Retinal Disease: Much Progress, Some Pain

by Michael Lachman

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The last quarter of 2011 witnessed a number of important milestones in the retina device field, including the first commercial implants of two novel products for late-stage retinal disease and failure to win Food and Drug Administration (FDA) approval for a novel drug delivery implant. On the biopharma side, the end of 2011 was highlighted by the FDA approval of an important new treatment for wet age-related macular degeneration (AMD).

An event-filled year in the retina market began with the publication in April 2011 of one-year results from the landmark 1,208-patient, 43-center CATT trial. (*See "Market & Industry Briefs"* — Medtech Insight*, May 2011.*) CATT compared off-label intravitreal *Avastin* (bevacizumab) versus on-label *Lucentis* (ranibizumab) for the treatment of AMD, and the findings suggested that Avastin offers equivalent safety and efficacy at a fraction of the cost. The cost per injection of Lucentis is $1,950, whereas the cost per injection of Avastin, when portioned into doses that are appropriate for intravitreal injection, is about $50. In the study, both drugs performed well, with 95% of patients showing no progression of vision loss. Both anti-VEGF drugs are manufactured by **Genentech Inc./Roche**, and Lucentis is marketed by **Novartis Pharmaceuticals Corp./Novartis AG**.

The published results of the CATT trial confirmed what most retina specialists had already believed to be true about the relative efficacy of Avastin and Lucentis for AMD, and these views had already been reflected in actual treatment patterns in the US. According to William L. Rich III, MD, medical director of health policy for the American Academy of Ophthalmology (AAO), the ratio of Avastin/Lucentis usage in the US was approximately 60%/40% in 2010, versus approximately 58%/42% in 2009. Dr. Rich expects to see a more significant shift toward Avastin when 2011 usage data becomes available in May 2012, driven by results of the CATT trial. However, reported US sales of Lucentis in Q3 and Q4 2011, the first full quarters following CATT publication, showed a fairly steady quarterly sales trend rather than a sequential decline. In each of these two quarters, reported sales levels of approximately $435 million were consistent with reported sales in Q2 2011. (*See Exhibit 1.*) This might suggest a trend toward greater use of Avastin for newly treated patients, while Lucentis continues to be used for patients that are already receiving this drug.

During the "Retina Great Debate" session at the *AAO Annual Meeting*, held in October 2011, physicians debated the pros and cons of off-label Avastin over Lucentis. The key arguments in support of Lucentis centered on the fact that it is manufactured and packaged in high precision, sterile facilities, while Avastin must be portioned for ocular use by compounding pharmacies. This additional handling can introduce endotoxins and other contaminants, adding an element of risk for patients. The pro-Avastin rebuttal argued that such statements are "scare tactics," that ophthalmologists use many off-label drugs in the eye, and that the actual incidence of infection resulting from Avastin use in the eye has been very low.

