Devices Expand Their Role in Retinal Disease

by Michael Lachman

Four years following Food & Drug Administration (FDA) approval of the anti-VEGF (vascular endothelial growth factor) drug ranibizumab (*Lucentis*) from **Genentech Inc./Roche**, this new drug class remains the standard of care for the treatment of neovascular (wet) age-related macular degeneration (AMD) and has been widely adopted for off-label treatment of other retinal diseases. *Lucentis* has raised the bar significantly with respect to visual outcomes that the retinal specialist can offer to patients, but the burden of regular intraocular injections and the high cost of the drug have prompted physicians, biopharmaceutical companies, and medical device companies to pursue alternatives.

While many physicians have opted for off-label use of bevacizumab (*Avastin*) as a less expensive alternative to *Lucentis*, companies are pursuing new drugs that may have more favorable dosing profiles, device-based technologies that may reduce the dosing frequency of *Lucentis*, and implantable drug-delivery vehicles designed to deliver drugs to the back of the eye that may be applicable to a broad range of retinal therapies. At the same time, there is continued progress in the development of drug delivery devices that target the ocular surface and anterior segment of the eye to address the noncompliance and inconsistent dosing that are associated with eye drops.

Lucentis vs *Avastin:* The Jury's Still Out, but Cost Remains Paramount

Each dose of *Lucentis* costs about $1,900 for the drug alone, and patients with wet AMD may require dosing as frequently as monthly for an indefinite period of time. In order to reduce the cost of AMD treatment, many retinal specialists have been using off-label *Avastin*, a similar anti-VEGF drug from Genentech/Roche that is approved for intravenous administration to treat several forms of cancer. When portioned into dosages that are appropriate for intraocular injection, off-label *Avastin* costs about $50 per dose. At the American Academy of Ophthalmology (AAO) Retina Subspecialty Day Program, held during the AAO's 2010 meeting in October, John T. Thompson, MD, an assistant professor at the **Wilmer Eye Institute** at **Johns Hopkins University**, pegged the full two-year cost of *Lucentis* dosed monthly, including diagnostics and injections, at $58,750. Dosed on an as-needed (PRN) basis, the two-year cost of *Lucentis* drops to $25,500. In comparison, the two-year cost of *Avastin* is between $7,400 and $11,400, depending upon dosing regimen. According to William L. Rich III, MD, medical director of health policy for the AAO, the current ratio of *Avastin*/*Lucentis* usage in the US stands at 60%/40%.

There are six major randomized clinical trials underway worldwide comparing *Lucentis* and *Avastin*, enrolling an average of 600 patients per trial. (*See Exhibit 1.*) The largest and potentially most impactful is the Comparison of AMD Treatments Trial (CATT), sponsored by the US National Eye Institute/**National Institutes of Health**, which enrolled 1,208 patients at 44 US clinical sites between February 2008 and December 2009. All patients in CATT have reached the one-year follow-up point and one-year results will be reported this spring. Results from the other studies will be reported throughout 2011 and 2012. The CATT study could dramatically affect the relative usage of *Lucentis*

Exhibit 1

Global Comparative Trials: *Avastin* Versus *Lucentis*

Study Name	Country	Enrollment Sept. 2010	Enrollment Goal	Enrollment Start	Complete
CATT	United States	1,208	1,200	Feb 2008	Dec 2009
IVAN	United Kingdom	600	600	April 2008	Sept 2010
VIBERA	Germany	150	360	2008	Dec 2010
MANTA	Austria	271	320	June 2008	Dec 2010
LUCAS	Norway	230	450	March 2009	Spring 2011
GEFAL	France	300	600	Fall 2009	Spring 2011

SOURCE: Daniel F. Martin, MD, Cole Eye Institute/Cleveland Clinic, at AAO Retina Subspecialty Day, October 2010

and *Avastin*, depending upon whether *Avastin* proves to be equivalent to *Lucentis.*

Regarding treatment burden, *Lucentis* is typically injected monthly for three months; however, while the label suggests continued dosing on a monthly basis, actual dosing regimens vary by physician and patient. In clinical studies, patients dosed every three months often experienced a loss of visual benefit over time. At AAO, Carl D. Regillo, MD, a retinal eye specialist at the Wills Eye Institute, pointed out that individualization of dosing is the norm, using either monthly follow-up visits and treating as needed or treating at every visit but gradually extending the follow-up duration if the macula is "dry" (treat and extend dosing). By individualizing therapy, dosing typically falls somewhere between monthly and quarterly. The CATT study is examining both fixed and variable dosing regimens for *Lucentis* and *Avastin* and may shed additional light on this issue.

