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by Lynne Peterson

SUMMARY

Takeda's PROactive trial of high dose (45 mg) Actos vs. placebo missed its primary endpoint. Actos did show a 16% reduction in the composite of death, stroke, and MI, but it was also associated with a doubled risk of heart failure. European doctors said they would increase their use of TZDs after the trial, but TZD use will still be very limited. ♦ European doctors are not very excited about Lilly/Amylin's Byetta – unless it is proven to increase beta cell mass. There were no new data on exenatide-LAR, but it was described as "very powerful." ♦ Byetta has an advantage in efficacy and weight loss over DPP-4s (like Novartis's vildagliptin), but it also is an injectable with a lot of nausea, so sources believe there will be a role for both agents. ♦ There was little enthusiasm for inhaled insulins at EASD, and sources predicted that European approval may be slow for Pfizer/Nektar/ Sanofi-Aventis's Exubera and other products. ♦ Phase III data on Lilly's ruboxistaurin in diabetic retinopathy looked very good.

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EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD)

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FIRST GLOBAL GUIDELINE FOR DIABETES MANAGEMENT

Stricter blood glucose goals but the U.S. doesn't agree

The first Global Guideline for Type 2 Diabetes was at EASD by the International Diabetes Federation (IDF). The Guideline calls for a more aggressive approach to management of Type 2 diabetes worldwide, with a recommendation for maintaining blood glucose levels (HbA_{1c}) <6.5%. Two-thirds of diabetics in Europe and the U.S., for example, are not currently achieving target blood sugar levels. Dr. Eugene Hughes, Chairman of Primary Care Diabetes Europe, called the new HbA_{1c} goal "a daunting standard that we will try to achieve."

IDF, which is an umbrella organization of associations from 150 countries, including the American Diabetes Association (ADA), is taking a very unusual approach with this Guideline. Rather than setting one standard, and expecting poor countries to have the same resources as richer countries, it has established three levels of care that can be applied, depending on the healthcare resources available in a country. Dr. Stephen Colagiui, a professor of medicine at the University of New South Wales in Australia, was one co-chair of the IDF Task Force on Clinical Guidelines. He called the Guideline "globally applicable as it is sensitive to resource and cost-effectiveness." Dr. Philip Home, a professor of diabetes medicine at the University of Newcastle upon Tyne in the U.K., who also co-chaired the IDF task force added, "Diabetes is the largest epidemic humanity has ever experienced. IDF recognizes that immediate action is required, and by sharing evidence-based practice globally we can help alleviate the burden of Type 2 diabetes."

The three approaches in the Guideline are:

- ***Comprehensive care*** includes the most up-to-date and complete range of health technologies available, regardless of the quality of the evidence supporting their use.
- ***Standard care*** is evidence-based care which is cost-effective in most countries with a well-developed healthcare system and national healthcare funding systems. The Guideline says this level of care should be available to every diabetic, and this level of care should be the aim of every healthcare system.
- ***Minimal care*** is the lowest level of care that anyone with diabetes should receive. It seeks to achieve the major goals of diabetes management, but it is provided in poorly funded healthcare settings, where medical resources and fully-trained healthcare professionals are unavailable. Only low-cost or very cost-effective interventions are included at this level.

The Guideline is supposed to apply globally, but the ADA doesn't agree with the new goals and doesn't plan to adopt them. Richard Kahn, Ph.D., Chief Scientific and Medical Officer of the ADA, said, "The ADA has its own clinical practice guidelines, and those are what we urge people to follow. Our goal is HbA_{1c} <7%."

METABOLIC SYNDROME

The debate continues over whether or not it is real

Is there dissent in the ranks? In late August 2005, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a joint statement advising doctors not to diagnose or treat metabolic syndrome but, instead, to treat all cardiovascular (CV) risk. At the EASD meeting, many attendees appeared to disagree with this decision.

The EASD/ADA statement declared: "*While there is no question that certain cardiovascular risk factors are prone to cluster, we found that the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a cardiovascular risk marker.*"

Dr. Paul Zimmet, Foundation Director of the International Diabetes Institute and Professor of Diabetes at Monash University in Melbourne, Australia, said the EASD/ADA statement threw "the whole world into chaos." At a well-attended satellite symposium, Dr. Zimmet conducted an impromptu electronic poll, and 88% of attendees said they still believe in the concept of metabolic syndrome, which caused him to quip, "I think the membership disagrees with some of its leadership...Metabolic syndrome is clearly a useful predictor of future diabetes."

Officials of both EASD and ADA defended their statement. ADA President Dr. Robert Rizza said, "I am not at all disturbed by the fact that there is a difference of opinion…That is why science works so well. The real issue is whether the concept of metabolic syndrome adds value to treatment of persons with diabetes…Conduct the same poll next year."

EASD President Dr. Ele Ferrannini of Italy said, "I'm not terribly impressed with polls. The answer is usually predictable based on the question…but the (metabolic syndrome) concept has been extremely popular because it is new, and new is attractive. It also seems to bring together lots of disparate observations, which is always a pleasing thing now that medicine is so sectorial…It is definitely a popular concept." The ADA's Dr. Kahn said, "Certainly, the poll doesn't surprise me…The real issue is whether it informs patients or physicians to be labeled with metabolic syndrome …and there doesn't appear to be any evidence that a metabolic syndrome diagnosis is helpful…To step back and say this (metabolic syndrome) doesn't exist is like trying to stop and reverse a train, but more and more people are challenging the concept…I think the tide is actually turning on this concept."

The EASD/ADA statement also puts it at odds with the International Diabetes Federation (IDF), which recognizes metabolic syndrome as "a cluster of the most dangerous heart attack risk factors: diabetes and pre-diabetes, abdominal obesity, high cholesterol, and high blood pressure."

Dr. Rizza suggested it is time for IDF to rethink that position, "One reason for controversy is to step back and say we now have a lot of information, let's, me and you, critically re-examine the data as a community." Dr. Ferrannini added, "ADA and EASD are scientific organizations. IDF has a different mission, so perhaps the pragmatic value – whatever that is, and I don't necessarily agree it is very high – may be more significant for that organization…than a scientific society that should scrutinize the science behind it."