EYLEA Wins FDA Approval For Wet AMD Treatment

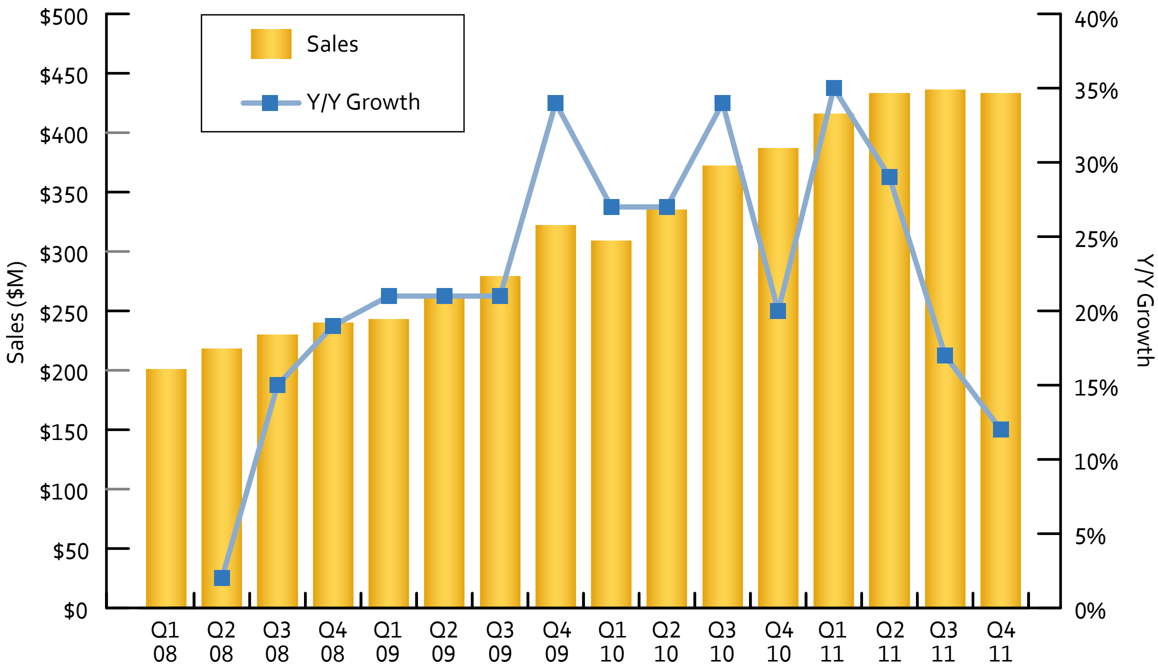
On November 18th, **Regeneron Pharmaceuticals Inc.** announced that the FDA had approved *EYLEA* (aflibercept) injection, previously known as VEGF Trap-Eye, for the treatment of wet AMD, making it the second approved anti-VEGF treatment for AMD. Approval was based on the company's VIEW 1 and VIEW 2 clinical studies, which enrolled 2,412 patients. In both studies, the primary efficacy end point was the proportion of patients who maintained vision, defined as losing fewer than 15 letters (three lines) of visual acuity at week 52 compared to baseline. The two-milligram dose of EYLEA, injected at intervals of every four weeks and every eight weeks following three initial monthly doses, demonstrated efficacy that was clinically equivalent (noninferior) to Lucentis injected every four weeks. (*See Exhibit 2.*)

The key advantage of EYLEA over Lucentis, as labeled, is the need for fewer monitoring visits and injections. At the announced price of $1,850 per EYLEA injection, the cost of seven required injections in the first year would be $12,950, and the cost of six injections in the second year would be $11,100. This compares very favorably to the cost of on-label monthly injections of Lucentis, which totals $23,400 per year. However, in real-world clinical usage involving PRN (as needed) dosing of Lucentis, there are an average of eight monthly injections in the first year and five in the second year, bringing the annual cost of Lucentis during the first two years down to $15,600 and $9,750, respectively.

In a poll taken at the end of the *AAO Annual Meeting* "Retina Great Debate" session, 60% of physicians in attendance said that Avastin, not Lucentis or EYLEA, should be the primary treatment for wet AMD. This is consistent with the current rate of Avastin usage for AMD in the US and suggests that EYLEA may compete with Lucentis primarily in the 40% of the market that is not already dominated by off-label Avastin use. Nevertheless, Regeneron got off to a strong

Exhibit 1

Lucentis Quarterly US Sales And Growth Trends, Q1-2008 – Q4-2011



Note: US sales in dollars estimated from reported sales in Swiss francs (CHF).

SOURCE: Roche

Exhibit 2

EYLEA Efficacy Outcomes At One Year In VIEW 1/VIEW 2 Studies

	VIEW 1			VIEW 2		
	EYLEA @ 8 Weeks	*EYLEA @* 4 Weeks	*Lucentis @* 4 Weeks	*EYLEA @* 8 Weeks	*EYLEA @* 4 Weeks	*Lucentis @* 4 Weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
% of patients who maintained visual acuity (<15 letters BCVA loss)	94%	95%	94%	95%	95%	95%
Mean change in BCVA (letters gained from baseline)	7.9	10.9	8.1	8.9	7.6	9.4
% of patients who gained at least 15 letters of vision from baseline	31%	38%	31%	31%	29%	34%

Notes: Last observation carried forward (baseline values are not carried forward). *EYLEA* data is for 2 mg dose; *EYLEA* 8 week dosing is after initiation with 3 monthly doses; BCVA = Best Corrected Visual Acuity.