Despite the widespread use of *Avastin* as a low-cost alternative for AMD, sales of *Lucentis* continue to grow four years after product launch, driven by an increase in new patient share as well as longer AMD treatment durations, according to Roche. (*See Exhibit 2.*) The company reported US *Lucentis* revenues of 1.018 billion Swiss francs (approximately $955 million) for the first nine months of 2010, representing 29% growth over the same period in 2009. For the full year 2009, US *Lucentis* sales grew 24% to 1.198 billion Swiss francs (about $1.10 billion). In order to directly address the treatment burden associated with *Lucentis,* Genentech/Roche is in early-stage development of a sustained-delivery formulation of *Lucentis* through a license and development agreement with **SurModics Inc.** The formulation uses SurModics' proprietary biodegradable microparticle drug delivery system. The company is also pursuing other ophthalmic indications for *Lucentis.* In Q2 2010, Roche received FDA approval to market *Lucentis* for the treatment of patients with macular edema secondary to retinal vein occlusion, and the firm is investigating the drug for the treatment of diabetic macular edema (DME) as well. Final data from the Phase III RIDE and RISE trials investigating *Lucentis* in patients with DME are expected to be released in the first half of 2011.

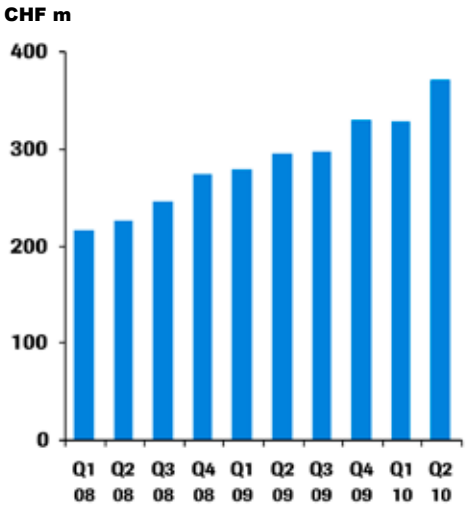
Ionizing Radiation to Reduce the Anti-VEGF Treatment Burden

Drug delivery systems are not the only device based approaches under development that aim to extend the benefits of *Lucentis* for wet AMD patients. Two products that incorporate ionizing radiation, which has demonstrated strong inhibitory effects on new and established neovascular vessels, are being studied in combination with *Lucentis,* 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. The company's first pivotal trial, CABERNET, compares brachytherapy plus *Lucentis* to *Lucentis* alone in over 490 treatment-naïve subjects. The three-year study completed enrollment in late 2009. The company's second pivotal trial, MERLOT, is still enrolling in the UK with targeted enrollment of 363 subjects, all of whom require chronic anti-VEGF therapy.

Exhibit 2

***Lucentis* Quarterly US Sales Trends, 2008-1H 2010**



SOURCE: Roche

At the AAO in October, NeoVista released one-year results from the MERITAGE study, which enrolled 53 patients who were already on chronic anti-VEGF therapy, had already received an average of 12 injections, and had an overall trend toward worsening vision. At 12 months post-treatment, 47% of the patients showed improved vision and another 32% had stable vision. In addition, the mean number of anti-VEGF injections during the 12 months following brachytherapy intervention was

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3.9 (with 25% of patients injection-free at 12 months), versus a mean of 12.3 injections leading up to treatment.

The other product in this category is the *IRay* System from **Oraya Therapeutics Inc.** *IRay* is a stereotactic radiosurgical device designed to enable precise delivery of low-energy X-rays to treat wet AMD. Treatment involves a nonsurgical, 10- to 20-minute office-based procedure that delivers three X-ray beams through the sclera focused on the central macula. The system has CE mark approval and is currently under investigation in a European multicenter blinded, sham-controlled study. The study will enroll at least 150 patients who will receive anti-VEGF therapy and either a sham radiation exposure or one of two radiation doses. End points include vision outcomes and frequency of anti-VEGF injections.

