GLAUCOMA DEVICES: Progress On Multiple Fronts

by Michael Lachman

The worldwide glaucoma market, worth over $4 billion annually, has been dominated for decades by drug therapy, which accounts for approximately 95% of the total market. The emergence of a high-growth glaucoma device segment based on minimally invasive surgical implants has been anticipated since the middle part of the last decade, but long product development and regulatory approval time lines have delayed the start of this new market cycle. (*See "Device Companies Set Their Sights on Glaucoma "* — Medtech Insight*, October 2007.*) However, the US Food and Drug Administration approval in June 2012 of the *iStent Trabecular Micro-Bypass Stent* from **Glaukos Corp.**, along with recent progress by a number of companies with competing technologies, is generating renewed interest in glaucoma devices.

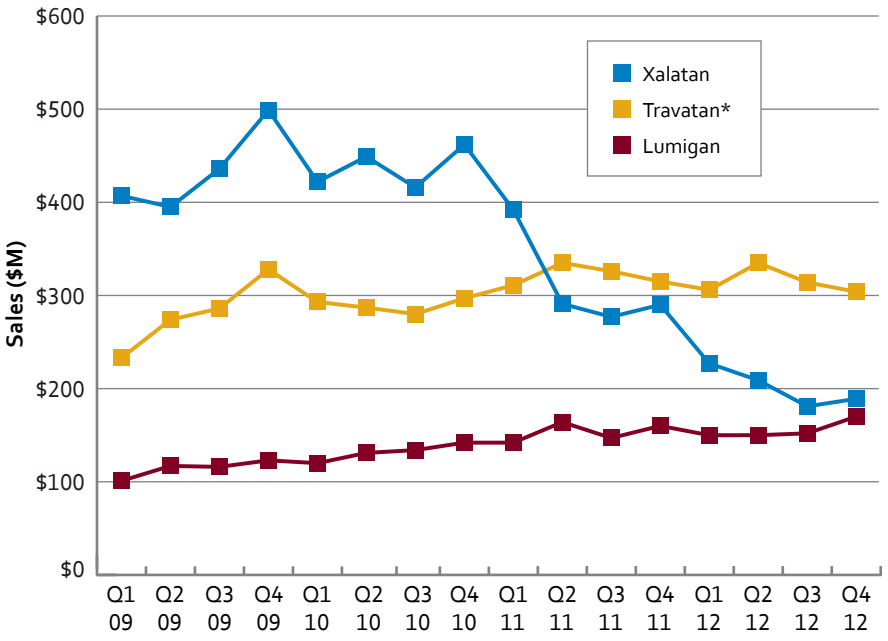
The other key milestone from the past two years is **Pfizer Inc.**'s patent expiration of *Xalatan* (latanoprost), the world's leading glaucoma medication, which lost patent exclusivity in the US in March 2011 and in Western Europe in January 2012. Before this patent expiration, annual sales of Xalatan totaled $1.7 billion, and the global glaucoma market exceeded $5 billion. The annual sales run rate for Xalatan has declined to approximately $800 million. Other market leaders in the glaucoma medication space include **Alcon Inc./Novartis AG**, with annual glaucoma sales of $1.3 billion, **Allergan Inc.** ($1.1 billion), and **Merck & Co. Inc.** ($0.4 billion). (*See Exhibit 1.*) Latanoprost is the most widely prescribed of the prostaglandin analogs, which are dosed once daily and represent first-line glaucoma therapy in most of the developed world. Although there has not been a new class of drugs approved for glaucoma since the introduction of latanoprost 17 years ago, the genericization of this gold-standard drug is important because it raises the cost-effectiveness hurdle for all new glaucoma drug and device therapies under development.

Challenges Of Treating A Multifactorial Neurodegenerative Disease

Glaucoma is a progressive, sight-threatening disease in which damage to the optic nerve, usually due to elevated intraocular pressure (IOP), leads to gradual and irreversible vision loss. Glaucoma is second only to cataracts as the leading cause of blindness in the world, and it is second to macular degeneration as the leading cause of blindness in the US, with over 120,000 Americans blind from the disease. It is estimated that more than four million Americans have glaucoma, including about three million with primary open-angle glaucoma (POAG), the most common form, although only about half are aware that they have the disease. In fact, glaucoma so often goes undetected in its early stages that many patients suffer irreversible vision loss, typically a narrowing of their visual field, before they are even diagnosed.

Exhibit 1

Prostaglandins For Glaucoma – Quarterly Global Sales Trends, 2009–2012



Note: Alcon sales include entire glaucoma pharmaceutical franchise, primarily Travatan; 2010–2012 proforma sales reported by Novartis; 2009 sales reported by pre-merger Alcon.

SOURCES: Pfizer, Allergan, and Alcon/Novartis

» The fact that glaucoma remains a leading cause of blindness, despite the availability of five different classes of effective IOP-lowering topical medications, most of which are generic today, suggests a great need exists for improved treatment options.