SOURCE: Regeneron Pharmaceuticals

start with EYLEA, recording $24.8 million in EYLEA sales in the fourth quarter of 2011. The company expects EYLEA sales to reach $250-$300 million in 2012, up considerably from its original estimate of $140-$160 million.

AMD Brachytherapy Fails Pivotal Trial

Ionizing radiation, which has demonstrated strong inhibitory effects on new and established neovascular vessels, is being studied in combination with anti-VEGF therapy, with the goal of providing the same or better visual outcomes while reducing the number of required injections. The *VIDION ANV* Therapy System from **NeoVista Inc.** delivers strontium-90 beta radiation directly over a retinal lesion using a 20-gauge probe that is introduced into the eye via vitrectomy surgery. The system has received CE mark approval and is available commercially in several European countries and in other regions.

Earlier this month, two year results from the company's first pivotal trial, CABERNET, were presented by retinal specialist Pravin U. Dugel, MD, at the *Bascom Palmer Eye Institute 50th Anniversary Scientific Meeting* in Miami. The CABERNET study compared epimacular brachytherapy (EMBT) plus Lucentis to Lucentis alone in 457 treatment-naïve subjects, using a noninferiority study design with a primary endpoint of visual acuity and a 10% noninferiority margin. Patients were treated at 42 sites worldwide and enrollment was completed in October 2009.

The company's previous, 53-patient MERITAGE study suggested that EMBT therapy may be able to stabilize or even improve vision and reduce the number of required anti-VEGF injections in patients who had failed to respond adequately to anti-VEGF therapy alone. However, outcomes from the pivotal trial, which focused on patients who had not received prior anti-VEGF treatment, were disappointing.

In the CABERNET trial, EMBT failed to meet its primary visual acuity endpoint at two years. The group treated with EMBT plus two mandatory Lucentis injections over the first month lost a mean of 2.5 letters of vision and required an average of four additional "rescue" injections of Lucentis over a two year period. In comparison, patients in the control arm gained a mean of 4.4 letters of vision, while receiving 10 scheduled Lucentis injections plus an average of one additional rescue injection over two years. Investigators were surprised by how well the control group performed given the results of Genentech's PIER study, in which patients treated with the same 10 scheduled Lucentis injections, without additional rescue injections, lost an average of 2.3 letters of vision at two years.

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Interestingly, the roughly two-thirds of EMBT-treated patients in CABERNET that required one or fewer Lucentis rescue injections responded well to treatment and achieved visual outcomes that were similar to the control group. However, according to Dr. Dugel, "Whether that subgroup of patients who appear to benefit from this device can be reliably and consistently identified in our clinics is not known and remains a challenge." With respect to safety, CABERNET did demonstrate an acceptable safety profile for EMBT.

Dr. Dugel noted that CABERNET was started in 2006 when there were few treatment alternatives for wet AMD. "In retrospect, the study should not have included treatment-naïve patients, but rather previously treated patients only. And, in retrospect, the study should have placed a lot more importance on probe placement," he said.

NeoVista continues to market the VIDION system in Europe and to service its existing customer base. The company also continues to study EMBT in the chronic patient population that was addressed in the MERITAGE study. Last month, enrollment was completed in the United Kingdom-based MERLOT study, which enrolled 363 patients who had failed to respond adequately to anti-VEGF therapy alone. One-year results are expected in early 2013. There is no word yet on the firm's next move with respect to the US regulatory approval process – had CABERNET been successful, the company had planned to complete its Premarket Approval (PMA) filing during the first half of this year.

Reimbursement Established For AMD Implantable Telescope

Late last year, **VisionCare Ophthalmic Technologies Inc.** achieved an important milestone when the Centers for Medicare and Medicaid Services granted transitional pass-through payment status and established a billing code for the company's *Implantable Miniature Telescope* (*IMT*). This will enable hospital outpatient facilities to obtain reimbursement for covered procedures using the IMT, including the facility fee of approximately $1,500 and the cost of the device, which is $15,250. VisionCare is working with individual carriers to establish physician reimbursement levels, which are expected to be in the range of $1,800. Reimbursement and coding have not yet been established for the ambulatory surgery center setting; this is expected within the next one to two years.

