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SUMMARY

Cataract surgery has slowed in Europe, but it has picked up somewhat in the U.S. with the new multifocal lenses. ♦ LASIK volume is flat in Europe and in a fall slump in the U.S. ♦ IntraLase's femtosecond laser flap-maker is finding converts among European refractive surgeons. ♦ There was a lot of excitement in Europe over new AMD therapies, and doctors are quietly starting to use Genentech's Avastin off-label. ♦ Phase III data on Lilly's ruboxistaurin indicate it is effective and safe in treating diabetic retinopathy. Lilly plans to submit the drug this year, and it wouldn't be surprising to see the drug get fast-track approval from the FDA.

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UPDATE ON OPHTHALMOLOGY IN EUROPE AND REFRACTIVE SURGERY TRENDS IN THE U.S.

In Europe, cataract surgery volume and reimbursement are down, causing many ophthalmologists to turn their attention to retina and refractive surgery. Yet, European surgeons reported refractive surgery volume relatively flat year-to-year. The refractive surgery situation is only a little better in the U.S., where doctors reported LASIK volume for 2005 will be flat to slightly ahead of last year.

European ophthalmologists gathered in Berlin from September 26-28, 2005, for a joint meeting of the Association of European Ophthalmological Societies (SOE) and the German Society of Ophthalmology (DOG). The meeting was well-attended by general ophthalmologists as well as cataract and refractive surgeons and retina specialists, with new treatments for age-related macular degeneration (AMD) a hot topic. Unlike most international medical conferences, this meeting was not entirely in English; some parts were only in German, but most were either in English or had translation services available.

Fifteen refractive surgeons in the U.S were also interviewed on LASIK trends in America. They reported that procedure volume for 2005 is likely to end up flat to only slightly ahead of 2004.

New products

Iridex, Lumenis, Bausch & Lomb, and Schwind officials at SOE/DOG all said they had no significant new products being introduced either at the meeting or in the near future. WaveLight Laser Technologies launched its new Rondo microkeratome at the European Society of Cataract and Refractive Surgeons (ESCRS) meeting in Lisbon in mid-September, but it was not being shown on the exhibit floor. It should be available in Europe in March or April 2006, but Rondo has the advantage of a management feature – which can be turned on or off – that can prevent one blade from being used for a second procedure. Another WaveLight official pointed out that the company will be introducing its own femtosecond laser in 2006, to compete with IntraLase.

The President of the German Society of Ophthalmology said, "What I think we will have here that is new and extensively presented is diagnostics of the posterior pole of the eye, where we have imaging for the cornea and the retina in AMD." Another German doctor added, "There is one area where you would find developments earlier in Europe, and that is in surgery. The U.S. does have problems, mainly legal problems, in advancing new technologies, especially when it comes to implants…In that, Europe is far more liberal…There are two or three implants for glaucoma surgery – valves you put in the eye to allow fluid to come out easily. They have been tested or even approved in Europe."

Therapies for Wet AMD

Drug	Company	European status	Speaker comments
Visudyne (PDT) monotherapy or PDT + intravitreal triamcinolone acetonide (IVTA)	QLT	Standard of care	Combination superior to the PDT monotherapy results in the TAP trial. Increasing clinical evidence. Study results supportive of a mean change of +1.4 lines and 30% of patients increased lines. Acceptable safety.
Macugen (pegaptanib)	Eyetech/ Pfizer	Not approved but compassionate use program underway	% of patients with improved vision offset by increase in patients with worsened vision
Lucentis (ranibizumab)	Genentech/ Novartis	Trials ongoing	Review of MARINA data, no mention of Avastin off-label use
Retaane (anecortave)	Alcon	Approval pending Prevention trial ongoing	C-02-60 trial examining whether Retaane can slow progression from dry AMD to wet AMD

AGE-RELATED MACULAR DEGENERATION (AMD)

There was considerable interest in new AMD treatments at SOE/DOG, and attendance at all the retina and AMD sessions was heavy. Doctors even had to be turned away at Alcon- and Novartis-sponsored sessions where speakers reviewed the various therapies in development for wet AMD.

Intravitreal triamcinolone acetonide (IVTA) + PDT with QLT's Visudyne (verteporfin) – Use growing

The success of this therapy has blunted ***some*** of the enthusiasm in Europe for the new anti-VEGF therapies. It also is a cost-effective therapy, which is especially appealing in Europe. And by adding IVTA to PDT significantly reduces the number of PDT treatments required annually (to about 1.2). Thus, it appears that while PDT usage may go down, it won't go away with the approval of expensive anti-VEGF therapies.