Although glaucoma is a multifactorial disease and its etiology is not well understood, POAG is generally associated with an increase in IOP caused by a buildup of fluid (aqueous humor) arising from clogging or blockage of the eye's natural drainage system. None of today's medications and devices is FDA approved for directly treating the neurodegenerative disease known as glaucoma, but instead they are aimed at lowering IOP, a risk factor for the disease. However, there is growing appreciation for other mechanisms of action that could be addressed by treatment. Earlier this year, in his keynote address at the *Glaucoma 360 New Horizons Forum*, sponsored by the Glaucoma Research Foundation, Louis B. Cantor, MD, chairman of ophthalmology and director of the glaucoma service at the Eugene and Marilyn Glick Eye Institute at **Indiana University**, noted that glaucoma is not just an eye disease, but also a central nervous system disorder. He cited a recent study that highlighted structural brain abnormalities, including irreversible losses of brain volume and function, resulting from reduced visual input to the brain associated with glaucoma.

Cantor noted that loss of retinal ganglion cells (RGCs) is another important factor in glaucoma. Neuroprotection strategies may guard these cells from injury and offer the potential for the cells to be rescued before they die. A number of drugs for RGC protection are under investigation, including Alpha-2 agonists and neurotrophic factors, although no neuroprotective agent has yet been proven in a pivotal clinical study to be effective for glaucoma. Allergan announced in 2008 that its second Phase III study of oral memantine as a neuroprotection-based treatment for glaucoma had failed to meet its primary endpoint.

According to Kuldev Singh, MD, professor of ophthalmology at **Stanford University**, who also spoke at the *New Horizons Forum*, "Some would say that we're still 10 years away from a neuroprotective agent. Others are more optimistic, thinking we'll have something sooner, and yet others feel that we'll always be 10 years away." Looking more broadly at the glaucoma drugs in the pipeline, Singh does not believe that there is anything that will supplant the prostaglandins over the next five to 10 years. "Having said that, there's an incredible unmet need and a big market opportunity for a good adjunct that's safe and well tolerated, used once or twice a day with a prostaglandin," he added.

Drug-Delivery Technologies Aim To Address Patient Compliance

The fact that glaucoma remains a leading cause of blindness, despite the availability of five different classes of effective IOP-lowering topical medications, most of which are generic today, suggests a great need exists for improved treatment options. While many patients are well-controlled on today's medications, many are not – even those taking three or four medications. Also, patient noncompliance is a well-documented issue with glaucoma medications; this is always an issue with chronic medications, but with glaucoma the situation is made worse because the disease is largely asymptomatic until vision loss is advanced, and instillation of eyedrops is difficult for the largely elderly population affected by the disease. Roughly half of glaucoma patients, over a six- to 12-month time frame, stop taking their medications. Also, once-daily drops, and even those dosed more frequently, provide inconsistent medication levels to the eye. Many of the reformulations of glaucoma drugs over the past decade were designed to reduce dosing frequency and/or improve tolerability, both of which aim to address compliance issues.

A number of companies are developing drug-delivery technologies to provide sustained release of latanoprost and other glaucoma medications to address the issues of poor compliance and inconsistent dosing. Many experts in the field believe that taking compliance out of patients' hands would have a more profound impact on glaucoma care than would a new drug that only marginally improves IOP compared with current drugs.

Companies developing glaucoma drug-delivery devices include **Ocular Therapeutix Inc.**, **QLT Inc.**, **pSivida Corp.**, **Icon Bioscience Inc.**, **Amorphex Therapeutics LLC**, **Euclid Systems Corp.**, and **Replenish Inc.**

Ocular Therapeutix is developing drug-delivery devices based on its proprietary polyethylene glycol hydrogel technology. To address glaucoma, the company has developed an absorbable drug-eluting hydrogel punctum plug that provides steady release of the prostaglandin travoprost over two to three months. The hydrogel plugs have greater drug capacity than silicone plugs, and provide linear, steady release throughout therapy. A Phase II pilot study demonstrated

stable IOP reduction of about 7 mmHg, typical for prostaglandin drops, over a two-month period using a single plug, with no increase in hyperemia (redness). The company plans to study a three-month duration travoprost plug this year, with possible initiation of Phase IIb in late 2013.

Also in trials are therapies from QLT and pSivida. QLT has a drug-delivery platform consisting of a drug core embedded within a punctal plug, which it acquired from **For-Sight Labs LLC** in 2007. The company has completed enrollment of two Phase II dose-evaluation studies of its latanoprost delivery system for glaucoma. pSivida is partnering with Pfizer to develop *Durasert*, a bioerodible, long-term sustained-release implant that delivers latanoprost. It is administered by an eye care professional into the subconjunctival space of the eye in a minimally invasive procedure. A Phase I/II clinical trial is underway.

Meanwhile, several other products are in preclinical development. Icon Bioscience is developing *Verisome* drug-delivery technology, which is in preclinical development for glaucoma and in clinical development for two other ophthalmic indications. The glaucoma product, IBI-60089, is a biodegradable liquid that is injected into the anterior chamber of the eye through a small-gauge needle to provide sustained release of latanoprost, with a duration of up to six months with a single injection. Once injected, the liquid forms a sphere that degrades over time and is fully eliminated as drug is released. The company plans to initiate a Phase I/II clinical trial this year.