Dr. Ferrannini put the blame on cardiologists for promoting a metabolic syndrome diagnosis, "The concept of metabolic syndrome has had different names before…It was born into the diabetes family, and then as a young lady the marriage was arranged to cardiology, and there is where the problem arose. I think our colleagues the cardiologists have capitalized on the pragmatic value of the concept by saying it is educationally important that both doctors and patients realize that if you have one element or risk factor you should screen for the others because of the statistical likelihood of clustering…That where there is one, the chances of the other being present is relatively high. That is fine…I have no quarrel with the pragmatic usefulness of the concept…but jumping from that to a disease entity that stands alone…is a different step that requires more science. All we are saying is, 'Let's do the additional research that will clarify the issues, and evaluate clearly whether or not the syndrome is predictive of cardio-vascular risk or any other risk – for example, whether it predicts diabetes in non-diabetics.'"

Last week, there were suggestions that the major cardiac organizations – the American Heart Association (AHA), the American College of Cardiology (ACC), and the European Society of Cardiology (ESC) – also may not agree with ADA and EASD. AHA President-Elect Dr. Robert Eckel said doctors already recognize metabolic syndrome, "The syndrome is a world-known phenomenon…Physicians around the world recognize it…The syndrome is accepted by the world."

Yet, at EASD, the ADA's Dr. Kahn flatly declared, "In America, there will not be any drug approved for the indication of metabolic syndrome in the next few years… maybe for all time. I think there are many questions about the concept of metabolic syndrome…That does not preclude a drug being approved with many different actions – on glucose, blood pressure, and other things, such as body weight…but an indication for metabolic syndrome will not happen in the U.S."

Outside the U.S. the prospects for a drug with an indication to treat metabolic syndrome isn't much better. Dr. Ferrannini said, "It seems unlikely unless you have a unique definition in the first place that doesn't confuse people and unless you have some clear idea about pathogenesis, if not the etiology, of the problem…Also for economic reasons, it would be difficult and too optimistic to imagine there would be a finger snap sort of indication for that." Dr. Rizza added, "My prediction is that in the next five years there will be drugs approved with multiple indications…but they won't be approved for this whatever-it-is syndrome…Science will win out…The data will ultimately tell us if there is value to the term or not."

INSULIN INJECTOR PENS
More popular in Europe than the U.S.

The European doctors estimated that >90% of their patients use injector pens to administer insulin in Europe, but the pens just haven't caught on in the U.S. Asked why this is, doctors generally blamed Lilly. A U.K. doctor said, "In the U.S. Lilly was the dominant insulin provider, and Lilly didn't push pens – perhaps because the first Lilly devices were not as good as the Novo Nordisk device." Another source said, "Lilly controlled the U.S. (insulin) market, and Lilly initially didn't have a pen to compete with Novo Nordisk, so Lilly discouraged doctors from using a pen. Then, when Lilly did get a pen, it was inferior to the Novo Nordisk pen, so Lilly still didn't push pens. Now, Lilly has a good pen, but they can't and don't really market it." A U.S. doctor commented, "Pen use was driven by Novo Nordisk, but Lilly didn't have a pen (initially), and Becton Dickinson had the syringe market." Another U.S. doctor said, "Lilly just can't market. At first Lilly wasn't interested in pens, and now it can't sell them."

ROSSO STUDY RESULTS
Self-monitoring of blood glucose has mortality benefit

A large, epidemiological cohort study in Germany found that people with Type 2 diabetes who regularly self-monitor their blood glucose have significantly lower morbidity and mortality rates than people who do not self-monitor. The study was based on 3,268 diabetics, with a mean follow-up of 6.5 years.

ROSSO Study Results

Measurement	Self-monitoring n=1,479	No self-monitoring n=1,789	p-value	Relative risk reduction with self-monitoring
Morbidity (non-fatal event)	7.2% 109 patients	10.4% 186 patients	.002	Down ~33%
Mortality (deaths)	2.7% 41 patients	4.6% 79 patients	.004	Down ~50%

PPAR AGONISTS

GLAXOSMITHKLINE'S Avandia (rosiglitazone)

An independent, U.K. study found that spironolactone is the most effective agent for reducing Avandia-induced edema.

NOVARTIS'S LBM-642

This dual PPAR-α/γ agonist is in Phase I trials. Preclinical data indicate it is associated with weight loss and some signals of satiety. A researcher said, "LBM-642 may be weight neutral or even be associated with some weight loss. There definitely isn't any weight gain with this…Any drug with weight gain would be a no-go for Novartis."

New rat data indicated that over four weeks, the animals gained ~140 g on vehicle, ~40 g on fenofibrate, ~260 g on Takeda/Lilly's Actos (pioglitazone), and ~25 g on LBM-642 (5 mg/kg). Researchers concluded LBM-642 prevents weight gain independent of food intake, is comparable to Actos in increasing insulin sensitivity, reduces both subcutaneous and visceral fat better than fenofibrate, and lowers triglycerides more than Actos or fenofibrate.

TAKEDA/LILLY'S Actos (pioglitazone)
PROactive trial misses primary endpoint but shows benefit in prevention of composite of death, stroke, and MI

Type 2 diabetics who have already had a heart attack or stroke can cut their risk of death, a repeat MI, or stroke by 16% with Takeda's Actos (pioglitazone). That's the finding in a study of 5,238 diabetics in 19 European countries. More than 33 million people have Type 2 diabetes in Europe and more than 18 million in the U.S.

European doctors said the results are likely to make them increase their thiazolidinediones (TZD) use – but from miniscule levels to low levels. Among the comments were:

- *Ireland:* "My TZD use will go up from <1% of Type 2 diabetics to perhaps 7%-8%, and I'll favor pioglitazone now."
- *U.K. #1:* "The results were interesting, and I may increase TZD use from 10% of Type 2 patients to 20%.
- *U.K. #2:* "I won't change my TZD use. I think this is a class effect like ACE inhibitors."
- *Sweden #1:* "I had hoped for better results. I'm sorry they didn't present the data on the insulin-only patients; the heart failure could be in those patients."
- *Germany:* "PROactive won't change what I prescribe. I use very little TZDs now – less than 1% of my patients are on a TZD – and that won't change over the next year."

- *Sweden #2:* "The results were not impressive, and it is not a class effect."

PROactive was a three-year prospective, randomized, double-blind, placebo-controlled outcome study comparing the highest tolerated dose of Actos (up to 45 mg) to placebo as add-on therapy to other medications, with or without insulin. Patients were followed for an average of 2.8 years. The baseline characteristics of these Type 2 patients were released previously, showing 75.4% with hypertension, 57.5% with angina, 23.6% with claudication, 23.2% with retinopathy, 14.1% with nephropathy, 5.7% with transient ischemic attack (TIA), and 1.4% with leg amputation.