ALCON'S Retaane (anecortave) – Company still hopeful

The presentations at SOE/DOG on Retaane were surprisingly positive. Data that the FDA found less-than-persuasive seemed to impress European doctors, and it appears that Alcon will be able to sell Retaane – at least to this group. The push appears to be for combination therapy with PDT or an anti-VEGF. A source said Alcon is in talks with European regulators to see what more data they want.

EYETECH/PFIZER'S Macugen (pegaptanib) – Lack of excitement

European doctors plan to use Macugen – but cautiously because of the price. There was a lot of interest in AMD treatments, but no sense of excitement or doctors particularly anxious to get started with Macugen.

GENENTECH/NOVARTIS'S Avastin (bevacizumab) – Europeans are starting to discover this possible category killer

There was less buzz at SOE/DOG about off-label use of intravitreal Avastin (which is approved in both the U.S. and Europe to treat colorectal cancer) than at the American Society of Retina Specialists (ASRS) meeting in Montreal in July 2005. A U.S. doctor at the European Ophthalmology meeting commented, "We are just starting it (intravitreal Avastin). That will be a tidal wave. Everyone understands the mechanism…It may gather a lot of early usage. The concern is that Avastin will get ahead of a good trial, like IVTA did."

Off-label use of Avastin also has not caught on as quickly in Europe as in the U.S. However, it was briefly discussed at the conference, and sources said use is starting to pick up. Most European doctors who treat AMD who were questioned about intravitreal Avastin said they are either very quietly using it or are planning to start. A source said the slower, quieter approach in Europe is due, at least in part, to pressure from Novartis, "There is a lot of financial pressure by Novartis on this topic...Novartis does [supports] a lot of [research] funding in Europe, and they are putting a lot of pressure on us…There is a lot of excitement here in Europe about intravitreal Avastin, and a lot of people are doing it, but no one is talking about it." *Remember:* Genentech will sell Lucentis in North America (U.S., Canada, and Mexico), but Novartis has exclusive marketing rights in Europe and elsewhere outside North America. An Italian doctor said, "I'm starting intravitreal Avastin now. It is probably the future." An Austrian doctor said, "I'm quietly using (intravitreal) Avastin off-label."

The results of the SANA trial of systemic Avastin, which were first presented at ASRS, were reviewed at this conference, and the take-away was somewhat more positive. A speaker commented, "Systemic therapy also has advantages… [including, you] don't need frequent re-treatment…And it looks like longer durability…Preliminary data indicate lower systemic doses work as well."

Asked if Avastin might be effective in diabetic macular edema (DME), the speaker said, "Yes, but do you want to submit someone with a systemic disease to a systemic treatment? …We don't know if there is an increase in thromboembolic events in those patients."

GENENTECH/NOVARTIS'S Lucentis (ranibizumab) – A winner unless trumped by Avastin

At an AMD symposium at SOE/DOG that was ***not*** sponsored by industry, speakers reviewed the data on Lucentis – both as monotherapy and in combination with PDT, and there was a definite emphasis on the lower number of PDT treatments required with the combination – on average, 1.3 PDTs per year with Lucentis vs. 4.3 PDTs without it. When no one in the audience had any questions, the moderator quipped, "The results are much better than anyone expected…We are speechless with enthusiasm."

Asked if non-responders could be identified, a speaker said, "To the patient, it is obvious. It is the patient who continues to lose vision. We have to change the definitions now. It was always our hope or intention to convert active lesions to dry lesions, so we mostly looked on angiograms, and then at visual acuity, but we never expected improvement…We can be a lot more optimistic now…We can look at stable vision with no loss and expect vision to improve in real responders…We are trying to find characteristic features and standards to measure this success, and angiography and OCT (optical coherence tomography) will play an important role… but this is a learning curve."

Asked how long Lucentis therapy will need to be continued, a speaker said, "We know from the two-year Macugen data that patients lost all the benefit if treatment was discontinued after a year…They had multiple injections but still were sensitive to withdrawal of therapy. With Lucentis, we are just going into the second year…But there were previous Phase I/II studies and extension studies…(In these,) most patients not treated for six to nine months had a stable benefit…They did not lose vision; they remained stable. We have good hope that patients won't be treated monthly for their lifetime, but that if you treat during the active growth phase, you will stop it…But those trials are ongoing."

