clinical phase, demonstrate that the Argus II Implant and tack or the tack alone can be safely removed.

Safety of Long-Term Use and Retinal Stimulation

Prior to implantation, 29 of 30 subjects had bare light perception in the implanted eye (one subject had no light perception). At the latest follow-up visit, all but one of these subjects maintained bare light perception in the implanted eye. The one subject who did not experienced a visual decline to no light perception in both eyes. The parallel decline in the fellow eye suggests that the decline in light perception in this one subject was due to normal disease progression, as opposed to damage caused by the device or electrical stimulation. These data show that the Argus II Implant and its chronic use have not led to a significant decline in residual light perception when compared to the fellow non-implanted eye.

In addition, all subjects have used the Argus II System for a minimum of two years (the observation period that all subjects have reached at the time of data cut-off for this report). Some subjects have been using the System for over 4 years. The fact that subjects continue to perceive electrically-induced visual percepts during routine use of the Argus II System also provides strong evidence that the electrical stimulation provided by the System, which was limited to stimulation levels below the FDA-approved chronic-use charge density limit of $0.35 mC/cm^2$, is not damaging the neural tissues in the eye.

These data support the safety of long-term chronic stimulation with the Argus II System and indicate that it presents an acceptable risk to patients.

Device Long-Term Reliability

The Argus II Implant was monitored throughout the study. After a cumulative total of over 105 subject-years of implant, there has been only one implant failure related to loss of RF link. An investigation concluded that the decline in RF link in this one implant was likely due to damage to the coil overmold at the time of implantation by sharp forceps. The forceps used in this early case are no longer used in the implantation of the Argus II implant.

These results demonstrate the long-term hermeticity and functionality of the implant.

11.3 ADDITIONAL FACTORS

Uncertainty

Designing a clinical study for a small, underserved patient population carried with it recognized challenges, among them the impossibility of carrying out a large randomized trial and the lack of accepted, validated endpoint measures. Second Sight successfully met each of these challenges: First, by designing a study large enough to produce sufficient safety and probable benefit data (n=30 subjects) but small enough to enroll in a reasonable time (just over 2 years with 10 enrolling centers and a concerted effort); and second, by using recognized scientific advisors to design endpoint measures before commencing the study and refining some endpoints while the study progressed. While the small available subject population limited the ability to run a larger study, a strong case can still be made for safety by comparing the safety results in the study to the closest comparable established ophthalmic devices and treatments.

Other factors mitigated the uncertainty when determining reasonable assurance of the safety and probable benefit:

1) The trial was conducted at multiple centers (n=10) in the U.S. and 3 countries in Europe, thus providing greater assurance that the results can be generalized to the larger population and that the training program for surgeons and clinicians is satisfactory (i.e., the techniques are not so specialized that only a few clinicians can master them).
2) The direct effect of the device could be assessed with a control at every timepoint as the device can be turned “ON” and “OFF.” This reduced the likelihood that the results were due to a placebo effect. In addition, for certain tests, the fellow eye acted as an additional control.

3) The study was conducted in accordance with recognized standards for clinical trials (ISO 14155) and the results were routinely monitored by 4 governmental agencies that required periodic reports from the study (i.e., FDA in the U.S., Afssaps (now called ANSM) in France, MHRA in the UK, and Swissmedic in Switzerland).
4) The sites were routinely monitored by Second Sight Clinical Research Associates to ensure compliance with the protocol and the validity of the data collected.

Characterization of the disease

Retinitis pigmentosa (RP) is the most common type of a large and heterogeneous group of hereditary retinal degenerations that causes progressive, irreversible impairment of photoreceptors and retinal pigment epithelium. The progression of the disease is generally slow, but the eventual impact on vision and quality of life is often devastating. Patients afflicted with RP for 25 years are usually left with a visual field of 10 degrees or less. As the disease progresses and further photoreceptor loss occurs, even this constricted field may be lost.