The key benefit was on the major secondary endpoint – a 16% reduction in risk of the composite of heart attacks, strokes, and premature death (12.3% Actos vs. 14.1% placebo, p=.027). However, the trial did not meet statistical significance in any of these measurements considered alone, though an investigator said the trial was not powered to show a difference in the individual measurements, "We had powered the study for a 20% reduction in the composite primary endpoint…Late revascularization was one of the components, and that proved not to be as we had expected five years ago."

The study chairman, Dr. John Dormandy, Professor of Vascular Science at St. Georges Hospital, University of London, U.K., estimated that adding Actos to other diabetic medications in 1,000 people would avoid 21 first MIs, strokes, or deaths. Looked at another way, 48 patients would need to be treated for three years to avoid one first major cardiovascular event.

The trial failed to meet its primary endpoint. The trial was powered to show a 20% improvement in time from randomization to first occurrence of any cardiovascular event (defined as the composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, coronary revascularization, revascularization in the leg, or amputation above the ankle), but it showed only a 10% improvement (21.0% Actos vs. 23.5% placebo, p=.095).

The composites of the primary endpoint not included in the key secondary endpoint – death, non-fatal heart attacks, stroke, acute coronary syndrome, CABG, and leg amputation – all trended (but were not statistically significant) in favor of Actos except leg bypass, which was slightly worse with Actos**.**

The trial did show significant benefits with Actos on other endpoints, causing Dr. Dormandy to declare it a "breakthrough for patients who are at high risk from heart attacks, strokes, or premature death because it is the first time an oral (diabetes) agent has been shown to have this benefit in a prospective study."

The 3-year data from the PROactive trial also showed Actos:

- Increased HDL by 19% (vs. 9% increase with placebo).
- Reduced blood glucose (HbA_{1c}) by 0.5% more than placebo.
- Reduced TGL by 11% (vs. increase of 2% with placebo).
- Decreased systolic blood pressure by a median of 3 mmHg more than placebo (p=.03).
- Decreased progression to permanent insulin use by 50% vs. placebo.

PROactive found no unexpected adverse events, but more patients were diagnosed with heart failure on Actos than on placebo in the unadjudicated data. When it came to hospitalizations for heart failure, there was little difference between Actos and placebo, and there was no difference on death from heart failure. Prof. Erland Erdmann, a cardiologist at the Medizinishce Klinik III der Universitat zu Koln, Germany, said, "My feeling is that the edema which may have occurred was falsely considered as heart failure."

The EASD independent reviewer Dr. Hannele Yki-Jarvinen of the University of Helsinki, Finland, said the good news is that the primary endpoint was reduced by 10%, but the bad news is that the incidence of heart failure with Actos in the trial was twice as high as the reduction in cardiovascular event, though she admitted heart failure may have been either over or under diagnosed in the trial.

She also pointed to several unanswered questions:

- Is it safe to use insulin with Actos?
- What is the prognosis of patients who develop heart failure on Actos?
- When does heart failure occur – e.g., during the first year of therapy?
- Who is at greatest risk of developing heart failure?

PROactive investigators insisted that there was not a heart failure problem with Actos in the trial. Dr. Erdmann said, "My feeling is this drug doesn't cause heart failure at all, but it does cause fluid retention, and ≥10% will have edema. Heart failure is primarily myocardial dysfunction because of edema. This drug causes primarily edema, but it doesn't affect the heart negatively. If someone has myocardial dysfunction, I wouldn't give this drug because fluid overload might harm the patient, but a bit of edema is not dangerous for other patients – like the elderly woman who has edema in her ankles at the end of the day but no heart failure."

Dr. David Kendall, Medical Director of the International Diabetes Center at the University of Minnesota, agreed, saying, "It is my expressed opinion that Actos and compounds like the PPARs don't cause heart failure. They can unmask heart failure in patients with pre-existing ventricular dysfunction (systolic or diastolic)…We know that these compounds promote modest fluid retention, just as salty meals would in an at-risk individual…These (drugs) are not com-

pounds that cause heart failure." However, the Actos label warns that it "can cause fluid retention that may lead to or worsen heart failure."

Will PROactive change clinical practice? In the U.S. only about 20% of Type 2 diabetics are currently on therapy with oral TZDs – Takeda's Actos or GlaxoSmithKline's Avandia (rosiglitazone). The numbers are even smaller in Europe. Dr. Dormandy predicted the PROactive results will encourage more use of Actos, "Earlier comparative clinical studies have already demonstrated that pioglitazone has a unique profile by proving benefits beyond glycemic control on certain markers of CV risk, for example by improving the atherogenic lipid profile. However, until the new and exciting results of PROactive were announced, the clinical significance of these effects of pioglitazone were unknown." Dr. Erdmann agreed, "Fewer than 10% of my Type 2 diabetics are currently on a TZD, and slightly more than half of that is rosiglitazone. Over the next year, I expect my use of pioglitazone to more than double. I will now probably only prescribe pioglitazone." But Dr. Yki-Jarvinen said, "The study did not provide the answer to this question (of who should be treated with Actos)...but it showed pioglitazone is at least marginally beneficial, at least in those Type 2 patients who do not develop heart failure."

The results of PROactive were less positive than experts at a Takeda-sponsored media briefing (the day before the official presentation) had suggested would be important to adoption of Actos as standard therapy. Dr. Kendall said, "Clearly, the magnitude of the effect with these results will impact (usage). A 25% relative risk reduction for ACE inhibitors and statins have really made them standard of care, particularly for patients with diabetes. If the relative risk reduction (with Actos) were 20%-25%, it would put us in a position where it is essential to consider this as a part of our approach."

Baseline Characteristics of PROactive Trial

Measurement	Actos	Placebo
Mean age	61.9%	61.6%
Duration of diabetes <5 years	28.5%	28.9%
BMI	30.7%	31.0%
HbA_{1c}	7.8%	7.9%
Prior MI	47.2%	46.1%
Prior stroke	18.7%	18.9%
Prior PCI or CABG	30.9%	30.6%
Coronary artery disease	47.8%	48.4%
Peripheral arterial obstructive disease	19.3%	20.5%
Medication use		
Sulfonylurea alone	19.5%	18.7%
Metformin alone	9.7%	9.9%
Statin	42.5%	43.2%
Fibrate	10.1%	11.2%
ACE inhibitor	62.6%	63.0%
Beta blocker	54.6%	54.5%
Nitrate	39.1%	39.7%
Antiplatelet medications	85.3%	82.6%

Another question is whether doctors will consider this a class effect of oral TZDs, extending the benefit to Avandia. PROactive investigators and other experts generally agreed that the data cannot be extrapolated from Actos to Avandia.