OCCULOGIX'S Rheopheresis – Silence

There wasn't even a mention of this at the SOE/DOG meeting. A German doctor who was asked specifically about it said, "The University of Cologne has been working with that and reporting good results. But it has been around for six or seven years, and if it were that good, people would be doing it by now."

DIABETIC RETINOPATHY

From 30%-49% of diabetic patients have diabetic retinopathy, and of these, more than 20% have moderate-to-severe diabetic retinopathy. Diabetic retinopathy (DR) is the most common chronic microvascular complication of diabetes and the most common cause of blindness in adults.

DR blindness is caused by either diabetic macular edema (DME) or proliferative diabetic retinopathy (PDR). Pharmacologic therapy at present is directed at controlling hyperglycemia, hypertension, proteinuria, and hypercholesterolemia – ACE inhibitors, ARBs, statins. All of these conditions do have an effect on DR, but at present there is no approved pharmacologic treatment specifically for DR.

IVTA offers temporary improvement of DME, but, especially at higher doses, raises IOP, causes cataracts, and is associated with endophthalmitis. Despite a lack of data from large, prospective, randomized clinical trials and lack of information on proper dosing, IVTA is used to treat DR.

On the horizon are several possible therapies – some of which may be combined. ***How will doctors choose among these therapies when and if they all become available?*** A speaker at SOE/DOG pointed out that there are advantages to each: "PKC, for example, is a once-a-day pill. Somatostatin (Novartis, octreotide) is an intramuscular injection once-a-month. Anti-VEGFs are intravitreal…You have to differentiate between all the compounds…and some of them seem to be very promising for DME and proliferative DR – the PKC beta or growth factor (somatostatin) ones…It depends on the compound and the disease…I think there will be a very differentiated approach to the different stages and problems of the disease...and probably combinations of some of these compounds with laser or vitrectomy or even two compounds."

Among the agents on the near horizon are:

- **EYETECH/PFIZER'S Macugen (pegaptanib)**

Macugen is approved in the U.S. to treat AMD, but it is not yet available in Europe. A European doctor commented, "Macugen is approved in the U.S., so you could consider off-label use of it in DME as well as PDR."

- **NOVARTIS'S Sandostatin LAR (octreotide)**

This somatostatin analog works through inhibition of growth hormone and IGF-1. Small controlled trials have found octreotide reduces progression of DR – in one study 27% with octreotide vs. 42% with control. Octreotide also appears to reduce the need for laser treatment: 1 eye in the octreotide group vs. 9 eyes in control. An SOE/DOG speaker said, "Another small study from our group of daily subcutaneous daily injections…found – in patients with extensive panretinal photocoagulation for PDR – a reduction of vitreous hemorrhage and a reduction in the need for vitrectomy…The VA (visual acuity) also was significantly better preserved in the octreotide-treated group. A speaker said, "Off-label treatment with it has had pretty good results with a once-a-month intramuscular injection."

Currently, two Phase III studies are ongoing, a 585-patient trial in Europe, and a 311-patient trial in the U.S. and Canada. The primary endpoint of both these trials is progression of DR. Results are expected in 2006.

➢ LILLY'S ruboxistaurin mesylate – Very positive

Oral, once-daily ruboxistaurin is significantly better at preventing sustained moderate visual loss than placebo. The first data presentation of the results of the pivotal, Phase III PKC-DRS2 trial in moderate-to-severe non-proliferative diabetic retinopathy (NPDR) was at SOE/DOG. The trial showed sustained moderate visual loss (SMVL) with ruboxistaurin, the first PKC-β inhibitor, with (SMVL) 40% less than with placebo (5.5% vs. 9.1%, p=.034). The trial met its primary endpoint and most secondary endpoints.

This data will be presented again at the American Academy of Ophthalmology on Saturday, October 15, 2005, at a late-breaker subspecialty session. No additional information will be presented since investigators are seeking publication in a major medical journal. Lilly reportedly plans to submit the drug to the FDA by the end of 2005, and it would not be surprising if it is granted fast-track status.

