In the United States, approximately 100,000 people have retinitis pigmentosa (RP), and the number worldwide is estimated at 1.5 million. This inherited, progressive retinal condition causes rod and cone photoreceptor cells to degenerate, leading to total or near-total blindness. Although a nutritional regimen has shown promise in delaying RP progression, there is yet no treatment that can undo the sight-robbing damage once it has occurred.

But patients received more than a glimmer of hope with the February 2013 FDA approval of the Argus II Retinal Prosthesis System (Second Sight Medical Products) for use in advanced RP. (It received the European CE mark in 2011.)

The Argus II is an epiretinal-stimulating device designed to improve visual functioning in people who are blind—or, more accurately, to give people who are blind from severe RP the ability to perceive black and white images and motion. Although it is currently the only such device approved in the United States, others are pressing forward in development, notably the Alpha IMS, manufactured by Retina Implant AG in Germany.

Now that this critical approval barrier has been crossed, what are the implications for RP patients and their ophthalmologists? Three retina specialists take a look at where we are now—and what impediments remain—in the development and adoption of retinal prostheses.

What Does This Approval Mean?
Argus II was approved as a “humanitarian use device,” an FDA category for devices that treat or diagnose fewer than 4,000 people in the United States per year. This type of approval does not require proof of effectiveness; rather, Second Sight had to provide evidence to the FDA showing that the probable benefits of Argus II outweigh its risks and that no comparable device is available for treating RP.

Now, Argus II can be offered to all RP patients who meet the treatment criteria, not just those in clinical trials. According to product labeling, patients must be at least 25 years old, with a diagnosis of retinitis pigmentosa, with bare light or no light perception in both eyes, and a history of previous useful form vision. Moreover, they must be phakic or pseudophakic as well as willing and able to receive the recommended postimplant clinical follow-up, device fitting, and visual rehabilitation.

A long process of development.
The hard-won FDA approval for Argus II followed more than 20 years of planning, device development, and testing by a team led by Mark Humayun, MD, PhD, of Doheny Eye Institute and Second Sight, and Robert J. Greenberg, MD, PhD, of Second Sight, and Robert J. Greenberg, MD, PhD, of Second Sight. “This is a clear demonstration of restoring sight in patients,” said Grace L. Shen, PhD, director of the Retinal Disease Program at the National Eye Institute. NEI has spent roughly $29.7 million on the development of Argus I and II, including preliminary work.

The device consists of an eyeglass-mounted video camera for capturing images, a video processing unit (VPU)
worn on the belt, and a microelectrode array (Fig. 1) that is surgically im-
planted onto the retina via a pars plana sclerotomy. The VPU transforms video
images into electronic data, transmitted wirelessly to the microelectrode
array, which stimulates the underlying ganglion cells to produce patterns of
light. Argus I, which utilized a 16-mi-
croelectrode display, was implanted
into the first of six patients in 2002 at
Doheny Eye Institute in Los Angeles.
The currently approved Argus II model has a 60-electrode array for improved
spatial resolution.

Research Shows Gains With Argus II
Although the FDA did not require proof of effectiveness, there is some
evidence of gains in visual function-
ing with Argus II. In the FDA hearing
on Sept. 12, 2012, several patients who
participated in the clinical trials gave
anecdotal reports of improvement
following implantation and training,
such as being able to perceive motion
as well as curb edges and crosswalk
markings or tree limbs in their path.
Another described gaining the ability
to sort white, black, and gray socks.3

Recently published research shows
that some Argus II recipients are able
to read large letters and words of up
four to letters on a computer screen.4 The
research included 21 patients whose
duration of experience with the Argus
II ranged from 8.6 months to 34.8
months (average, 19.9 months). In the
first round of testing, patients were
asked to identify letters of various sizes
and typographic complexity; those
who could identify at least 50 percent
of single letters within 60 seconds per
letter were further tested with smaller
letters and, ultimately, short words.