- *Bart Staels, Ph.D., Professor of Pharmacy at the University of Lille, France:* "There are differences between pioglitazone and rosiglitazone which are most clear at the level of control of dyslipidemia…There is a difference in triglyceride control, a difference in the magnitude of effect on small LDL particles, and we know there are risk factors."
- *Dr. David Kendall:* "I don't think we can say this is a class effect in the absence of other data. Given the quite distinct differences in how these compounds – pioglitazone and rosiglitazone – affect not only the genes

Results of the PROactive Trial

Measurement	Actos	Placebo
Discontinuations	427 patients	438 patients
Primary endpoint #1: All-cause mortality, non-fatal MI, stroke, acute coronary syndrome, coronary revascularization, revascularization in the leg, or amputation above the ankle	21.0% (p=.095)	23.5%
Principal secondary endpoint: All-cause mortality, non-fatal MI, or stroke	12.3% (p=.0273)	14.4%
First events in the primary endpoint		
Death	110 patients	122 patients
Non-fatal MI	85 patients	95 patients
Silent MI	20 patients	23 patients
Stroke	76 patients	96 patients
Major leg amputation	9 patients	15 patients
Acute coronary syndrome	42 patients	63 patients
Revascularization	101 patients	101 patients
Time to first event in secondary endpoint		
Death	129 patients	142 patients
Non-fatal MI excluding silent MI	90 patients	116 patients
Stroke	82 patients	100 patients
Total events for each component of the primary endpoint, regardless of when they occurred		
Death	177 patients	186 patients
Non-fatal MI	131 patients	157 patients
Stroke	92 patients	119 patients

PROactive Metabolic Results

Measurement	Actos	Placebo	p-value
HbA_{1c} change from baseline	-0.8%	-0.3%	<.001
TGL	-11.4%	+1.8%	<.001
HDL	+19.0%	+10.1%	<.001
LDL	+7.2%	+4.9%	.003
LDL/HDL ratio	-9.5%	-4.2%	<.001
SBP change from baseline	-3.0 mmHg	0	.033
Weight change	Up 3.6 kg	Down 0.4 kg	<.05

involved in the regulation of lipids and vascular behavior, but the distinct difference in dyslipidemia, especially HDL and triglycerides…Changes in HDL are more favorable with pioglitazone than rosiglitazone, so assigning a class effect is premature and should not be done."

- *Dr. Jack Leahy of the University of Vermont:* "The problem for GlaxoSmith-Kline is that there are lipid differences (between the two drugs), even if they are not necessarily important, so I don't think you can say it is a class effect. PROactive will give Lilly and Takeda a marketing advantage."
- *Dr. Richard Kahn of the ADA:* "It is absolutely not a class effect."

The PROactive results also may not be able to be extrapolated to newer drugs, such as Bristol-Myers Squibb's Pargluva (muraglitazar), which an FDA advisory committee recommended for approval last week. Dr. Kendall said, "That is very young data, and it is exceedingly premature to assign these same effects to a class used in only a few thousand patients."

Other points investigators made included:

- They all insisted this is not a class effect. The study chair, Dr. Dormandy, said, "It is very dangerous to extrapolate from one drug in a class to others because they have very different effects, and we know there are differences in the TZDs, for instance on lipids. And we know there are other classes of drugs like beta blockers where individual drugs have very different effects. No, you don't extrapolate this data."
- Commenting on the trial missing its primary endpoint, Dr. Dormandy said, "There was a 16% reduction in strokes, heart attacks, and death. It is for doctors and patients to decide if that is worth having…If you are the one, 16% is worth it."
- The blood pressure decrease was not considered the reason for the beneficial effects of Actos.
- There was more weight gain with Actos (3.6 kg) than with placebo. Dr. Pierre Lefèbvre of Belgium said, "This led to some patients leaving the trial because of that."
- Statin use was comparable in the two arms of the trial, with 43% of patients on a statin at baseline and about 55% at the end of the trial.
- LDL cholesterol was 115 mg/dL at baseline, and the changes in lipids that were seen during the trial were the same in statin and non-statin treated patients.

Takeda-sponsored Study Comparing Actos and Avandia

Measurement	Actos n=369	Avandia n=366	p-value
Mean change in HbA_{1c}	~ Down 0.7	~ Down 0.6	.129
Mean change in triglycerides	~ Down 12%	~ Up 15%	<.001 favoring Actos
HDL	~ Up 15%	~ Up 8%	<.001 favoring Actos
LDL	~ Up 15%	~ Up 23%	.002 favoring Avandia
Mean weight change over time	~ Up 4.4 pounds	~ Up 3.5 pounds	.164
Change in pedal edema from baseline to Week 24			
Worsening edema	13.4%	12.8%	Nss
Improving edema	5.8%	7%	Nss
No change	18.1%	15.1%	Nss
No edema	62.7%	65.1%	Nss

- PROactive will change clinical practice. Dr. Erdmann said, "I think it is obvious that when you have a new drug that has an impact on MI, death, stroke, I would propose to use it, and I cannot withhold it from my patients."

Comparison of Actos and Avandia

A Takeda-sponsored study compared edema and weight gain with these two agents as monotherapy over 24 weeks.

OTHER APPROVED AND INVESTIGATIONAL DRUGS

LILLY'S ruboxistaurin
Soon to be submitted to the FDA for diabetic retinopathy

The Phase III data in diabetic retinopathy were presented at the European Ophthalmological Societies meeting in Berlin in September 2005. *(See **Trends-in-Medicine** "Update on Ophthalmology in Europe," October 2005).* A Lilly official said the company is "very interested in launching several trials but not currently enrolling patients in any trial of ruboxistaurin."

LILLY/AMYLIN'S Byetta (exenatide)
Interest but wariness in Europe

Byetta has not yet been approved in Europe, but at EASD Lilly was educating doctors – and the media – about it. The only new data were discussion of the 24-month results of an ongoing study. Previously only 30-week and 82-week (18-month) data were available from this trial. Compared to the 30-week data, the 24-month open-label extension results with 10 µg Byetta BID showed stable HbA_{1c} and continuing weight loss.

Doctors asked about their enthusiasm for – or experience with – Byetta commented:

- *Germany:* "Byetta is a very promising drug. It increases beta cell mass."