Patient tolerance for risk and perspective on benefit

Because of the profound impact that blindness has on their daily lives, patients suffering from RP often have a very high tolerance for risk in exchange for potential improvements in functional vision and quality of life that can be gained from partial restoration of vision.

Second Sight routinely receives phone calls from patients and their family members from all over the world inquiring about how they can obtain the Argus II System. Many of these patients are willing travel great distances and/or temporarily relocate near an implanting center to receive the device. In addition, both the subject who had the Argus II device explanted and the subject whose Argus II device stopped working have requested a new Argus II Implant. These inquiries and requests speak to the great desire of blind individuals for a treatment that will provide some vision restoration.

Given that there are no treatments currently available for these patients, they are likely willing to take greater risks, and they should be given the choice to take those risks. Of course, this choice must be an informed choice, and patients must be properly counseled about the risks and probable benefits of the Argus II System by their physician. The additional controls in place for an HDE-approved device, provide the necessary patient protections in this regard (See “Risk mitigation” below).

Availability of alternative treatments

Currently, no other treatments (devices, drugs or biologics) are commercially available in the United States to treat individuals with severe to profound RP.

Risk mitigation

Devices approved under the HDE regulation require IRB approval and most IRBs also require a special patient consent form for use of the device. This process will ensure that patients are well informed on the risks associated with the surgical implantation and use of the device prior to making a decision about whether to be implanted.

Second Sight has also developed a comprehensive training program for surgeons as well as for the clinicians that will be doing fitting and the therapists who will provide visual rehabilitation services. Patients will also be trained on how to properly use the system so they can maximize the benefits that the system can provide. These training programs will ensure that the device is implanted and used in accordance with the labeling.

Continued Access Study and Post-Market study

Second Sight has already been collecting long-term follow-up on the 30 subjects enrolled in the clinical trial. Many of these 30 subjects have completed the initial 3 year commitment in the study and have signed up for the 2 year study extension. In addition, Second Sight recently obtained approval from the FDA to continue the IDE study for an additional 2 years, to allow for the collection of 7 years total follow-up data on all subjects.

In addition to this extended follow-up on the 30 subjects in the clinical trial, Second Sight intends to conduct a post-approval study in the U.S. Second Sight has already initiated such a post-market surveillance study in Europe, where CE Mark was approved in 2011.

These efforts to collect long-term follow-up data and post-market data will allow for the continued monitoring of safety and benefit of the Argus II System as it enters commercial use.

Novel technology to address an unmet medical need

The Argus II System represents a “first of its kind” technology for the treatment of blindness due to severe to profound RP. No other treatments are available for this patient population in the US. It is likely the safety profile of this device will

improve over time as additional experience is gained with its use. In the current 30 subject trial, the rate of adverse events decreased as the study progressed.

It is also likely that future improvements of the device may provide increased levels of benefit. Improvements to the implant could benefit future patients, while improvements to the external systems could benefit both future patients and current patients (since the external systems are upgradeable). This precedent was set by other neurostimulator devices such as cochlear implants, which improved significantly over the years since being first approved for the market.

Since the trial began and the FLORA assessment was implemented, Second Sight has developed and is implementing a formal program of instruction with the device that complements traditional rehabilitation. The results of the FLORA show that subjects have benefited from the device. The experience with rehabilitation suggests that instruction from experienced rehabilitation specialists is giving each subject the opportunity to increase their efficiency with the device and assists with learning how the device can be integrated with their current lifestyle.

The Argus II System presented in this HDE application represents the culmination of over 10 years of effort by Second Sight and over 20 years of research. Approval of this HDE application will not only finally afford blind RP patients access to a treatment, it would also allow Second Sight to continue to innovate this technology for the benefit of blind patients and encourage others to pursue this research as well.

Finally, while the focus of this application is on the safety and probable benefit of the device for RP patients, one must also consider that the RP patients are not the only ones who could potentially benefit from the Argus II device. Blind patients require assistance and support from their family members and caregivers. By providing RP patients with greater independence and improvements in quality of life, this also directly helps those who support them. Furthermore, it is important for patients, their families and caregivers to know that, through the HDE process, the FDA supports the work to improve the lives of people with RP. This will provide them with the hope that new technologies can be approved in the US to help them combat this disease.