The PKC-DRS2 trial was a 36-month, randomized, double-masked, placebo-controlled, parallel, multicenter study. It evaluated the dose with the greatest effect in the smaller and earlier PKC-DRS trial – 32 mg/day. Eligible patients had a best-corrected ETDRS visual acuity (VA) score of ≥45 letters in an eye with level ≥47A to ≤53E retinopathy without prior panretinal photocoagulation. Sustained moderate visual loss (SMVL) was defined as moderate visual loss (MVL) occurring on at least two consecutive visits six months apart. MVL was defined as a ≥15 letter decrease in best visual acuity in the study eye from months 30-36, or for a patient's last six months of study participation for those who discontinued early. Prior focal or grid photocoagulation was allowed.

In the PKC-DRS2 trial, mean VA stayed the same or improved over the 36-month follow-up period, while placebo patients steadily lost VA. Dr. Lloyd Aiello of the Joslin Diabetes Center, who presented the initial results of PKC-DRS2, said the drug was "remarkably well tolerated." Ruboxistaurin has been given to >2,400 patients for up to four years, and no clinically significant adverse events or lab abnormalities have been reported. He said there were three key positives from the trial:

1. This data mimic an earlier and smaller study, PKC-DRS.
2. Twice as many patients had a 3 line (15 letter) gain in VA from baseline with ruboxistaurin than placebo. The number of patients was too small to see that in the earlier study, he said.
3. Now, there is an anatomical endpoint that confirms the VA data – the progression of macular edema to 100 μ of the center. Ruboxistaurin reduced progression of DME to within 100 μ of the center of the macula in study eyes. Dr. Aiello commented, "We are preventing progression to that level."

36-Month Results of the PKC-DRS2 Trial

Measurement	Ruboxistaurin 32 mg QD n=385	Placebo n=388	p-value
Demographic and baseline measures			
Diabetic retinopathy (DR) study eyes	584	599	---
Two DR study eyes per patient	71.8%	73.6%	Nss
DR Level <47	9.1%	10.4%	Nss
DR Level 47	60.4%	61.2%	Nss
DR Level 53	30.5%	28.3%	Nss
DR Level >53	0	0.2%	Nss
Prior focal photocoagulation	47.4%	42.7%	.105
Results			
Primary endpoint: SMVL	5.5%	9.1%	.034
% of eyes gaining ≥15 letters	~ 4.8%	~ 2.3%	.027
% of eyes with DME progression within 100 μ of center of macula	~ 43%	~ 49%	.071
Mean best corrected VA by visit (in letters)			
Baseline	77.4	77.2	.740
10 months	~ 77.9	~ 76.6	---
20 months	~ 77.5	~ 76.0	---
30 months	~ 77.3	~ 75.5	.051
36 months	~ 77.8	~ 75.7	---
% of eyes with DME progression to within 100 μ of center of macula			
In study eyes with DME severity of 0-3	~ 37%	~ 35%	Nss
In study eyes with DME severity of 4-7	~ 50%	~ 66%	.003
% of eyes with SMVL in DR study eyes by DME severity level			
0-2	0	~ 3%	---
3-7	~ 3%	~ 4.5%	---
8-11	~ 5.2%	~ 10.5%	---
% of eyes with SMVL in DR study eyes by DR severity level			
<47	~ 1.7%	~ 1.9%	---
47	~ 2.5%	~ 4.0%	---
53	~ 5.5%	~ 11.0%	---

Baseline Characteristics of Ruboxistaurin Studies in Diabetic Retinopathy

Measurement	PKC-DRS2 trial n=684	PKC-DRS trial n=128	p-value
Average age	59.3	56.1	<.05
BMI	32.8	30.7	<.05
HbA_{1c}	8.1	8.7	<.05
Mean arterial blood pressure	97.3 mmHg	100.4 mmHg	<.05
Type 1 diabetes	11.7%	19.5%	<.05
Insulin use	56.4%	67.2%	<.05
Eyes (study eye + fellow eyes <PDR at baseline)	61%	49%	<.05
Eyes with DME at center of macula	34%	26%	<.05
Study eye VA (ETDRS letters correct)	77%	80%	<.05

Asked how he would use ruboxistaurin if it were approved today, Dr. Aiello said he initially would use it for the same patients that were studied in the PKC-DRS2 trial, "I'm conservative. The only data we have is this study. For patients in this study, there is a clear effect, so I'd give it to the same patients as in the trial – with an HbA_{1c} <13, moderate-to-very severe PDR…I wouldn't offer it (off-label) to prevent progression of diabetic retinopathy." He said he really would like to treat patients earlier, but wants Lilly to sponsor a study in that patient population first.