Amorphex Therapeutics is developing *TODDD* (Topical Ophthalmic Drug Delivery Device), a soft elastomeric device, handled much like a contact lens, which rests on the sclera under the upper eyelid. The device is larger than previous in-the-eye drug-delivery inserts to enable it to incorporate more drug, and it is designed to better fit the anatomy of the eye and lid. It is made of a proprietary material that releases incorporated drug over an extended time period – from days to several months. The drug to be delivered is polymerized into the device's material matrix and can be released continuously over three days to as long as 90+ days. The device can be configured as a matrix, with drug dispersed throughout; as a depot carrier, with drug contained in distinct chambers; or as a combination. Amorphex is incorporating a number of glaucoma drugs into TODDD, including prostaglandins and timolol, and TODDD with on-board drugs is currently in preclinical development.

Euclid Systems is in preclinical development with collagen-based drug depots for sustained delivery. The devices can take two forms: injectable collagen that polymerizes in situ and implantable collagen films/wafers that can degrade in minutes or up to as long as 6+ months. In vitro studies have shown 140 to 180 days of sustained release of latanoprost from collagen wafers.

Replenish is developing the *MicroPump System*, a small, programmable ocular drug pump implanted beneath the conjunctiva of the eye to deliver nanoliter-sized doses of drug via a cannula that extends into the anterior chamber of the eye. The pump could be refilled every few months over a multiyear implant duration.

Laser Trabeculoplasty: Bridge To Surgery

Glaucoma patients who fail to achieve IOP control even with multiple medications may be offered selective laser trabeculoplasty (SLT), which is usually the first device-based intervention attempted. SLT employs a 532-nm wavelength Nd:YAG green laser, in an office-based procedure, to target the trabecular meshwork. Rather than burning holes in the meshwork, which was the mechanism of action of the earlier argon laser trabeculoplasty (ALT) approach, SLT selectively targets melanin-containing pigmented cells in the meshwork to stimulate aqueous outflow without causing thermal collateral damage to adjacent healthy tissues. The market leader in SLT is **Lumenis Ltd.**, which introduced the technology in the US in 2001.

SLT has demonstrated IOP reduction similar to that achieved with optimal medical therapy in many patients, with few complications. Moreover, the treatment can reduce or eliminate the need for glaucoma eyedrops and their associated compliance issues and cost. Although the IOP-lowering effect of SLT is not typically permanent, treatment can be repeated. For these reasons, SLT has moved forward in the glaucoma treatment continuum over the past decade, and is used in some cases as a first-line therapy.

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Surgery In The Glaucoma Continuum Of Care

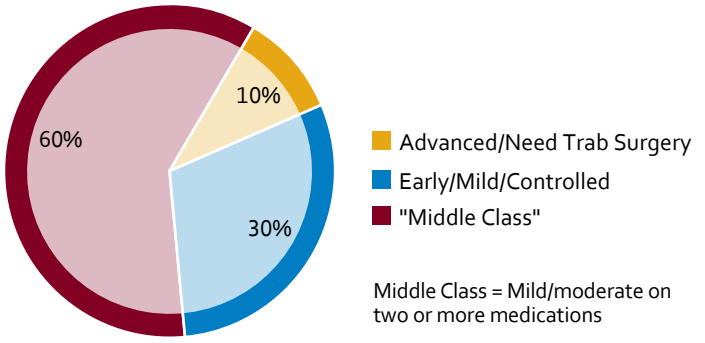
Because traditional glaucoma filtration surgery is invasive and involves a high rate of complications, it has historically been reserved for patients who have failed to achieve IOP control with multiple medications and SLT. All of today's surgical techniques for the treatment of glaucoma work by facilitating drainage of aqueous from the eye's anterior chamber to lower IOP. They differ from each other on the following dimensions:

- Ab interno approach (through a clear corneal microincision) versus ab externo approach (from the outside of the eye, through the sclera);
- Outflow drainage target: Schlemm's canal, suprachoroidal space, or subconjunctival space; and
- Use of an implant versus no implant.

Trabeculectomy has been the gold standard surgical procedure for glaucoma for over four decades, with well-established effectiveness in lowering IOP to the low- to mid-teens (measured in mm Hg). Based on the criteria described above, trabeculectomy is an ab externo procedure that drains fluid to the subconjunctival space without use of an implant. In this procedure, the conjunctiva and sclera are cut open, a scleral flap is created, and a plug of scleral tissue and a portion of the trabecular meshwork are removed, creating a fluid path from the anterior chamber. Aqueous drains into a small reservoir or blister, called a filtration bleb, created under the conjunctiva. Because the bleb is subject to scarring, leakage, and infection, it must be monitored and maintained for the life of the patient.