12 CONCLUSIONS

The Argus II Retinal Prosthesis System was designed to provide electrical stimulation of the retina to induce visual perception in people with severe to profound retinitis pigmentosa (RP). In the clinical trial, the System provided a range of visual function to subjects from simple light detection to basic form vision.

This visual information translated in several ways into the subjects' everyday lives. On the functional side, it helped them carry out basic visual tasks, such as locating doors and windows, avoiding obstacles, sorting light and dark clothes, and aiding in navigating. Equally important for many patients were the improvements in quality of life the restored vision provided. Many subjects commented that the vision provided by the System allowed them to feel more connected with people in their surroundings, because, for example, they could see when people were moving in front of them, and could tell when someone was approaching them or had moved away. Subjects also commented that they enjoyed being "visual" again; they provided many specific examples of the pleasure they derived from the System, such as locating the moon, seeing the changing light levels on a TV, and tracking groups of players as they move around the field at an athletic event.

There are currently no commercially available treatment options (i.e., drugs, devices or biologics) for these patients. The FDA has recognized that this group of subjects represents an "orphan" population, and the Argus II system has been designated a Humanitarian Use Device.

When combining the safety and performance data, this study of the Argus II Retinal Prosthesis System demonstrated that the probable benefit of its use outweighed the risks of illness or injury in people who were almost completely blind in both eyes (bare light perception or no light perception) and had no other treatment options.

While some adverse events associated with the implant and surgical procedure were observed during the trial, they were treatable using standard techniques. Against this risk is the profound possibility of recovering at least some visual function, functional vision and improvements in quality of life. For subjects who once had full vision, only to lose it to a chronic, progressive disease, the return of any visual function, even as basic as hand motion, can provide significant benefits, both functional and psychological.

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14 APPENDICES

14.1 APPENDIX A – EXCERPT FROM MASSOF ACTIVITY INVENTORY

GOAL 6 (DAILY MEAL PREPARATION): How important is it for you to be able to prepare your daily meals without anyone else's assistance?

- ☐ Not important (If checked, skip to next Goal)
- ☐ Slightly important
- ☐ Moderately important
- ☐ Very important

Tasks	Impossible to do without someone else's help	Very difficult	Moderately difficult	Slightly difficult	Not difficult	Not applicable
• How difficult is it for you to prepare your daily meals without anyone else's assistance?	☐	☐	☐	☐	☐ (If checked, skip to next Goal)	☐ (If checked, skip to next Goal)
1. How difficult is it for you to read recipes?	☐	☐	☐	☐	☐	
2. How difficult is it for you to transfer liquids without spilling?	☐	☐	☐	☐	☐	
3. How difficult is it for you to read timers or clocks?	☐	☐	☐	☐	☐	
4. How difficult is it for you to find utensils?	☐	☐	☐	☐	☐	
5. How difficult is it for you to measure ingredients?	☐	☐	☐	☐	☐	
6. How difficult is it for you to read labels on packages, cans, or bottles?	☐	☐	☐	☐	☐	
7. How difficult is it for you to read stove or oven dials?	☐	☐	☐	☐	☐	
8. How difficult is it for you to find food items?	☐	☐	☐	☐	☐	
9. How difficult is it for you to pour or mix without spilling?	☐	☐	☐	☐	☐	
10. How difficult is it for you to read a thermometer?	☐	☐	☐	☐	☐	
11. How difficult is it for you to avoid burning yourself?	☐	☐	☐	☐	☐	
12. How difficult is it for you to judge browning or doneness of food?	☐	☐	☐	☐	☐	
13. How difficult is it for you to cut, chop, or dice food?	☐	☐	☐	☐	☐	

14.2 APPENDIX B – VISQOL QUESTIONNAIRE

1) Does my vision make it likely I will injure myself (i.e., when moving around the house, yard, neighborhood, or workplace)?
- ☐ It is mostly unlikely I will injure myself because of my vision.
- ☐ There is a small chance.
- ☐ There is a good chance.
- ☐ It is very likely.
- ☐ Almost certainly my vision will cause me to injure myself.