The IMT is implanted in one eye of end-stage AMD patients, aged 75 or older, with stable but severe to profound bilateral vision impairment (best-corrected distance visual acuity worse than 20/160), which constitutes legal blindness. About 400,000 Americans fall into this eligible category, with about 40,000 new cases per year. End-stage AMD causes severe to profound central vision loss in both eyes, due to either wet AMD that has progressed to scarring of the macula despite drug treatments or dry AMD that has progressed to geographic atrophy, its most advanced form. In the implanted eye, the IMT renders enlarged central vision images over a wide area of the retina (beyond the central blind spot) to improve central vision, while the nonoperated eye provides peripheral vision for mobility and orientation. Postoperative training sessions with a low-vision occupational therapist are important to patient success with the device.

Although the IMT received FDA approval in July 2010, VisionCare did not launch the product in the US until reimbursement was established, and the first commercial patient was treated in November 2011. VisionCare has developed a patient-directed marketing and education program, *CentraSight*, which provides information about all of the steps of the process, from diagnosis through postop rehabilitation, along with reimbursement resources.

RETINAL IMPLANTS

Second Sight Achieves First Commercial Implant In Europe

Since the company's founding in 1998, **Second Sight Medical Products Inc.** has been developing technology to restore vision to blind patients. Over the past year, the company has made significant progress in bringing its *Argus II Retinal Prosthesis System* to market in both the US and Europe.

The Argus II system provides electrical stimulation of the retina to elicit visual perception in blind subjects with severe to profound retinitis pigmentosa. The system consists of four components: a tiny camera and transmitter mounted on eyeglasses that capture and process an image; an implanted receiver that wirelessly receives this data and sends the signals through a thin cable to the back of the eye; an array of 60 electrodes that is secured to the retina and emits electrical pulses in response to the signals; and a wireless microprocessor and battery pack worn on the belt that powers the entire device. The electrical pulses induce responses in the retina that travel through the optic nerve to the brain, which perceives patterns of light and dark spots corresponding to the electrodes stimulated. Patients learn to interpret the visual patterns produced into meaningful images and can gain the ability to achieve basic object recognition, identifying such things as doors, windows, and sidewalks.

The Argus II received CE mark approval in Europe during 2011 and reimbursement has been established in Germany and Italy. The first commercial implant took place in late October in Italy. The Argus II system will be priced and reimbursed at €73,000, or about $95,000, with additional reimbursement for the facility and the surgeon. The commercial rollout in Europe will be focused on a limited number of centers of excellence and will be gated by availability of reimbursement and company resources. While the eventual indication in the US will be limited to retinitis pigmentosa, the label in Europe is broader, and could include other causes of degeneration of the outer retina, such as AMD. The company estimates that there are up to 40,000 patients who would be candidates for the Argus II in the US and Europe combined.

In the US, Second Sight applied for FDA approval in 2011 under the Humanitarian Device Exemption (HDE) pathway and anticipates approval this year. The application is supported by clinical data from a 30-patient study involving ten centers in the US and Europe. These patients have now been followed for about four years. All implanted patients achieved at least light perception, and the best patients could read large letters (1-2 inches in height). Most patients were able to perform mobility tasks and follow a white line, which is a surrogate for staying within a crosswalk while crossing the street. There have been no product failures in the study, an achievement the company attributes to significant preclinical work in animals and long-term testing of the device in a simulated in vivo environment.

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Second Sight is currently developing a next-generation device with a higher density of electrodes. The company has been issued over 100 US patents and in August 2011 was recognized for its innovation by being issued Patent Number 8,000,000 by the United States Patent and Trademark Office.

Retina Implant Expands CE Mark Study

» A different type of retinal prosthesis is under development by Retina Implant AG, which is working on an approach that involves the implantation of a small microchip underneath the retina.

Meanwhile, a different type of retinal prosthesis is under development by **Retina Implant AG**, which is working on an approach that involves the implantation of a small microchip underneath the retina. Rather than using a camera and transmitter to send an image to the chip, the eye's own optical system (cornea and crystalline lens) transmit images to the retina as in a normal sighted eye. In order to supply enough stimulation to the retinal nerve cells, the signal must be amplified, requiring that the chip receive power via an external or implanted power source. According to the company, blind patients in clinical trials have been able to recognize shapes of people and objects and read letters and words.