Exhibit 2

Glaucoma Patient Breakdown Seen In A Typical Practice



SOURCE: Ike K. Ahmed, MD

A modification of trabeculectomy that has grown in popularity over the past five years is the inclusion of the *Ex-PRESS* Glaucoma Filtration Device, which was developed by the Israeli company **Optonol Ltd.** and acquired by Alcon in 2010. Used in conjunction with trabeculectomy to standardize the procedure and reduce complication rates, this stainless steel stent diverts aqueous humor from the anterior chamber to the subconjunctival space to form a filtration bleb. It measures about 3 mm in length and 400 µm in diameter, with lumen sizes of 50 µm and 200 µm. Clinical studies have shown that trabeculectomy with Ex-PRESS provides reductions in IOP and number of medications similar to trabeculectomy alone, but with a significantly lower rate of postop complications. It is estimated that about 20,000 Ex-PRESS devices were implanted in the US in 2012 and over 40,000 were implanted worldwide.

Last year, traditional glaucoma filtration surgery received a boost with the FDA approval and commercial launch of *Mitosol* for this indication. Developed and marketed by **Mobius Therapeutics LLC**, Mitosol is an on-label version of mitomycin-C, an antimetabolite drug used to modulate wound healing and prevent scarring following glaucoma surgery and other procedures. It has been used off-label in ophthalmology for decades. The FDA-approved product addresses many problems associated with off-label use, such as sourcing from compounding pharmacies, issues related to sterility and toxicity, handling and disposal, storage and shelf life, and dosing/potency irregularities. As of April 1, Mitosol became a Medicare reimbursed Part B drug.

For refractory glaucoma patients who have failed all previous treatments, including filtering surgery, tube shunts have represented the final option. These devices, which may or may not contain valves, consist of a flexible tube that drains aqueous from the anterior chamber of the eye to a silicone reservoir attached to the sclera. Leading tube shunts include the *Baerveldt* Glaucoma Implant from **Abbott Medical Optics Inc./Abbott Laboratories Inc.** and the *Ahmed* Glaucoma Valve from **New World Medical Inc.**

MIGS: Transition To A New Surgical Paradigm

According to Ike K. Ahmed, MD, of the **University of Toronto**, a leader in the development of new surgical approaches for glaucoma and consultant to many of the emerging companies in the field, there are good reasons why surgery

makes up only a small portion of glaucoma treatment today. "Current choices of trabeculectomy, external filtration, and tube shunts have shown very good efficacy, but have substantial early and late postoperative complication profiles that scare us away from proceeding to surgery early on." Ahmed describes three classes of glaucoma patients: 30% of patients have early/mild disease that's well controlled with one medication, and 10% have advanced disease that requires trabeculectomy or tube shunt surgery. The "middle class" comprises the remaining 60% of patients who have mild/moderate glaucoma and are on two or more medications; this group represents the greatest need and opportunity for improved treatments. (*See Exhibit 2.*)

Recent innovation in the field of glaucoma surgery has focused on more interventional approaches, driven by the desire to make these procedures safer and less invasive. The ultimate goal is to move surgical treatment forward in the care continuum to earlier-stage patients with mild-to-moderate disease, filling the gap between medications/lasers and trabeculectomy/tube shunts. (*See Exhibit 3.*) The primary benefit of such an approach is reduced dependence on medications and the associated issues related to compliance and IOP fluctuation.

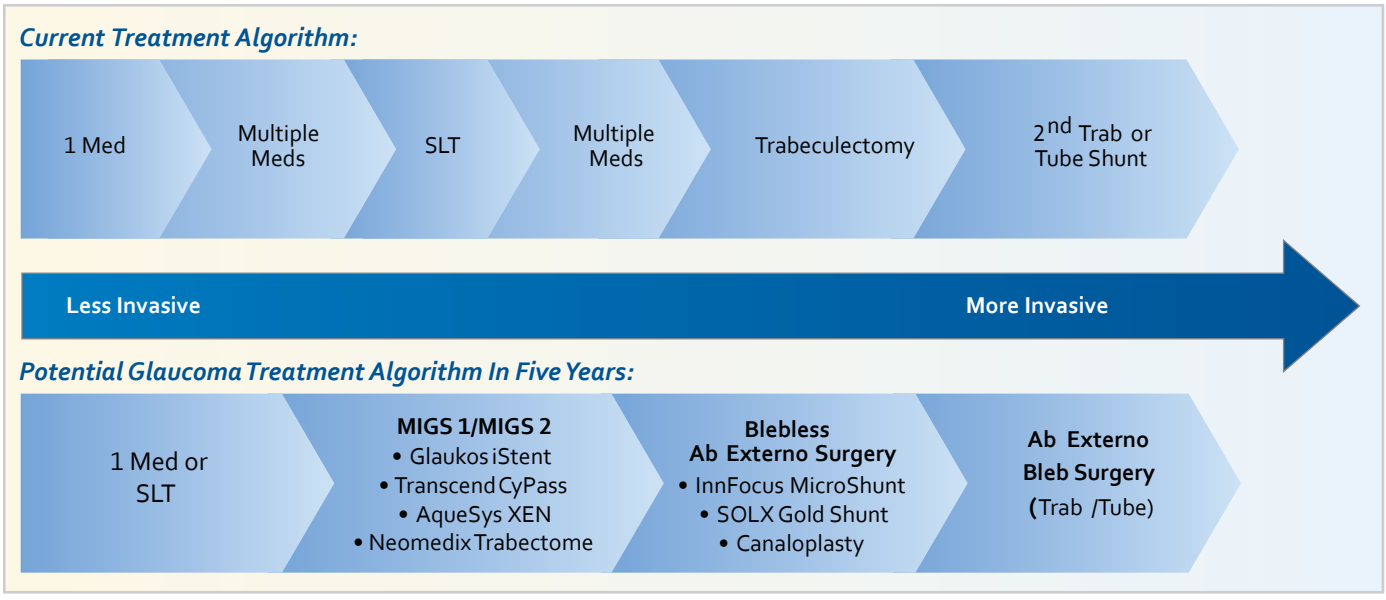
Ahmed coined the term "MIGS" (micro-invasive glaucoma surgery) to describe procedures that utilize a minimally traumatic ab interno approach, through a ≤2-mm corneal incision, to achieve at least modest IOP reduction with a high safety profile and rapid recovery. Outflow targets in MIGS include all three locations highlighted above: Schlemm's canal, the suprachoroidal space, and the subconjunctival space. Importantly, the ab interno approach can be combined with cataract surgery because the surgeon already has small-incision access to the anterior chamber. Researchers have documented that cataract surgery alone results in IOP reduction in patients with elevated IOP, and many of the clinical trials for MIGS devices have been performed in combination with cataract surgery. It should also be noted that several new devices are designed to be implanted via an ab externo approach. Although they do not fall under the umbrella of MIGS as defined above, they offer many of the same benefits to patients. (*See Exhibit 4.*)