2) Does my vision make it difficult to cope with the demands in my life? My vision:
- ☐ Has no effect on my ability to cope with the demands of my life.
- ☐ Does not make it difficult at all to cope with the demands of my life.
- ☐ Makes it a little difficult to cope.
- ☐ Makes it moderately difficult to cope.
- ☐ Makes it very difficult to cope.
- ☐ Makes me unable to cope at all.

3) Does my vision affect my ability to have friendships? My vision:
- ☐ Makes having friendships easier.
- ☐ Has no effect on my friendships.
- ☐ Makes friendships more difficult.
- ☐ Makes friendships a lot more difficult.
- ☐ Makes friendships extremely difficult.
- ☐ Makes me unable to have friendships.
- ☐ Not applicable; I have no friendships.

4) Do I have difficulty organizing any assistance I may need?
- ☐ I have no difficulty organizing any assistance I may need.
- ☐ I have little difficulty organizing assistance.
- ☐ I have moderate difficulty organizing assistance.
- ☐ I have a lot of difficulty organizing assistance.
- ☐ I am unable to organize assistance at all.
- ☐ Not applicable; I never need to organize assistance.

5) Does my vision make it difficult to fulfill the roles I would like to fulfill in life (e.g., family roles, work roles, community roles)? My vision:
- ☐ Has no effect on my ability to fulfill these roles.
- ☐ Does not make it difficult to fulfill these roles.
- ☐ Makes it a little difficult to fulfill these roles.
- ☐ Makes it moderately difficult to fulfill these roles.
- ☐ Makes it very difficult to fulfill these roles.
- ☐ Means I am unable to fulfill these roles.

6) Does my vision affect my confidence to join in everyday activities? My vision:
- ☐ Makes me more confident to join in everyday activities.
- ☐ Has no effect on my confidence to join in everyday activities.
- ☐ Makes me feel a little less confident.
- ☐ Makes me feel moderately less confident.
- ☐ Makes me feel a lot less confident.
- ☐ Makes me not confident at all.

14.3 APPENDIX C – ANTICIPATED ADVERSE EVENTS

1. Infection
   - If an infection is presumed, attempt to confirm with microbiological testing
2. Inflammation is not an AE if it is < Kimura class 2 and lasts for < 1 month unless it raised IOP above 30mmHg.
3. Hypopyon
4. Hyphema is an AE if it:
   - Occurs in the immediate post-operative period and lasts > 1 month post surgery OR
   - Occurs later than one month post surgery , is mild (or worse) and lasts > 1 month OR
   - Is '8-ball hyphema' OR
   - Causes high IOP (>30 mmHg).
5. Vitreous hemorrhage is an AE if it:
   - Occurs in the immediate post operative period and lasts > one month post surgery OR
   - Occurs later than one month post surgery, is mild (or worse) and lasts ≥ 1 month OR
   - Obscures the view of the retinas such that ultrasound is needed to assess OR
   - Leads to IOP >30mmHg
6. Retinal Folds are AEs if the affect the array placement or the tack.
7. Vascular Congestion/Occlusion
8. Cystoid Macular Edema/Choroidal Hemorrhage
9. Conjunctival Erosion is an AE if there is device exposure.
10. Suture irritation is an AE if it requires surgical intervention.
11. Scleral Erosion
12. Choroidal detachment is an AE if –
    - It is ≥to 4 disc diameters OR
    - It displaces the array OR
    - Choroidals are 'kissing' OR
    - It lasts for longer than 1 month OR
    - It is associated with a flat anterior chamber.
13. Conjunctival congestion is an AE if it:

- Occurs in the immediate post-operative period (within 1 month post-operative) and lasts > 1 month OR
- Occurs later than one month post surgery, is mild (or worse) and lasts > 1 month.