Once patients get into severe diabetic macular edema (DME), he would consider adding an anti-VEGF to ruboxistaurin, but he declined to choose among the anti-VEGF agents, "Theoretically, the combination makes sense."

The dose-finding PKC-DRS trial was testing whether ruboxistaurin can slow the progression of non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR), and the trial missed this primary endpoint. However, it did meet the secondary endpoint of the occurrence of moderate visual loss (loss of ≥15 letters by ETDRS, a change from 20/20 to 20/40) in patients with diabetic macular edema (DME) at baseline scale.

NEUROPROTECTION

So far, $22 billion has been spent on neuroprotection trials with no positive results, an SOE/DOG speaker reported. All the trials in traumatic brain damage and stroke have been negative, but in chronic progressive diseases – ALS, vascular dementia, and Alzheimer's Disease – there have been some positive trials. The speaker commented, "The only hope, I think, is to focus on chronic diseases, where there is time to intervene…Progression can be slowed, but if the outcome is the same, the benefit is really small…What we need to do is increase the number of neurons that survive the disease process…So far, though, there is no evidence-based rationale for treating glaucoma with other than IOP lowering drugs."

In the U.S. it is estimated that 175,000 people are currently visually impaired due to glaucoma, and that number is expected to rise 50% to 265,000 by 2020. Interestingly, progression rates in glaucoma are ***not*** always linear. A SOE/DOG speaker said, "Patients going blind from glaucoma may have faster rates of progression than those who do not… Neuroprotection seems to have significant promise for the future. This is the ladder we are climbing for the moment."

Biomedical research into cellular/molecular biology may yield new therapies:

- **Genetic research into epidemiology/ treatment.** A speaker said, "There have been some exciting developments here. We may be able to test for genes and see if a patient has more risk of developing the disease (glaucoma) than the general population. And genes are being used in treatment."
- **Stem cells and cell-based therapies.** These are aimed at replacing damaged neural cells.
- **Neuroprotection.** Trials in glaucoma include:
  - **ALLERGAN'S Alphagan (brimonidine),** an alpha-2 adrenergic agonist.
  - **ALLERGAN'S memantine.** Forest Laboratories has the rights to memantine (Namenda) for Alzheimer's Disease, but Allergan has the rights for ocular disease. An SOE/DOG speaker said, "The memantine study is very exciting. It is a world-wide study, costing millions of dollars. It is the first prospective study looking at neuroprotection…Allergan had the courage to set the study up, and we wait with interest to see if it improves patients' lives and quality of life."

CATARACT SURGERY AND LENSES

Reimbursement for cataract surgery is flat across Europe and down in Germany. In Germany, the situation is especially difficult with limits on how many patients can get surgery, a ceiling on payments, and cuts in reimbursement. Some ophthalmologists who used to do only or mainly cataract surgery have started doing retina or refractive surgery. A European doctor commented, "It's getting worse. Cataract surgeons are having to add retina treatment to survive." In this environment, European doctors are proving slow to adopt multifocal lenses, and the outlook is for European multifocal lens use to remain limited for the next couple of years.

Among the new products doctors at SOE/DOG said they were interested in were glaucoma valves, such as New World Medical's Ahmed, which is distributed in Germany by Technomed.

Cataract Lenses, Especially Multifocal and Accommodating IOLs

Company	Product	Comments
Alcon	AcrySof ReStor	Pseudo-accommodative Bifocal lens – good for large pupils but may have problems with computer screen vision Refractive/diffractive lens (50% light at far)
AMO	ReZoom	Refractive lens Pupil dependent A far-dominant lens (100% light at far)
AMO	Tecnis	Diffractive lens, but not a multifocal or accommodating IOL Near-dominant lens so better near than far vision Requires less physician/patient time than ReZoom
Eyeonics	Crystalens	Hinged Approved only for cataracts Accommodative
Medennium	SmartIOL	Injectable, full-size, accommodating IOL

Among the comments European doctors had about multifocal and accommodating lenses were:

- *Austria:* "Cataract procedures are fairly flat in Austria…I haven't started using multifocals yet, but I will start."
- *Germany #1:* "There is a ceiling on the number of operations, a ceiling on payments, and the government is cutting reimbursement. So, doctors are moving to retina and refractive surgery…Only large, active centers and doctors who do cataracts as a 'hobby' can afford to do cataract surgery any more. A medical group with 500-1,000 procedures a year can't afford to do them. So, there also is some concentration (of cataract surgery into specific physician groups) going on. It is a similar situation in other European countries."
- *Germany #2:* "I don't use any multifocal lenses because of the cost. As long as the cost remains high, I won't use them."
- *Germany #3:* "I don't use any multifocals, and I don't plan to start because I don't think they are indicated in our patients."
- *Germany #4:* "I rarely use multifocals now, but use is increasing a little…Multifocal lenses are still used in a very small number of patients because of the hassle factor – the time – and the money. You can't spend as much time with cataract patients as you do with refractive surgery patients."
- *Spain:* "In a year, about 10% of my patients will get multifocal lenses."
- *Croatia:* "In two years, multifocals could be 20% of my cataract patients…I don't like accommodating lenses – only multifocals."
- *Serbia:* "I plan to start using multifocal lenses, probably ReStor because of a long-term relationship with Alcon. In two years, multifocals will probably still be <10% of my (cataract) patients."

Asked to compare the Alcon ReStor, AMO ReZoom, and AMO Tecnis lenses, few European doctors could offer any real differentiators. Most said it is too early to decide how they stack up against each other. An Austrian doctor said, "I'm not aware of the differences between ReStor and ReZoom." A Polish doctor said, "We are doing our own comparison of the two lenses now, so I have no idea yet how they compare." A Croatian doctor said, "I've just started using ReStor. I'm convinced it is better than ReZoom – but mostly because of the marketing. I will try ReZoom." A German surgeon said, "It is too early to say. I've done a few ReStors, and I'll do my first Tecnis soon." Another doctor commented, "I've tried a few Tecnis lenses because the sales rep gave them to me. I didn't think they were anything special, but the patients were satisfied."

In Germany, when a multifocal lens is used in a cataract patient, the government won't pay for the surgery or the lens, and German doctors said they hope their country adopts a reimbursement scheme more like U.S. Medicare, where Medicare pays for the surgery and a basic lens but patients can now pay extra to upgrade to a multifocal lens. However, there was no indication that this is likely to happen any time soon.

Refractive Surgery in Europe

Interestingly, monovision LASIK is not popular in Europe. A German doctor estimated that <5% of European patients get this procedure.

Procedure volume

LASIK volume in Europe is relatively flat this year compared to 2004, and in Germany procedure volume actually has dropped a little. A German surgeon said, "For procedure volume to get going, we need more positive media coverage and a better German economic situation. People have the money, but they are afraid of the economy." An industry source said, "The German market is depressed because of politics and the economy – and German patients are always afraid of surgery on the eyes."

Pricing

There does not appear to be any significant LASIK price cutting going on in Europe. The President of the European Ophthalmologic Society said, "Europeans are not price sensitive. There are doctors charging €1,100 per eye, and doctors charging €2,600 per eye, and there is no real volume difference between them. The low-priced centers are not increasing their business, and the higher priced doctors are not losing patients.

Custom LASIK

A German doctor commented that the doctors doing custom LASIK are the same ones buying IntraLase. Another German surgeon said, "From 25%-30% of my patients get custom LASIK, but I don't charge extra for it." A third source said, "About two-thirds of my procedures are with custom LASIK, and I charge extra for it."

Phakic IOLs (also known as ICLs)

European doctors who were asked about these lenses were surprisingly uninterest-ed in them. None were using the Staar Visian lens. A German doctor said, "I use (AMO's) Verisyse, and it's a good lens, but I need to talk it up most times. I haven't used the Staar lens. I'm afraid of cataract formation with it because a colleague told me he had 20% cataracts at two years. He was happy with that, but I wouldn't be." Another German doctor said, "Forget the Staar lens. I use Verisyse, and I've had good experience with it, but use will remain about the same." A Polish doctor said, "I currently use Verisyse for <10% of my cataract patients, but this will increase."