VEGF Trap-Eye: *Lucentis*-Quality Vision with Half the Injections?

The next purely pharmaceutical-based threat to *Lucentis* and *Avastin* for the treatment of wet AMD, based on potential dosing advantages, could come from *VEGF Trap-Eye*, developed by **Regeneron Pharmaceuticals Inc.** in partnership with **Bayer HealthCare LLC/Bayer AG**. Like *Lucentis*, *VEGF Trap-Eye* binds to all forms of VEGF-A, but it also has a high affinity for VEGF-B and placental growth factor (PLGF). In the Phase II CLEAR-IT 2 Extension Study, AMD patients maintained a significant improvement in visual acuity while receiving an average of only one injection every 4.6 months. (*See "AAO Highlights: Back (of the Eye) to the Future,"* Medtech Insight, *January 2010.*)

In November 2010, the companies announced encouraging top-line results from two Phase III studies, each of which randomized over 1,200 patients. *VEGF Trap-Eye*, injected every two months, met the primary end point of statistical noninferiority to monthly *Lucentis* in patients who maintained or improved vision over one year. In the North American VIEW 1 study and the international VIEW 2 study, for the cohort injected every two months with *VEGF Trap-Eye*, maintenance of vision was achieved in 95.1% and 95.6% of patients, respectively. These results were statistically noninferior to the 94.4% rate of vision maintenance in both studies for patients injected monthly with *Lucentis*.

The ability to inject patients every two months, without the need for intervening visits to monitor progress or provide additional dosing, would reduce the treatment burden for both patients and retinal specialists. Patients continue to be treated and monitored for a second year in both studies, with a slightly modified dosing schedule. Regeneron and Bayer plan to submit regulatory applications for *VEGF Trap-Eye* in the US and Europe during the first half of 2011, based on one-year results.

Implantable Drug Delivery Devices: Development Is Accelerating

Implantable devices that permit long-term sustained release of ophthalmic drugs can reduce the treatment burden of frequently injected medications. With the recent proliferation of intraocular injections of anti-VEGF agents and corticosteroids for a variety of retinal diseases, product development in ophthalmic drug delivery technology has accelerated. However, only three such devices have received FDA approval over the past 15 years, and approved indications have been limited, partially because of side effects, such as cataract formation and elevated intraocular pressure (IOP), associated with these devices. Introduced in 1996, **Bausch & Lomb Inc.**'s ganciclovir intravitreal implant (*Vitrasert*), consisting of an antiviral drug with a polymer coating, was the first FDA-approved implantable ophthalmic drug delivery device. It has an orphan indication for AIDS-related cytomegalovirus retinitis. B&L's next sustained release implant was *Retisert*, FDA-approved in 2005, which releases the corticosteroid fluocinolone acetonide (FA) over a 30-month period and has orphan drug status for the treatment of chronic noninfectious uveitis. A third implantable product, *Ozurdex* from **Allergan Inc.**, consists of the steroid dexamethasone in a solid polymer drug delivery system. It was FDA approved in 2009 for macular edema associated with retinal vein occlusion and in 2010 for noninfectious posterior uveitis.

Alimera Sciences Inc. hopes to be the first to reach the US market with a drug delivery implant aimed at DME; however, a recent setback will delay the product's approval. In

December, the FDA notified Alimera that its new drug application (NDA) for approval of *Iluvien*, a sustained-release steroid implant for DME, is insufficient and that additional, updated safety and efficacy data will be required. The company says it has the updated data and is completing the requested data analysis, but news of the delay sent the firm's shares down by 35%. Regulators also noted good manufacturing practice (GMP) deficiencies at two of Alimera's third-party manufacturers, which the company says are addressing the issues.

Alimera's *Iluvien* is an intravitreal insert that is inserted into the back of the eye using a proprietary 25-gauge needle through a self-sealing wound. Each insert is designed to work for up to three years by slowly releasing FA, the same steroid delivered by *Retisert*, directly into the vitreous. *Iluvien* was licensed by Alimera from **pSivida Inc./pSivida Ltd.**, which also developed *Vitrasert* and *Retisert*. DME, the primary cause of vision loss in diabetic patients, results from leaky blood vessels and swelling in the central retina and affects over 300,000 new patients each year in the US. It is typically treated using laser photocoagulation, often in combination with off-label injections of *Lucentis* or *Avastin*, or the corticosteroid triamcinolone acetonide, which works via anti-inflammatory and anti-permeability mechanisms. A sustained-release steroid has the potential to provide these benefits without frequent intraocular injections and the inconsistent dosing that accompanies them.