Surgical Approaches To Drainage Into Schlemm's Canal

Several surgical devices are designed to facilitate drainage of aqueous from the anterior chamber into Schlemm's canal, bypassing blockage and resistance by the trabecular meshwork. Because fluid flow remains internal to the eye, there is no need for a subconjunctival filtering bleb, which represents an im-

Exhibit 3

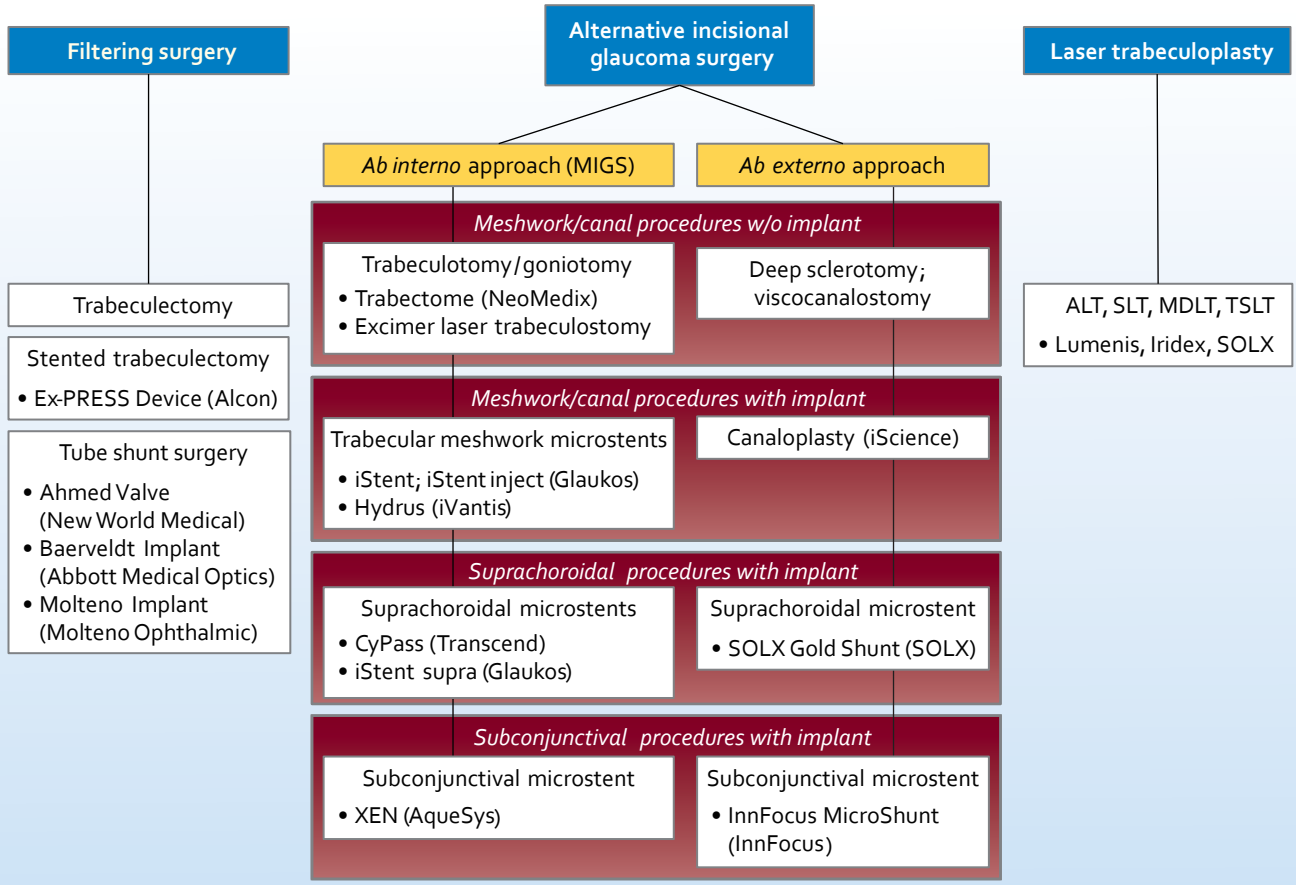
Current Glaucoma Continuum Of Care And Five-Year Projection