14. Scleral Perforation – unintended perforation of the sclera
15. Scar or fibrosis formation, including epiretinal membrane
16. Ocular fibrin (anterior or vitreous) is an AE if it
    - Occurs in the immediate post-operative period and lasts >1month post surgery OR
    - Occurs later than one month post surgery, is mild (or worse) and lasts > 1 month OR
    - Obscures the view of the retina
    - Raises IOP above 30mmHg.
17. Retinal Tear or retinal break is an AE
18. Retinal Detachment should be classified as:
    - Rhegmatogenous (AE) OR
    - Subretinal fluid
        - Subclinical - ≤1 disc diameter and well demarcated is <u>not</u> an AE.
        - Clinical - >1 disc diameter is an AE classified as either rhegmatogenous or tractional
19. Retinal edema
20. Retinal/subretinal hemorrhage is an AE only if it causes dislocation of the array.
21. Cataract
22. Corneal Opacity is an AE if it:
    - Covers the visual axis OR
    - Is infectious in nature.
23. Corneal degeneration
24. Corneal vascularization is an AE if it covers the visual axis.
25. Corneal epithelial defect is an AE if it persists > 2 weeks post-surgery.
26. Iris/Pupil changes are AEs if they
    - Lead to atrophy associated with significant functional or structural defects of the iris OR
    - Lead to high IOP.
27. Increased intra-ocular pressure (IOP)

- Intra-ocular pressure increase more than 10 mmHg above baseline or intraocular pressure greater than 30 mmHg