In clinical studies of *Retisert*, B&L was able to demonstrate that sustained release FA is effective in treating the visual loss associated with DME, but the company discontinued development of the device for this indication based on very high rates of cataract formation and elevated IOP. Although *Iluvien* also leads to these same side effects, it is hoped that a slower drug-release rate and more posterior location within the eye will reduce complication rates and improve upon the risk/benefit ratio that was seen with *Retisert*.

Alimera is conducting the FAME Study, which consists of two Phase III trials involving 956 patients. (*See Exhibit 3.*) In this study, *Iluvien* met the primary end point of statistically significant difference in percentage of patients with three-line or greater improvement in best-corrected vision versus a sham treatment at month 24. As expected, treatment also resulted in increased rates of elevated IOP and cataract formation, although the low-dose formulation delivered a better safety profile than the high-dose formulation without sacrificing efficacy. The NDA for the low-dose formulation of *Iluvien* was filed in June 2010 with 24-month follow-up data, while patients continued to be followed through 36 months, concluding in late 2010. *Iluvien* is also being studied in Phase II clinical trials for wet and dry AMD and for retinal vein occlusion. Other products currently in Phase III studies for DME include *Lucentis* and Allergan's *Ozurdex* dexamethasone implant.

Other Implantables in Development

Other implantable drug delivery devices in development address a range of retinal diseases. **Eyetech Inc.** is developing an extended-release microparticle technology to decrease the dosing frequency of the inject-

Exhibit 3

Clinical Results of FAME Study: Two Parallel, Phase 3 Trials for *Iluvien* in DME

	Control: Sham Procedure	Low Dose *Iluvien*
Number of patients – Trial A	95	190
Number of patients – Trial B	90	186
Primary end point		
Patients gaining at least three lines of vision – Trial A	14.7%	26.8% ($p = 0.029$)
Patients gaining at least three lines of vision – Trial B	17.8%	30.6% ($p = 0.030$)
Patients gaining at least three lines of vision – Trials A+B	16.2%	28.7% ($p = 0.002$)
Secondary end point		
Decrease in excess foveal thickness – Trials A+B	101 microns	156 microns
Safety		
IOP > 30 mm Hg – Trials A+B	2.7%	16.3%
Cataract formation – Trials A+B	46.3%	80.0%
Cataract Surgery – Trials A+B	23.1%	74.9%

SOURCE: Alimera Sciences Inc.

Compared to implantable polymeric depots, the ODTx device may be more amenable to delivery of proteins and complex macromolecular drugs.

able anti-VEGF agent pegaptanib (*Macugen*), from every six weeks to every four to six months. The company hopes to initiate first-in-man clinical trials by late 2012.

Neurotech USA Inc. is pursuing controlled, continuous, long-term delivery of biologics to the retina through *Encapsulated Cell Technology* (*ECT*). *ECT* implants contain cells that have been genetically modified to produce a specific therapeutic protein and are encapsulated in a semipermeable hollow-fiber membrane, creating an "implantable bioreactor." Oxygen and other nutrients flow into the device to keep the cells alive while the cells continue to produce the therapeutic protein, which diffuses out of the implant at the target site. Neurotech's lead product, currently in Phase II studies for retinitis pigmentosa and dry AMD, consists of encapsulated human cells genetically modified to secrete ciliary neurotrophic factor. The company is also conducting Phase I studies targeting DME and wet AMD.

On Demand Therapeutics Inc. (ODTx) has developed an injectable ocular implant made up of multiple, sealed reservoirs that store and protect drugs until a laser is used to initiate the on-demand release of the drugs to the back of the eye. Using an office-based, noninvasive laser to open individual reservoirs, a retinal specialist can initiate periods of sustained drug release at several time points over the course of a year or more. This approach can allow for "drug holiday" periods when there is no drug being released. Compared to implantable polymeric depots, the ODTx device may be more amenable to delivery of proteins and complex macromolecular drugs, which have limited stability in the body, because they are hermetically sealed within the device until released on-demand with the laser.