SOURCE: Ike K. Ahmed, MD

Exhibit 4

Classification Of Surgical Procedures To Increase Aqueous Outflow In Open-Angle Glaucoma



SOURCE: Adapted from Steven D. Vold, MD, founder and CEO, Vold Vision

portant advantage over traditional glaucoma surgery. Two approaches, trabeculotomy and canaloplasty, have been available for some time in the US, whereas two additional techniques, both involving microstents, represent more recent innovations.

NeoMedix Inc. manufactures the *Trabectome*, a 19.5-gauge bipolar electrosurgical instrument with irrigation and aspiration that is used to perform an ab interno trabeculotomy without the use of an implant. The device is inserted through a corneal incision, in a stand-alone procedure or in combination with cataract surgery, to ablate and remove a 60-degree to 120-degree strip of trabecular meshwork and the inner wall of Schlemm's canal. The Trabectome received 510(k) clearance from the FDA in 2004 and was first used in the US in 2006. Clinical studies have shown a reduction in IOP to about 16 mmHg, along with decreased dependence on medications.

Canaloplasty, developedby **iScience Interventional**, is an ab externo procedure that aims to increase outflow across the trabecular meshwork and into Schlemm's canal through an entirely different mechanism. During the procedure, Schlemm's canal is circumferentially catheterized and viscodilated using the company's flexible *iTRACK* microcatheter. A suture is then passed along the circumference of the canal and tied to create tension, distending the meshwork inward and stenting the canal open. In a study of patients with mean preoperative IOP of 24 mmHg, at three years postop, canaloplasty resulted in mean IOP of 15 mmHg, and 14 mmHg when combined with cataract surgery, along with a significant reduction in medication use. Some patients have now been followed out to nine years.

Canaloplasty received 510(k) clearance in the US with an OAG indication in 2008, but a

Category I Current Procedural Terminology (CPT) code was not available until 2011. Over 25,000 procedures have been performed globally, although being a surgical technique that is perceived to be more challenging than alternative approaches has been a barrier to more widespread adoption. iScience recently went through a reorganization that downsized the company's sales and clinical training functions to preserve capital, while the firm works to develop more efficient ways to help physicians move quickly up the learning curve.

An important milestone in the glaucoma device market came in June 2012, when the iStent from Glaukos became the first MIGS device to receive FDA approval. The journey to FDA approval was a long one – the company was formed in 2001 and has raised over $126 million to date. More than 4,100 eyes have been implanted with the device globally. The tiny L-shaped stent, made from heparin-coated titanium, is the smallest FDA approved implant: it measures only 1.0 mm in length and 0.33 mm in height. One end resides in the anterior chamber of the eye, and the other in Schlemm's canal, creating a bypass of the trabecular meshwork.

In the iStent US Investigational Device Exemption (IDE) study, the treated group received cataract surgery followed by implantation of an iStent, and the control group received cataract surgery alone. At 12 months, 68% of iStent patients had achieved the target pressure of 21 mmHg or lower without medications, compared with 50% of patients who underwent cataract surgery alone. Consistent with this trial design, the labeled indication is for use of a single device in combination with cataract surgery to reduce IOP in adult patients with mild or moderate OAG and a cataract who are currently being treated with medication to reduce IOP. Medicare data suggest that of the 3.5 million annual cataract surgeries done in the US, 20.5% (or about 700,000) are performed on patients who also have mild/moderate glaucoma and would be candidates for iStent. At this time, use of iStent apart from cataract surgery, and use of multiple devices, would be considered off-label. However, studies have demonstrated that use of a second device provides additional IOP-lowering benefit.

Glaukos' US sales launch is supported by a direct sales force of over 20 reps, targeting about 500 glaucoma specialists and about 2,500 high-volume cataract surgeons. According to the company, sales are exceeding the initial internal forecast. All 13 Medicare carriers cover the procedure, under CPT Code 0191T, with a physician payment of $850 to $1,200. The total Ambulatory Surgical Center payment under Ambulatory Payment Classification 673 of $2,157 is $1,185 more than the payment for cataract surgery alone. As a follow-on product, Glaukos is developing the *iStent inject* (G2), which is one-fifth the size of the iStent – only 0.4 mm in length – and is injectable through a 26-gauge stab incision. This smaller version is currently in an expanded US IDE registration trial, with US approval estimated in the 2016–2017 time frame.