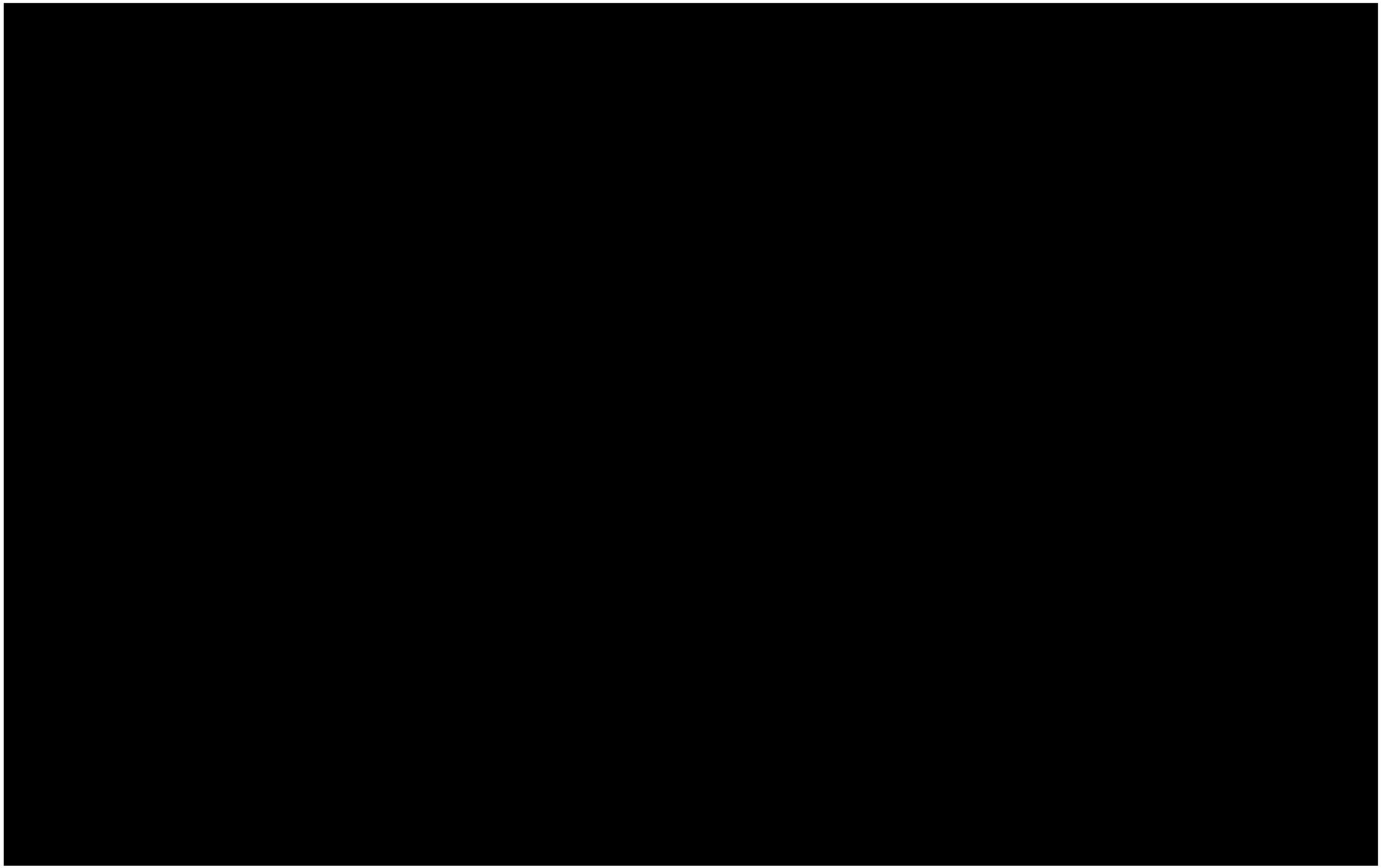
28. Hypotony (<5mmHg) is an AE if it
    - Persists for > 2weeks OR
    - Is associated with kissing choroidals OR
    - Is associated with a flat anterior chamber.
29. Ptosis
30. Ocular pain or discomfort in the implanted eye
31. Disturbed/difficult eye movement
32. Dry eye
33. Extrusion of band
34. Intrusion of band
35. Dislodgement of human sclera or equivalent allograft
36. Electric Shock
37. Migration of array
38. Loosening/extrusion of device
39. Increase in photophobia
40. Side effects of medications and/or interactions with concurrent mediations and underlying medical conditions
41. Respiratory failure – fail to wean from ventilator post-surgically
42. Blood loss requiring active intervention such as transfusion
43. Allergic reaction to anesthesia
44. Loss of light perception in eyes having pre-operative light perception