- *U.S.:* "I've used Byetta a little. The post-prandial blood sugar is fabulous…It will be wonderful in combination with basal insulin, but it hasn't been studied with that or approved for that yet. Patients want it for the weight loss."
- *U.K.:* "I'm not sure I would use Byetta. We are conservative, and we'd use insulin if a patient fails oral agents."
- *Greece:* "Byetta will do great if the beta cell preservation is true. That would be a milestone. I would use Byetta before insulin because of the weight gain with insulin…All of my patients who would have started insulin will go on Byetta before – even with the cost."

However, speakers and other doctors did offer some other interesting comments, including:

- **Byetta vs. Sanofi-Aventis's Acomplia (rimonabant, a CB_1 blocker).** A doctor who has been an investigator for both Byetta and Acomplia was asked whether Acomplia would give the same results as Byetta or whether the two drugs should be combined: "I consider for the future rimonabant being part of oral therapy…So, where you take a sulfonylurea plus metformin, I would go for rimonabant plus metformin. That is, for me, a similar approach for Type 2 diabetics. Then it is potentially possible that once you have a patient on rimonabant + metformin and are still not able to reach (HbA_{1c}) target, then add exenatide. Personally, I don't see a CB_1 blocker – and there are other CB_1 blockers in development – as a substitute for exenatide. I think the mechanism of action and the results you can obtain are different. I see more a CB_1 receptor blocker as part of the oral therapy approach."

- **Byetta vs. DPP-4s.** Asked about the outlook for Byetta if an oral DPP-4 were available:
  - "DPP-4s are not as effective as incretin mimetics."
  - "DPP-4s don't have the weight-lowering effect. They are weight neutral. They probably have some effect but not as strong as exendin (exenatide)…That is the major distinguisher."

- **The outlook for exenatide-LAR.** Among the comments were:
  - The Phase II data have been accepted for publication in the ***Annals of Internal Medicine.***
  - *A LAR investigator:* "It is, of course, a very interesting option…Giving patients a once-weekly injection with this would be very welcome." He noted that the Phase II trial was a short study with a limited number of patients, but he said, "The results seem to confirm what we have seen here (with exenatide)…The efficacy, safety, and tolerability of the LAR formulation seems to confirm what we have seen (with exenatide) and seems consistent with these (exenatide) findings…It is a little too early to comment on the data…It is a nice option in progress."
  - *A Lilly official:* He indicated the Phase II data are expected to be published next year, and it is not likely to be presented at a medical conference until the American Diabetes Association in June 2006. "We are further analyzing the data from that (Phase II) study. It looks like high dose tested (which he would not identify) has 2% HbA_{1c} lowering and was associated with a weight loss of 4.5 kg (9.9 pounds) after 15 weeks, which is pretty good…That (high) dose looks very promising. We will test further whether that is the optimal dose."
  - *U.S.:* "Exenatide-LAR is powerful. Our (physician) issue with Byetta isn't the injections, it's the nausea. The nausea is real and limiting."

- **The outlook for Byetta in Europe.** Lilly officials would not comment on the outlook for Byetta approval in Europe except to say they are "in the final steps of completing the clinical trials necessary for European submission that were necessary in addition to what the FDA required. We plan to submit it in 1H06."

Byetta 30-Week vs. 2-Year Results in Completers

Measurement	30 weeks	2 years	p-value
Mean change in HbA_{1c}	Down 1.0%	Down 1.1%	p=.001
Mean change in body weight with no diet or exercise counseling	Down 4.8 pounds	Down 11.4 pounds	Nss

MERCK'S sitagliptin (MK-043)
Byetta hasn't killed it

There is no weight loss with this oral, twice-daily DPP-4, which is in Phase III development, but a Merck source said it will still have a role because it is oral, has good efficacy, and is well-tolerated – no nausea or vomiting and no hypoglycemia. Phase III data are expected to be presented at either ADA or EASD in 2006. A source said, "The choice of this or Byetta will come down to oral vs. injectable, no nausea vs. nausea."

- Asked if sitagliptin could be combined with Byetta, a source said, "That hasn't been studied, but that study would be interesting to do."
- Asked if a fixed-dose, single-pill combination of sitagliptin and muraglitazar is being considered, a source said, "We certainly have to consider the lesson learned from the hypertension market (where combination therapy is common)."

- Asked if studies in combination with Pargluva (Bristol-Myers Squibb, muraglitazar) are planned, the same source said, "Our feeling is that a combination with a PPAR will be very important, especially after the PROactive trial. Most oral agents will be in combination. Combination therapy is the way diabetics will be treated. And the combination of sitagliptin and muraglitazar has appeal."
- Asked how sitagliptin compares to Novartis's vildagliptin (LAF-237), a source said, "We don't know yet. We need to compare dose, regimen, safety, efficacy, and there are not enough data on sitagliptin to do that yet."

MERCK KGA/BRISTOL-MYERS SQUIBB'S Glucophage (metformin)
Reduces the risk of cancer

Even though Glucophage has gone off-patent, Merck is making an effort to promote brand sales of Glucophage, and the company had some impressive data at EASD that it may lower the risk of dying of cancer. A retrospective study found that Type 2 diabetics who took metformin (Glucophage, sold by Merck KgA in Europe and Bristol-Myers Squibb in the U.S., but also available as a generic) had a 23% reduced risk of cancer death.

Researchers at the University of Dundee, Scotland, looked at two large databases: DARTS (Diabetes Audit and Research in Tayside Study) of about 13,000 diabetic patients in the U.K., and MEMO (Medicine Monitoring unit), which includes all pharmacy-dispensed prescriptions from the U.K.'s National Health Service (NHS). A total of 983 Type 2 diabetics were identified with cancer during the year after the diagnosis of their diabetes. This was compared to a case-matched control of 1,846 diabetics who did not develop cancer.

Researchers could find no factors – age, duration or severity of diabetes, sex, smoking, cholesterol levels, weight, etc. – to explain the difference except metformin use. The more metformin patients took and the longer they were exposed to the drug, the lower the risk of cancer mortality. There was even a trend for patients who only took metformin one time to have a reduced risk.

The conclusion was that taking metformin may be associated with a reduced risk of cancer in Type 2 diabetes, and the response may be related to exposure and duration of treatment. That is, the more metformin you've taken, perhaps the greater the protective effect. However, Dr. Bo Ahrén, Professor of Clinical Metabolic Research at Lund University in Sweden, said he is still not convinced metformin is cancer-protective, "I've seen the data. I believe the data, but it has to be confirmed."