New Drug Delivery Devices for the Ocular Surface and Anterior Segment

While implantable delivery devices can reduce the treatment burden of frequently injected ophthalmic medications, there is also significant room for improvement in the delivery of topical eye medications. Eye drops are straightforward and noninvasive, but are subject to well-documented high levels of noncompliance due to their inconvenience and the fact that many elderly patients lack the dexterity to reliably administer them. Eye drops also result in uneven dosing, because they are administered only once or a few times daily, and must contain large amounts of drug because they are quickly flushed from the eye.

Using a technology platform acquired in 2007 from **ForSight Labs LLC**, **QLT Inc.** is developing a punctal plug delivery system to slowly deliver drugs to the ocular surface over a three-month period. In this approach, a drug core is placed within a plug that is inserted into the punctum, which is a small hole and channel on the nasal end of the lower eyelid that drains excess tears into the nasal cavity.

QLT is in Phase II development of a punctal plug containing latanoprost (marketed by **Pfizer Inc.** as *Xalatan*) for ocular hypertension and open-angle glaucoma. In the first randomized, multicenter, masked study of 61 patients, the product was well tolerated and demonstrated sustained drug delivery, with a therapeutic response over three months. The company is working to expand the dose range in order to move closer to the dose given by latanoprost drops over a three-month period. QLT is also in preclinical development with a plug containing olopatadine (marketed by **Alcon Inc./Novartis AG** as *Patanol*) for allergic conjunctivitis. And, the company is working to refine the design of the punctal plug itself, in order to improve the retention rate, tolerability/comfort, ability to carry greater amounts of drug, and ease of insertion. As last reported by QLT, the retention rate stands at about 75% after eight weeks and up to 70% after 12 weeks.

Ocular Therapeutix Inc. (OTX) is developing a polyethylene glycol hydrogel-based drug-delivery platform that encapsulates drug-loaded microspheres. The microspheres can be deployed in a punctal-plug format for ocular surface and anterior segment delivery over a one- to four-month duration and as an injectable depot for intraocular and subconjunctival delivery and longer-term dosing (six months or longer). When configured as a punctal plug, the device may improve drug retention compared with

traditional punctal plugs because it expands after placement to conform to each individual patient's punctum. In addition, because the entire plug can contain encapsulated drug, drug capacity is increased. Current clinical and preclinical development activities involve fluoroquinolone anti-infectives, prostaglandins for glaucoma, steroids for dry eye, and allergy medications. In a small proof-of-principle clinical study with moxifloxacin-loaded punctal plugs, the company was able to demonstrate 100% plug retention and sustained drug release at clinically relevant concentrations over a 10-day postcataract surgery period.

OTX's hydrogel technology is finding its first commercial use in ophthalmology via the *ReSure* Adherent Ocular Bandage, which is CE marked and has been launched in Europe. The device is under clinical investigation in the US. The *ReSure* bandage is applied during surgery to protect clear corneal incisions and is sloughed off in tears over a three- to five-day postoperative period after incisional healing is complete.

Taking a very different approach, **EyeGate Pharmaceuticals Inc.** is developing an iontophoresis drug delivery system that utilizes a low-level electrical field to modify cell permeability and ionize drugs so that they can be delivered to targeted areas within the eye. A doctor or technician fills an applicator device with a drug in liquid form and programs the dosage and current into a handheld generator. An optometrist or ophthalmologist then places the drug-loaded applicator onto the surface of the eye, following instillation of an anesthetic drop, and the electrical field is applied. Over the course of one to four minutes, drug is driven across the sclera into the anterior and posterior segments of the eye through the process of electrorepulsion.

To date, over 900 treatments have been performed in over 300 patients in clinical studies. The company's most advanced clinical program is in the field of dry eye syndrome, involving a dexamethasone-derived steroid formulated for iontophoretic delivery. A Phase III study is currently enrolling, and a 2013 launch is targeted. A Phase II study of the *EyeGate* II Ocular Drug Delivery System with the same drug formulation has also been completed in uveitis. The system has received CE mark approval in Europe and the FDA has approved a 510(k) regulatory path in the US. EyeGate has also demonstrated feasibility of its system for the delivery of RNAi therapeutics, proteins, and nanoparticles. [A#2011400007]

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