Four patients “graduated” to the
third trial phase, in which they were
asked to read three 10-word sets (con-
sisting of two-, three-, or four-letter
words). Three of these patients suc-
ceded in reading at least 50 percent
of the words in each set, and two read all
10 words in at least one set.

The researchers noted that, among
the 21 patients who participated in the
first test, the time needed to identify a
letter varied widely, ranging from 6 to
221 seconds; similarly, there was wide
variation in the size of letter perceived.

According to the authors, it is not
clear what differentiated the high-per-
forming test subjects from the others.
Identifying these factors—which could
include age at diagnosis, age at implant-
ation, or genotype—will be critical in
selecting patients to receive a retinal
implant.5

Other Devices in Development
In addition to Second Sight’s postmar-
keting trials of Argus, three companies
have devices in human studies, cur-
rently either recruiting or under way,
as registered at www.ClinicalTrials.
gov. These include a subretinal
implant from Retina Implant AG
(registry numbers NCT01024803
and NCT01497379), an epiretinal
implant from Pixium Vision SA
(NCT01864486), and a prototype
suprachoroidal wide-view implant
from Bionic Vision Australia (NCT
01603576).

Another device innovator, the
Boston Retina Implant Project, has
completed more than two years of test-
ing its subretinal device in pigs and is
preparing for human testing.6

Alpha IMS. Apart from Argus, the
Alpha IMS from Retina Implant AG is
the farthest along in development and
is the only retinal prosthesis that has
undergone long-term testing in hu-
mans. In July 2013, it received the CE
mark in Europe.

Unlike Argus, it does not require
an external eyeglass-mounted camera.
Rather, it uses a wireless subretinal
chip, which moves with the eye, con-
taining 1,500 electrodes, which trans-
form the incoming light to electrical
signals. These signals, after passing
through an amplification circuit,
stimulate intact retinal cells to induce
visual perceptions.

Earlier this year, clinical trial results
were reported from nine blind patients
who were implanted with the Alpha
IMS device.7 The researchers reported
“reliable and luminance-dependent
signal generation” in all nine subjects
over a three- to nine-month period.

Differences in activities of daily
living, recognition of letters, and
safety were studied with the device
on or off. Eight subjects experienced
light perception; seven could localize
the source of light; and five detected
motion. The researchers were able to
measure grating acuity in six subjects
and visual acuity in two (up to 20/546
Snellen); three subjects could read
letters spontaneously. Five subjects re-
ported using their implant-dependent
visual function in carrying out activi-
ties of daily life.8

Substantial Barriers Remain
Despite these encouraging results,
researchers continue to grapple with
safety and technical challenges.

Safety. Among the 30 patients in the
Argus II study, 17 device- or surgery-
related serious adverse events (SAEs)
occurred, some of which were clus-
tered in the same individual. The most
common SAEs were endophthalmitis,
hypotony, and conjunctival dehis-
cence (three events each). However,
the researchers noted that they were
able to adapt their surgical methods in
the trial to reduce adverse events; for
example, no cases of endophthalmitis
were seen in the second 15 patients.7

Implantation surgery. In placing
epiretinal implants, it is difficult to
make them conform closely to the
retinal surface, and they are most
commonly tacked to the retinal surface
(Fig. 1).5 The implant may require later
retracking, as occurred in two patients
in the study.7

One of the surgical challenges for
subretinal implants is that the device
and cables must be placed without di-
rect visualization. In addition, silicone
oil tamponade is used to forestall reti-
nal detachment.8

Predictions for Adoption
Will these devices be widely adopted
by retina surgeons? “I don’t see that
happening yet,” said John T. Thomp-
son, MD, of Baltimore, who is presi-
dent of the American Society of Retina
Specialists (ASRS). “One reason is that
very few of our patients with RP have
visual acuity low enough to be eligible
for the visual prosthesis.”