Phakic IOLs/ICLs

Company	Product	Comments
Alcon	AcrySof	FDA approved in October 2003
Novartis/CIBA Vision	Vivarte	Anterior Angle fixated
Novartis/CIBA Vision	Phakic Refractive Lens (PRL)	Posterior Silicone, hydrophobic Floats on the aqueous humor without touching the anterior surface of the lens
AMO/Ophtec	Artisan/Verisyse	Anterior chamber Iris fixated Technically difficult but reversible
Staar Surgical	Visian	Posterior chamber FDA approvable letter Acrylic, hydrophilic

Following is information on specific surgical device companies:

ADVANCED MEDICAL OPTICS (AMO) / VISX

European sources generally thought AMO's acquisition of Visx is a positive for both companies. They believe there are synergies. And sources reported that Visx is starting to sell more lasers in Europe. The Visx laser was described as a "bit big" for the European market, but doctors who have one reportedly like it, and the company has a strong reputation. A competitor said, "AMO/Visx is a good combination of cataract and refractive surgery, which is a growing combination – in Germany, at least. Visx's share is going up." Another competitor said, "Visx is gaining market share because of its experience. Visx doesn't have the newest technology, but they are working on new things, which B&L isn't."

BAUSCH & LOMB

B&L has the largest installed base of excimer lasers in Germany – and perhaps Europe – but even company sources were not optimistic that the company can maintain market share. AMO/Visx, WaveLight, and Schwind are all making inroads, and sources stressed that B&L just doesn't have new technology in the pipeline. A source said, "B&L is not as active or successful as it used to be. They aren't selling new lasers, and there is switching going on." Another source said, "B&L lost its drive in developing new technology. The Technolas (laser) founder is no longer there."

However, B&L laser users said they are satisfied with the machines, but doctors who have more than one laser generally had more than one brand in their center. A German doctor said, "I'm very happy with my B&L Keracor, but I prefer our Schwind for myopic patients."

INTRALASE FS30 femtosecond laser

IntraLase's laser corneal flap-maker for LASIK is starting to catch on in Europe for the same reasons it did in the U.S. – it is a great marketing tactic. Peschke is the distributor for IntraLase in Germany, Austria, Switzerland, Denmark, Poland, and the Czech Repuplic. A Peschke official said the first university orders for an IntraLase have been placed in Switzerland and Poland. Until now, most buyers, he said, have been private practice doctors with a volume of >500 procedures a year. He said doctors who get an IntraLase use it for about 30%-50% of procedures in the first three months, but get up to 80%-90% use after six months. Surgeons who said they have an IntraLase agreed with these estimates.

A competitor estimated that about 10 IntraLase lasers have been installed in Germany and about four in Switzerland. An official said, "IntraLase has become a real competitor, and they will continue to gain market share (for now). We all need to be conscious of this. But in 2006, we will have a femtosecond laser of our own."

Some European doctors are charging extra – ~€350.00 – for procedures using an IntraLase, but other surgeons are absorbing the cost. A doctor commented, "We got our IntraLase in March, and we are now using it for 90% of patients. We don't charge extra, but it helps with marketing, and I feel safer and patients feel better with it."

Two competitors are on the horizon that may impact on IntraLase sales, at least in Europe:

- **20/10 PERFECT VISION'S Femtec laser.** A source said, "They would be serious competition for IntraLase if they had a working machine. It is very good technology, but they only have four prototypes."
- **ZIEMER OPHTHALMIC SYSTEMS**, a Swiss company. Reportedly, Ziemer will unveil a femtosecond laser, Da Vinci, at the American Academy of Ophthalmology meeting in Chicago in mid-October 2005. This is a compact, mobile, hand-held device.

A Schwind official said his company has nothing new in development that would compete with IntraLase, that Schwind is sticking to its microkeratome. He commented, "I think IntraLase is mostly a marketing gimmick. The experts and opinion leaders who have tried it at other centers haven't liked it."

REFRACTIVE SURGERY IN THE U.S.

Thirteen ophthalmologists (refractive surgeons) and an industry expert were interviewed about trends in refractive surgery. Doctors indicated LASIK procedures this fall (September-October-November 2005) are off to a rather slow

start – on a par with the summer and only slightly ahead of the same period last year.

- Compared to the summer, the number of procedures is up an average of 3%.
- Compared to last fall, procedures are up an average of 1%.

Dave Harmon of Market Scope indicated the situation may be even worse than this. He said, "July and August were a little above last year – up in the mid-single digits – nothing dramatic. But I've heard from several surgeons that volumes have fallen in the wake of the hurricanes and rising gas prices. Several doctors have called with concerns about a sudden decline in procedure volumes. The message is pretty consistent: The price of gasoline, the weak U.S. economy, and weak consumer confidence have combined to reduce the demand for refractive surgery."