The *Hydrus* Microstent, developed by **Ivantis Inc.**, represents a different approach to stenting of Schlemm's canal. The flexible device, made from nitinol, consists of a curved scaffold that is placed within the canal, with a proximal end that resides in the anterior chamber. The scaffold, which spans three clock-hours of the canal, gently dilates the canal to four to five times its natural diameter and provides access to multiple collector channels that lead from the canal, reducing resistance to aqueous outflow. The device is placed via an ab interno approach, and may be implanted in conjunction with cataract surgery.

iVantis Inc. was founded in 2007 and has raised $63 million to date. Over 700 patients, 400 of them in clinical trials, have been treated globally since December 2008. In a European series of 40 eyes with mild/moderate OAG, treated with the Hydrus Microstent without concurrent cataract surgery, mean IOP was reduced from 21.6 mmHg preoperatively to 17.9 mmHg at 12 months, with a reduction in mean meds from 1.7 to 0.2. The company's US IDE study, HYDRUS IV, is enrolling 558 patients at 30 centers. The company is also conducting two comparative-effectiveness studies outside the US versus the Glaukos iStent.

Surgical Approaches To Drainage Into The Suprachoroidal Space

Suprachoroidal outflow as a therapeutic target is supported by clinical experience with prostaglandin analogs, which work by increasing outflow to this space. The suprachoroidal space provides a significant negative pressure gradient and a larger absorptive surface area than the trabecular meshwork. At least three companies are developing microstents to drain fluid from the anterior chamber of the eye to the suprachoroidal space. Like the Schlemm's canal stents, these devices have the advantage of not requiring a bleb.

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» Glaukos is developing its own ab interno suprachoroidal stent, iStent supra (G3), which, at 4 mm, is longer than the original iStent and is made from poly(ether sulfone) with a titanium tip that resides in the anterior chamber.

Transcend Medical Inc. is developing the *CyPass Micro-Stent*, a biocompatible polyimide fenestrated stent measuring 6 mm in length with a 300-µm lumen, inserted via an ab interno approach. More than 1,000 patients have been treated with the device in five clinical studies. Transcend's US IDE study, the COMPASS Trial, recently completed enrollment of 505 patients and is comparing CyPass with cataract surgery versus cataract surgery alone. In a 90-patient study with uncontrolled OAG treated with CyPass in combination with cataract surgery, mean IOP was reduced from 25.3 mmHg preoperatively to 16.3 mmHg at 12 months, with a reduction in mean number of meds from 2.1 to 1.1. In a 134-patient cohort with uncontrolled OAG treated with CyPass alone, mean IOP was reduced from 27.4 mmHg preop to 18.9 mmHg at 12 months, with a reduction in mean number of meds from 2.4 to 1.6.

In a competing effort, Glaukos is developing its own ab interno suprachoroidal stent, *iStent supra* (G3), which, at 4 mm, is longer than the original iStent and is made from poly(ether sulfone) with a titanium tip that resides in the anterior chamber. This device is currently in an expanded US IDE registration trial, with US approval estimated for 2017–2019. On the reimbursement front, CPT Code 0253T has already been established and it will cover ab interno suprachoroidal microstents such as CyPass and iStent supra.

For an ab externo approach to suprachoroidal drainage, **Solx Inc.** has developed the *SOLX Gold Shunt*, a microimplant made from 24-karat gold that is implanted under a scleral flap. Unlike most of the other implants under development, the device is flat rather than tubular in design, measuring 6-mm long, 3.5-mm wide, and 60- to 120-µm thick. Over 3,000 of these devices have been implanted globally.

Solx is pursuing US regulatory clearance via a 510(k) with clinical trials. The company plans to submit clinical data to the FDA by early 2014, with possible clearance later in the year, making the Gold Shunt likely the next device in this category to be reviewed by the FDA. In the ongoing US clinical study supporting the 510(k) submission, the Gold Shunt is being implanted in patients with refractory glaucoma: IOP ≥24 mmHg, even on medications and after failed prior glaucoma surgery. The device has also been evaluated in patients with mild/moderate disease in some international studies. In a reported case series from Canada, mean IOP in refractory patients was reduced by 39% to 55%, from 25 mmHg to 35 mmHg preoperatively to 16 mmHg to 17 mmHg at 12 months, along with a 39% to 47% reduction in the number of required meds. Some of the company's international studies have follow-up out to five years.

The Gold Shunt has regulatory approval in Europe and Canada and is being marketed in Canada. Solx is developing a second-generation device that would be titratable after implantation, using a YAG laser to selectively open windows in the device to increase flow.

Surgical Approaches To Drainage Into The Subconjunctival Space

Drainage into the subconjuctival space represents a gold standard mechanism of action for glaucoma devices because this is the same space into which fluid is drained following trabeculectomy. This approach provides the potential for the greatest amount of IOP reduction because it bypasses both the trabecular meshwork and the venous resistance, but the challenge is to design procedures and devices that minimize or eliminate the filtration bleb associated with trabeculectomy. Two companies are developing microstents to drain fluid to the subconjunctival space – one via an ab interno approach, the other via an ab externo approach.