Researchers have not yet determined whether any particular tumor type was affected more than others or whether metformin could be used to prevent cancer in non-diabetics. Dr. Alistair Emslie-Smith of the University of Dundee said, "It is too early to think it (metformin) will become mainstream for patients to prevent cancer, but we know it has a role in pre-diabetic states…If long periods of metformin are shown beneficial, then maybe that will justify using it earlier in patients at high risk."

These findings were reinforced by a population-based retrospective cohort study from the 10,309-patient Saskatchewan Health database. That analysis found that patients on metformin had a cancer death rate of 3.5% compared to 4.9% (p=.001) for patients on a sulfonylurea. For every 1,000 patient-years, this translates to 6.3 cancer deaths on metformin and 9.7 on a sulfonylurea.

Retrospective Cohort Study from Saskatchewan Health Database

Measurement	Metformin n=6,969	Sulfonylurea n=3,340	p-value
Cancer deaths	245 patients 3.5%	162 patients 4.9%	p=.001
Cancer mortality rate per 1,000 patient-years	6.3 cases	9.7 cases	---
Hazard ratio	1.0	1.3	---

Both these studies follow an earlier finding in the UKPDS (U.K. Prospective Diabetes Study) of a non-significant 29% lower risk of cancer death in diabetic patients who took metformin compared to those who only changed their lifestyle (diet and exercise) – 3.5% vs. 4.9% (p=0.33). UKPDS also found a statistically significant 36% reduction in all-cause mortality with metformin: 13.5% vs. 20.6% (p=0.011).

There was another retrospective study in which metformin was found to reduce fatal and non-fatal events. The study was intended to look at the effect of metformin on the need for revascularization but instead it found a benefit on mortality, using two databases – PRESTO and SCRIPPS.

NOVARTIS'S vildagliptin (LAF-237)
An oral DPP-4 competitor for Byetta

Norvartis officials generally refused to discuss when and where the Phase III data on vildagliptin would be available. However, a Novartis source said the company plans to submit vildagliptin in 1H06.

Doctors appeared to find this agent very interesting. They like the oral administration and lack of nausea but worry that it doesn't cause weight loss and may be less effective than Byetta. A U.K. doctor commented, "It is very promising. There is no nausea, but there is no weight loss, which is quite important…LAF-237 appears more tolerable than Byetta, it is an oral, and it is more tolerable – but there is some very preliminary evidence that Byetta may be slightly more effective at lowering glucose…You might be able to use this

DPP-4 earlier than an injection, and all the evidence is that earlier is better."

At a Novartis-sponsored seminar, speakers emphasized that vildagliptin:

- Removes stress on beta cells and enhances beta cell survival. A speaker commented, "We have only one-year studies with vildagliptin. We need longer studies to show real protection."
- May prevent the transition from impaired glucose tolerance to diabetes, so it may be able to treat pre-diabetes.
- Has been associated with a low rate (<3%) of hypoglycemia in Phase I and II trials. A speaker said, "This needs to be studied in subgroups such as the elderly or patients with comorbidities…but we have not seen any correlation to age."

Potential advantages of vildagliptin over Byetta:

- **Oral formulation.**
- **No nausea or vomiting.** May prolong insulin clearance. A speaker explained, "This has only been studied a little, but a recent study in animals [mice] showed that GLP-1 prolongs insulin availability by reducing the clearance in mice."

Potential disadvantages of vildagliptin over Byetta:

- **Lack of weight loss with vildagliptin.** Does not affect liver enzymes, lipid levels, or body weight. A speaker said, "We know the DPP-4s are weight neutral. They apparently do not lower body weight, and this is the most distinguishing factor."
- **Hypertension side effect.** Vildagliptin has been associated with a worsening of hypertension (5-10 mmHg). A speaker said, "It has to be stressed that this was seen in only a few patients, and in a compilation of all the studies, there was no increase in blood pressure...On the other hand, it has been shown in a few studies, so we need to watch that carefully in the Phase III trials."

A mouse study comparing vildagliptin to Byetta found:

- Fasting and post-load glucose levels were significantly and similarly reduced with both agents from Day 4-15.
- AUC was incrementally reduced 40% with vildagliptin and 55% with Byetta.
- Vildagliptin and Byetta were equally effective at reducing fasting blood glucose on Day 16, improving glucose tolerance on Days 16 and 24, increasing the differentiation of beta cells on Day 16, and increasing B-cell neogenesis on Day 16.

NOVO NORDISK'S liraglutide (NN-2211)
A role even if exenatide-LAR is approved

Sources agreed that liraglutide, a GLP-1, will continue to have a place even if long-acting exenatide (LAR) works out. A Novo Nordisk official said, "Liraglutide will still have a role; it's not dead. We expect it will show weight loss, and it is oral."

INHALED AND ORAL INSULINS

The first inhaled insulin could be on the U.S. market by the end of this year, following a positive recommendation for Pfizer/Nektar/Sanofi-Aventis's Exubera by an FDA advisory committee in early September 2005. The outlook in Europe is for a longer regulatory timeframe and a harder marketing environment for Exubera and other inhaled insulins.

Diabetes specialists attending EASD proved a tough audience for companies with inhaled insulin products. At the end of a debate over the advantages of inhaled insulin, the audience indicated by at least a 2:1 show of hands that they are not in favor of inhaled insulin. Other comments by doctors at EASD on inhaled insulin included:

- *Greece #1:* "I think Exubera is very promising, especially for young people. I would use it for more than 50% of my patients. There is very high patient demand for this – especially by children and the elderly – but I wouldn't use it for insulin-using Type 2 diabetics."
- *U.K.:* "Exubera approval in Europe is a long way behind the U.S. Cost is a real issue in Europe, not approval. If it were approved, I would find it very difficult to get it reimbursed."
- *Greece #2:* "Inhaled insulin is the dream of all children and families, and the results so far are excellent. We will use Exubera off label in kids, though I have a few hesitations because it works like a growth factor, and you don't know what happens after 30-40 years…Cost is not an issue in Greece; the government will pay for it…In one year I could have more than 50% of my patients on it. I will definitely use it for Type 1 diabetics."
- *Finland:* "I'm not excited about inhaled insulin, and I'm not sure if I would use it. In a year, less than 5% of my patients will be on it."
- *Sweden:* "Exubera won't do well in Europe because of the device. It is too big and bulky…But I think the MannKind device is very good. Lilly also has a good device, but the company is slow to get that going."
- *U.S.:* "The only benefit to inhaled insulin is patient preference. My use will depend on the cost. I can't believe insurance companies will approve a more expensive delivery device that is not more efficacious…In a year, I would expect to have fewer than 10% of my patients on it, and there will be more use in Type 2 diabetics than in Type 1s."