U.S. ophthalmologists expect their 2005 procedure volume to be roughly comparable to 2004, and Harmon is lowering his estimate for 2005 from 1.45 million procedures to 1.415 million procedures. A Florida doctor said, "I expect things to be comparable to last year. The patterns are consistent." Another said, "It's pretty mixed. We're doing about the same as last year." A Missouri doctor said, "We are still predicting slight growth in our LASIK volume and moderate growth in our overall refractive volume for fiscal year 2005, which includes CK and refractive lens surgery with Verisyse and ReStor implants." Another surgeon said, "We expect volume to be consistent – and better if the economy improves. We're still doing 10% PRK." Harmon added, "The 35,000 shortfall (in my estimate) will come out of September-October-November-December. July and August will be up, but the last four months of the year will probably be down a little."

Competition among refractive surgeons and in pricing is impacting procedure volume, according to these doctors. Two surgeons added that CK has impacted LASIK volume. Harmon blames the slowdown more on weaker consumer confidence and the high price of gas. A California ophthalmologist said, "There are too many providers out there, and they are saturating the market." A Florida doctor said, "Competitive pricing is always a danger for any center. There are always people out there looking for bargains." An Ohio surgeon said, "We're seeing more and more specials being advertised by inexpensive providers."

New technology – conductive keratoplasty (CK), phakic IOLs, clear lens exchange, etc., appear to be having little impact on LASIK volume. Harmon said, "The new multifocal lenses are going in cataract patients; hardly anyone is putting them in RLE (refractive lens exchange) patients. Cataracts are the easy pickings for multifocal lenses. They are partly paid for by the government, the patients are already coming in for surgery, and it is an easy upgrade. Very few doctors are doing any marketing to 50-year-olds. Alcon's ReStor and AMO's ReZoom are used almost exclusively for cataract patients."

Of the new lenses, it appears ReStor and AMO's Verisyse are getting the most attention. Harmon said, "ReStor is getting a lot of attention because Alcon is behind it, and usage is growing pretty rapidly. But it is difficult to know if the growth will continue that rapidly. I think there will be an initial bubble, and then usage will flatten out. A lot of people want to try this lens. They may do 25-30 patients and then back off a little, follow the patients, and see how they do. I think they will be reluctant to really push it hard until they have six months or more experience with it. But there will be slow adopters coming on to fill in the gap. So, I think the steep ramp will level off, and then after a year or so use will climb again."

Staar Surgical's new phakic IOL, Visian – which has an approvable letter but is still awaiting final FDA approval – is getting a look by three doctors. Another doctor said he is having good results in clear lens exchange with both Alcon's ReStor multifocal lens and AMO's Verisyse phakic IOL, but he gave the edge to Verisyse. One surgeon said, "We will not put in lenses (clear lens exchange) in our practice; we restrict ourselves to the outside of the eye. I'm very excited about the Staar phakic IOL, and I refer patients for bifocal IOLs." A Florida doctor said, "We are looking very closely at Starr's new phakic IOL." A Missouri surgeon said, "The Verisyse implant has been very exciting in my practice. All of these patients are thrilled with the performance of this lens. We've had good results with the ReStor lens, but patients aren't as thrilled with this as the Verisyse patients are with their lenses." A Michigan source said, "We expect to start ReStor soon."

Looking ahead, a few doctors said they are considering a range of new technology, including phakic IOL, iris registration, CK, IntraLase, and orthokeratology. A California surgeon said, "Although I'm not a big fan of CK because of the short-term benefit, more and more people are asking about it and are interested in having it."

MISCELLANEOUS

CLARITY MEDICAL SYSTEMS

One of the items getting a lot of attention at the SOE/DOG meeting was Clarity's RetCam-2, for diagnosing retinopathy of prematurity (ROP). The device has been around for several years, but it is catching on in Europe more now. An official of Clarity, a private U.S. company, estimated that about 300 institutions world-wide (in 32 countries) have a RetCam. About half of these are in the U.S., where 80% of the "top" children's hospitals have a device. The company official also said a comprehensive diagnostic device with camera will be introduced in 12-18 months that could be used to screen adults for diabetic retinopathy, glaucoma, trauma, and eye tumors.

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