Retina Implant was founded in 2003, and the first 10 patients were implanted with the device in a small pilot study that began in 2005. The pilot study involved a wired, externally powered system, and the devices were explanted after thirty days. In May 2010, Retina Implant began enrolling a second clinical study intended to support CE mark approval. This study involves the first use of a long-term implant and a wireless, internally powered system. In November 2011, based on the results of the first nine patients implanted in a single center in Germany, the company expanded this trial to include 10-15 additional patients and five new centers in Germany, Hungary, and the United Kingdom. Retina Implant hopes to attain CE mark approval as early as this year. The Wills Eye Institute in Philadelphia will be the lead clinical trial site in the US clinical study, which is also slated to begin this year.

In addition to these companies, there are several others working on sight-restoring retinal implants, including three young companies established in 2009 that are attempting to apply the latest technology discoveries to this field. All three – **Nano Retina Inc.**, **2C Tech Corp. Inc.**, and **LambdaVision Inc.** – are profiled in this issue. (*See "Start-Up News," — this issue.*)

Major Setback For Implantable Drug Delivery Implant

Although the retinal device field is making progress in many areas, companies continue to struggle to meet shifting FDA approval requirements. In November, **Alimera Sciences Inc.** received a complete response letter (CRL) from the FDA stating that the agency was unable to approve the company's New Drug Application (NDA) for the *ILUVIEN* Drug Delivery Implant for diabetic macular edema (DME). This news took the investment community by surprise, as evidenced by the 80% decline in the company's market capitalization following the announcement.

Alimera had hoped that ILUVIEN, a sustained drug-delivery system that releases submicrogram levels of the steroid fluocinolone acetonide, would become the first FDA-approved drug-delivery implant to address DME. There are over 300,000 treatable DME patients in the US and there are no approved drug therapies. In December 2010, the FDA issued its first CRL for ILUVIEN based on data through month 24 of the FAME study. In that first CRL, the FDA asked for, among other things, analyses of the safety and efficacy data through month 36 of the FAME Study. Alimera submitted this 36-month trial data with its response to the FDA last May.

The combined 36-month data from the two FAME trials continued to demonstrate statistically significant efficacy, as measured by the percentage of patients with ≥15-letter improvement in vision over baseline. At the same time, the rates of adverse events were similar at the 24- and 36-month time points. At 36 months, cataract formation was observed in 81.7% of treated patients and 50.4% of controls compared to 80.0% and 46.3%, respectively, at 24 months. Elevated intraocular pressure was also observed at 36 months in 18.4% of treated patients and 4.3% of controls compared to 16.3% and 2.7%, respectively, at 24 months. According to Alimera, feedback from retina specialists suggests that these rates of adverse events are manageable in light of the product's demonstrated efficacy in this challenging patient population.

In addition, Alimera was able to show that much greater vision improvement was experienced by the subgroup of patients with persistent, chronic DME, or those that had suffered from DME for at least three years.

Alimera made the case that the benefit-to-risk ratio was particularly attractive in this subset of patients, which is identifiable prior to treatment with ILUVIEN. The company's market research had suggested that this was also the subgroup of DME patients that retina specialists had the greatest interest in treating with ILUVIEN, since visual improvement in these patients generally reaches a plateau following standard-of-care treatment with a laser.

However, in its most recent CRL, the FDA stated that the ILUVIEN NDA did not provide sufficient data to support safety and efficacy in the treatment of patients with DME and that the risks of adverse reactions shown for ILUVIEN in the FAME study were significant and were not offset by the demonstrated benefits. The FDA has indicated that Alimera will need to conduct two additional clinical trials to demonstrate that the product is safe and effective for the proposed indication. The company plans to meet with the FDA to clarify the next steps. If Alimera is required to conduct two new trials similar in size and cost to the two completed FAME studies (which involved 956 patients and cost about $75 million), the company has indicated that this would not be economically feasible, at least for the DME indication.

Alimera continues to pursue regulatory approval for ILUVIEN in Europe, where the market opportunity is similar in size to that in the US, and expects an approval decision from the Medicines and Healthcare products Regulatory Agency (MHRA) during the first half of 2012.

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