AEROGEN'S AeroDose – a dry powder inhaled insulin system. This development program has been suspended.

ASTRAZENECA – a dry powder formulation of inhaled insulin with enhanced absorption and a mechanical inhaler. It is not clear whether this project is on hold or whether the company has gone into "stealth" mode.

BRISTOL-MYERS SQUIBB – a dry powder formulation of inhaled insulin with a breath-activated inhaler.

COREMED'S Alveair – an inhaled insulin that appears to still be in preclinical development.

DURA'S Spiros – a dry powder formulation with a multidose breath-activated inhaler. This development program is currently suspended.

EMISPHERE'S Eligen – an oral insulin that is trying to overcome the problems that have killed other oral insulin efforts – deterioration in the GI tract and poor absorption – via the addition of a carrier. A pilot study of Eligen, which combines a carrier with oral insulin, confirmed:

- Oral administration is feasible.
- The onset of action is fast.
- Duration of action is short.

Researchers hope to improve the PD/PK of Eligen by optimizing the carrier/insulin ratio. A speaker said, "We hope further optimization might lead to additional improvement in post-prandial bioavailability and blood glucose control…But this trial is driven by only small pharmas…so we are hampered by manpower (shortages) and budget constraints… but we think these (early) results warrant more studies to look at variability and dose response…Oral insulin alone isn't very well absorbed…but the optimal ratio may still be even lower than (we've tried)."

GENEREX'S Oral-Lyn (buccal insulin) – a dry powder formulation, using a mechanical delivery device, but it is delivered by a buccal, not pulmonary, route. Oral-lyn is approved in Ecuador, but it has not yet be launched there. A source said there are no large-scale trials underway of this agent because the company doesn't have the funds to run one. Dr. Jaime Guevara-Aguirre, of the Institute of Endocrinology IEMYR in Quito, Ecuador – an investigator for Oral-lyn – reported on a small, 12-day study that found Oral-lyn (delivered with the RapidMist device) was comparable to pre-prandial Humulin (Lilly, human insulin) in inducing glycodynamic responses in 10 Type 1 diabetics receiving baseline glargine insulin. The study was intended to find a dose and formulation of Oral-lyn to be used in a larger multicenter trial. The researcher concluded: Split doses of Oral-lyn control meal-induced glucose in a fashion similar to pre-prandial injected Humulin, and Oral-lyn used as a meal insulin did not increase the parameters of glycosylation.

KOS PHARMACEUTICALS – a dry powder inhaled insulin with a very small inhaler that looks much like an asthma inhaler. Bioavailability is ~12%.

LILLY/ALKERMES' AIR – a dry powder inhaled insulin – human insulin inhalation powder (HIIP) – with a device that is a bit more elegant than the Exubera device. AIR allows a variety of doses, but a speaker noted that there can be a lot of wasted drug. Lilly and Alkermes have begun enrolling patients in Phase III trials – one in Type 1 diabetics and another in Type 2 diabetics – with safety the primary endpoint and efficacy the secondary endpoint in both. The studies will also enroll diabetics with chronic obstructive pulmonary disease or asthma. The trials are expected to take about two years to complete.

In 2006, Lilly and Alkermes also plan to start a Phase III study with efficacy as the primary endpoint.

A poster by Lilly researchers reported on an open-label, two-period, crossover study comparing patient-reported outcomes and treatment preferences of 137 Type 1 diabetics. The conclusion was that HIIP and subcutaneous insulin had comparable safety and efficacy, but HIIP was preferred by patients.

Patient-reported Outcomes with AIR

Measurement	AIR	Subcutaneous insulin	p-value
(higher score better)			
SF-36 vitality (scale 0-24)	15.8	15.6	Nss
Patient treatment satisfaction (scale of 0-36)	30.0	27.2	<.001
Insulin satisfaction (scale of 0-7)	5.5	4.4	<.001
Ease of use	5.6	5.4	Nss
Lifestyle impact	5.6	5.1	<.001
Diabetes symptom reduction (lower score is better)			
Cognitive distress	1.5	1.6	Nss
Fatigue	1.8	1.9	Nss
Hyperglycemia	1.4	1.5	Nss
Hypoglycemia	1.5	1.6	Nss

MANNKIND'S Technosphere – a dry powder formulation of "technospheres" using a mechanical inhaler. This has much more rapid onset of action than subcutaneous insulin or even rapid-acting insulin analogs. It also has higher bioavailability (~28%), and lower or comparable variability than subcutaneous insulin.

Data are expected in August or September 2006 from two Phase III trials – one trial in Europe (Russia) and South Africa and a second trial in the U.S. These are one-year trials which will have a subgroup of asthmatics included.

Other points about this agent included:

- T_{max} is 40-50 minutes, then it fairly rapidly disappears. This compares to a T_{max} of 120 minutes for subcutaneous insulin.
- Intra-subject variability is less with Technosphere. There is less AUC insulin and less AUC GIR vs. SQ insulin both at two-hour and three-hour observation periods.
- The majority of the effect occurs within three hours of dosing. In contrast, more than two-thirds of the glucose lower effect of regular insulin is delivered after three hours of an injection. A speaker concluded, "The timing of the Technosphere insulin effect corresponds better with meal absorption than that of SQ insulin."

NOBEX/BIOCON'S INS-105 – an oral, tablet-form insulin analog. Nobex is developing the drug, and Biocon (an Indian firm) will make it. A canine study found the clearance and biologic activity of INS-105 were indistinguishable from Humulin. Biologic activity lasted about two hours, and onset of action was rapid (C_{max} 10 minutes). A researcher, asked to compare this to Emisphere's Eligen, said, "Emisphere has a carrier, and this is a modification of the insulin molecule to make it less subject to destruction in the gut...The limiting factor is that you have to use a lot of insulin, but Biocon can manufacture it at a cheap price…I'm optimistic about the oral agents, though it is very early days."

NOVO NORDISK/ARADIGM'S AERx iDMS – a liquid formulation of inhaled insulin using an electronically-guided inhaler. A speaker noted that this product has a significantly faster onset of action than subcutaneous insulin, a similar onset of action to a rapid-acting analog, a duration of action similar to subcutaneous regular human insulin, and is well-tolerated. He described it as suitable as a meal-time insulin.