AqueSys Inc. is developing the *XEN* Glaucoma Implant, a permanent but soft gelatin implant that is tissue compliant and conforming, which helps prevent migration of the device. The device, which is implanted via an ab interno approach either with or without cataract surgery, is placed using a preloaded, disposable injector. Proper placement of the device is confirmed intraoperatively. The product shunts aqueous from the anterior chamber to the nondissected, spongelike tissue of the subconjunctival/intra-Tenon's space. The outflow is low and diffuse and does not produce an elevated, thin-walled bleb that is typical of trabeculectomy.

AqueSys was founded in 2006 by The Innovation Factory and was spun out as an independent company in 2009. The company has raised $47 million to date. AqueSys is developing three products: XEN, *XEN Mini*, and *XEN Nano* for mild, moderate, and severe disease, and has used the technology successfully in both early- and late-stage glaucoma. The company's initial US regulatory approval pathway involves a 510(k) with clinicals. In a multicenter international study, mean IOP was reduced from 23

mmHg preoperatively to 14 mmHg to 16 mmHg at one- to three-year follow-up, representing 30% to 38% IOP reduction from best medicated IOP and approximately 50% from "washout IOP." Reliance on glaucoma medications was significantly reduced as well.

InnFocus Inc. is developing an ab externo device for subconjunctival/sub-Tenon's space drainage, the *InnFocus MicroShunt*. The soft, flexible device measures 8.5 mm in length and 350 µm in diameter, with a 70-µm lumen. Similar to the AqueSys XEN device, the InnFocus MicroShunt provides low, diffuse outflow and does not produce a trabeculectomy-like bleb. To accomplish this, the permeability of the conjunctiva must be preserved and scar tissue formation must be minimized, which necessitates the use of an extremely biocompatible material. The device is made of SIBS (poly[styrene-*block*-isobutylene-*block*-styrene]), which according to the company is the only stretchy biomaterial that will not provoke scar tissue in the eye. This ultrastable, nondegrading polymer material has been used over the past decade on the *TAXUS* drug-eluting coronary stent from **Boston Scientific Corp.**, which has licensed the material to InnFocus. The InnFocus MicroShunt was CE marked in Europe in 2012. The company has raised $15 million to date, including $10 million from Boston Scientific, and is actively seeking a Series B round of funding.

InnFocus aims to achieve target IOP <14 mmHg, which studies have shown is a key threshold for prevention of vision loss. In a 21-patient study, mean IOP was reduced from 24 mmHg preoperatively (on full medications) to 11 mmHg at 12 and 24 months, with about 90% of patients achieving IOP ≤14 mmHg. Medications were reduced to a mean of 0.3 per patient, with 82% of patients completely medication-free. Although implantation utilizes an ab externo approach, InnFocus believes that the safety profile, duration, difficulty, and invasiveness of the surgery itself, as well as the required follow-up, all compare favorably to trabeculectomy.

Continuous Monitoring Technology Captures IOP Fluctuations

The need for continuous IOP monitoring is driven by two key factors. First, because IOP can vary greatly throughout the day, in-office "snapshot" measurements may not be representative of a patient's actual IOP over an extended period of time. Second, it is likely that not only mean IOP, but also fluctuations in IOP, have an impact on glaucoma progression. **Sensimed AG** of Switzerland has developed the *SENSIMED Triggerfish*, a disposable soft contact lens with an embedded sensor that provides noninvasive, continuous, 24-hour IOP profiles as well as modeling and analysis of lOP patterns. The patient would typically wear the device for one 24-hour period each year. The diagnostic data may be used by the physician to tailor drug selection, dosing, and timing for individual patients. In addition, Sensimed is analyzing IOP profiles and treatment information from large cohorts of patients in a centralized registry, to help doctors discriminate among types of glaucoma, identify progressive glaucoma, and provide personalized treatment based on evidence from similar cases.

Sensimed has been a commercial-stage company for over two years, with a CE mark and restricted commercialization in 20 countries. (*See "Glaucoma: Devices Go Eye-to-Eye With Drugs"* — Medtech Insight*, October 2010.*) The company hopes to launch in 25 additional countries in 2013, including the US and China. Sensimed has filed for US 510(k) clearance and has defined its US reimbursement pathway and obtained a CPT code. The firm has raised CHF 44 million (about $44 million) to date and expects to close on an additional $8 million to $10 million by Q2 2013.

Solx is taking a different approach to IOP measurement. The company is developing a fully implantable, wireless pressure sensor that would enable continuous IOP monitoring for glaucoma patients. The device is currently in preclinical development and human trials could begin as early as next year.

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» Similar to the AqueSys XEN device, the InnFocus MicroShunt provides low, diffuse outflow and does not produce a trabeculectomy-like bleb. To accomplish this, the permeability of the conjunctiva must be preserved and scar tissue formation must be minimized, which necessitates the use of an extremely biocompatible material.