The rate of implantation could change, though, as indications for the technology expand into areas like age-related macular degeneration or other diseases primarily involving the outer retina. “For patients eligible today,” added Dr. Thompson, “I would refer them to a medical center that has been offering the implant.”

Approval of the Argus—and ongoing efforts with the other devices—demonstrates effective translational research that incorporates new findings in retinal cell function, neural circuitry, and disease processes. Dr. Thompson described these developments as “a scientific tour de force.” He added that “ASRS is always interested in new tools to help our patients. We support the concept and hope the technology will extend to patients who are blind from retinal degenerative disease. The best hope right now is the visual prosthesis.”

Dr. Shen agreed that we have come a long way in making visual prostheses available as a possible treatment, but she noted that Argus and the other retinal prostheses in development are like the first personal computers. They are the beginning. “Once you show it can work, it can move quickly.”

A Surgeon’s Argus Experience in Saudi Arabia

In February 2013, J. Fernando Arevalo, MD—along with fellow vitreoretinal surgeons Stanislao Rizzo, MD, and Saba Al Rashaed, MD—implanted the first two Argus II devices in the Middle East at King Khaled Eye Specialist Hospital (KKESH) in Riyadh (Fig. 2). Dr. Arevalo leads the vitreoretinal division at KKESH as part of a research, education, and patient care collaboration between that institution and the Wilmer Eye Institute, where he is a professor.

Dr. Arevalo said that RP is unusually prevalent in Saudi Arabia and surrounding regions. “We’ve been flooded with inquiries from patients and doctors throughout the Middle East.”

Patient selection and commitment.

Patient selection criteria at KKESH are the same as in the FDA-approved labeling discussed above. Beyond that, Dr. Arevalo is very clear that patients must understand the procedure and the intense commitment required for rehabilitation training. For patients, the program begins with a battery of tests, followed by the surgery and 20 scheduled follow-up visits, including a rigorous rehabilitation program.

The surgical team tempers high expectations on the part of the patients and families with facts based on research findings. “We tell the patients that this is going to take time,” said Dr. Arevalo. As to the outcomes for the first two KKESH patients: “After just two months of rehabilitation and training, they are already able to see doors, people passing by, and outside buildings.”

Surgical training.

Dr. Arevalo learned the procedure from the Second Sight training team. For a surgeon who is new to the procedure, he said, the implantation of the epiretinal array can take about four hours—but only after several days of onsite education from the manufacturer that covers patient testing, surgical procedures, use of special instrumentation, and wet labs. “I would say that anyone who’s performed vitreoretinal surgery can learn to implant the array,” said Dr. Arevalo. Training is also required in rehabilitation techniques to help patients make effective use of the device’s input. He emphasized, however, that the commitment is not for everyone because it reaches far beyond the operating room into patient relationships, time management, and hospital issues.

As for the biggest surgical challenge, “It definitely has to be the tacking of the implant in the retina,” said Dr. Arevalo. The specially designed titanium retinal tack (Fig. 1B) is passed from the stimulating array, through the retina, retinal pigment epithelium and choroid, and finally through the sclera, where it is anchored. “Today’s surgeons learned vitreoretinal surgery after tacks were no longer in use,” he noted. “This surgery has revived retinal tacking.”

9 J. Fernando Arevalo, MD, is professor of ophthalmology at Wilmer Eye Institute, in Baltimore, and chief of the vitreoretinal service at King Khaled Eye Specialist Hospital, in Riyadh, Saudi Arabia. Financial disclosure: None.
10 Grace L. Shen, PhD, is the group leader and director of the Retinal Disease Program at the National Eye Institute, in Bethesda, Md. Financial disclosure: None.
11 John T. Thompson, MD, is in practice with Retina Specialists, Baltimore. Financial disclosure: Has received grant support from Genentech, Pfizer, and Regeneron.

MORE ONLINE. Watch a video of retinal implant surgery at KKESH at www.eyenet.org (available after Aug. 15).