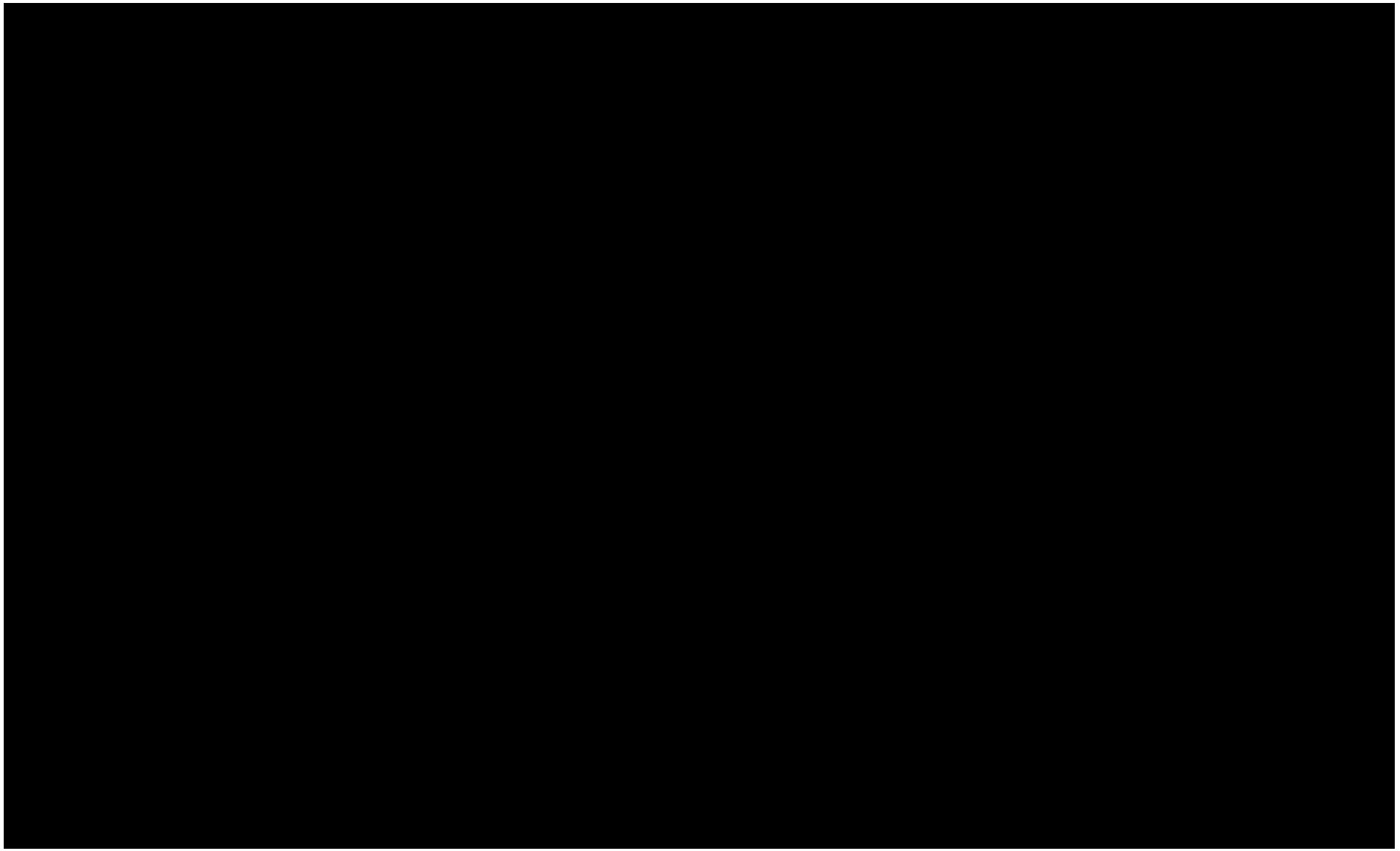
The following are not AEs:

- Corneal dryness
- Descemets Folds
- Retinal pigmentary changes

14.4 APPENDIX D - DETAILED NARRATIVE OF SAEs

[redacted]





14.5 APPENDIX E – PROTOCOL SYNOPSIS FOR THE POST-APPROVAL STUDY

This protocol is currently being run in Europe and the ClinicalTrials.gov identifier is NCT01490827. Please note that the FDA has not reviewed this proposed post-approval study.

Protocol Title:	Argus® II Retinal Prosthesis System Post-Market Surveillance Study
Protocol ID Number:	PM-01-01
Device:	Argus II Retinal Prosthesis System (Argus II)
Primary Objective:	To collect post-market surveillance data in order to monitor safety and visual function
Study Design:	Non-randomized, controlled, prospective, multi-center post-market study
Primary Endpoint:	Safety (i.e., adverse event rates)
Secondary Endpoint(s):	Visual Function and Activities of Daily Living
Post-Operative Study Duration for Each Study Participant:	Study Participants are enrolled 2 weeks post-implantation with follow-up for three (3) years
Proposed Duration of Study:	3 years for each participant
Diagnosis and Main Criteria for Eligibility:	Age 25 years or older; both males and females; with severe to profound outer retinal degeneration (not including Age-related Macular Degeneration [AMD]); with some residual light perception or with retinal response to electrical stimulation; with previous history of useful form vision
Number of Centers:	Up to 20 centers
Number of Study Participants:	Recruitment to continue until 45 participants have been enrolled, or until 30 participants reach 1 year follow-up (whichever is achieved sooner)