PFIZER/NEKTAR THERAPEUTICS/SANOFI-AVENTIS'S Exubera – a dry powder insulin with a mechanical inhaler that is likely to be the first inhaled insulin to be approved. It has more rapid onset of action than regular insulin but longer action than lispro (Lilly's Humalog) – sort of in-between those. One unit of Exubera equals three units of subcutaneous insulin.

At EASD, Dr. Jay Skyler of Miami FL presented the case in favor of inhaled insulin over subcutaneous insulin, stressing the ease and comfort of use, comparable or better blood glucose (HbA_{1c}) lowering to subcutaneous insulin in Type 2 diabetics, and the lack of unique safety issues with inhaled insulin. He concluded, "You can clearly substitute inhaled insulin for subcutaneous insulin…Many of you will remain skeptical…but you will be surprised at the uptake and the enthusiasm of patients."

Dr. Home of the U.K. disagreed. He admitted inhaled insulin is convenient and avoids injections, but he raised concerns about Exubera in terms of safety, cost, smoking, etc.

These and other speakers addressed issues that have been raised about Exubera and other inhaled insulins, including:

- **Adverse events.** These were described as predominantly mild, usually occurring within 60 seconds of dosing and decreasing over the treatment period. Cough is also more common with inhaled than subcutaneous insulin: ~25% vs. ~7%.
- **Antibodies.** A speaker said, "We checked insulin antibody levels...and they go up with inhaled insulin. When you go back to subcutaneous insulin, the antibodies fall again. We went crazy trying to find out if the anti-bodies cause a problem…We looked at hypoglycemia, hyperglycemia, pulmonary tests, etc., and we could not find any problems with the elevated antibody levels."
- **Asthma and COPD patients.** The efficacy in these patients has not been well studied.
- **Cost.** With this delivery method, more insulin is needed, so the insulin costs are three to five times higher. Plus there is an added delivery cost.
- **Deposition.** Only 10% of inhaled insulin is bioavailable, with 25% going into the peripheral lung. Sixty percent doesn't go into the body, going instead into the environment (breathed in and out). A speaker wondered whether this will have any impact on normal pets or children – Will it sensitize people?
- **Devices.** Dr. Home described the Exubera device as "really quite a bulky device," saying that this is relevant. He explained that patients may not want to carry a big device around with them all day or use something so obvious in front of people.
- **DLCO.** Over time, there is a change in mean DLCO, but it wasn't statistically significant in clinical trials, and the decline paralleled the comparator. Dr. Skyler said, "The FDA (panel) concluded this is not statistically significant and not a concern."
- **Dosing.** Exubera will come in two dosages: a blister pack of 1 mg (28 U) or 3 mg (84 U). However, three 1 mg blisters do not deliver the same dose as one 3 mg blister. Dr. Home said, "This is not a small change…It is a 30%-40% net difference…There are clear dosing problems with this instrument."
- **Hypoglycemia.** Dr. Skyler said the rate of hypoglycemia is the same with Exubera as with subcutaneous insulin. Another expert warned, "Expect more late post-prandial

hypoglycemia compared to rapid acting glargine, especially with activity and exercise."

- **Pulmonary fibrosis.** He said, "There is indeed a progressive decrease (in FEV_1) over time...but it is almost identical over time and never statistically significantly different from the comparator."
- **Smoking.** A speaker said that as long as patients continue to smoke, they can use inhaled insulin in a predictable way, but the company and regulators will recommend avoiding inhaled insulin if you smoke.
- **Use with long-acting insulin analogs.** A speaker said inhaled insulin is unsuitable to use with the new long-acting insulin analogs, due to overlap.
- **Long-term safety.** The number of patients who have been treated long-term with inhaled insulin is small. However, a speaker noted, "The changes in measures of lung function appear to be non-progressive and decrease slightly over time (in four-year data)."

DEVICES

CONTINUOUS GLUCOSE MONITORING

From 70%-75% of critically ill patients have hyperglycemia. Keeping the glucose levels at 80-100 mg/dL can reduce mortality and morbidity (blood infections, acute renal failure, the need for prolonged ventilation, critical illness PNP, length of intensive care stay by 40% in a surgical unit).

ABBOTT'S FreeStyle Navigator

This is a single user device that can be used for three to five days before it needs to be replaced. There is about an eight minute lag between the glucose measurement with this device and blood glucose.

Navigator has been submitted to the FDA, and Abbott hopes to have approval and launch in 2006. The initial FDA submission was for three-day use, but the company plans to modify the submission to five days.

MEDTRONIC'S Guardian RT CGMS

This device provides real time (RT) glucose values every five minutes by measuring glucose in interstitial fluid. It has programmable alarm functions for hypoglycemia and hyperglycemia. The sensor is easily replaced by the patient every three days, but it has to be calibrated twice a day against capillary blood (finger stick). Sensor data from the last three days also can be downloaded to a computer and reviewed. Guardian was being highlighted at the EASD meeting; it was launched in the U.S. in July 2005, but it is not expected to be available in Europe until about November 2005.

MENARINI DIAGNOSTICS' GlucoDay

This small, semi-invasive device is designed to be used in a medical intensive care unit to provide continuous glucose monitoring. It has CE Mark, but it has not yet been approved in the U.S. Researchers reported at EASD on the results of a study of 50 patients over 48 hours:

- Target glycemia was only reached 22% of the time. Glucose was >140 39% of the time, and <60 5% of the time.
- Mean insulin dose was 71 U/day.
- Despite a higher insulin dose, diabetic patients had a higher mean glycemia (170 vs. 129 p=.013) than non-diabetic patients.
- The GlucoDay detected peaks and valleys of glycemia much earlier than discontinuous monitoring.
- Patients had fewer adverse events with GlucoDay. Even patients receiving full dose heparin did not show bleeding complications.
- Continuous monitoring with GlucoDay was well-tolerated.

A U.S. doctor said a concern with continuous glucose monitors is hypoglycemia. The speaker responded that he didn't see any problems in the low glycemic range – only in the high glycemic range – at least in this small study. The moderator added, "This needs to be proven…This was just an observational study." The moderator also noted that the accuracy of the GlucoDay appears somewhat inferior, and the speaker responded, "We need to work with that." Another expert commented that there is a significant delay between the GlucoDay glucose measure and blood glucose levels.

PRECISENSE

A source said this company has a blood glucose sensor that is placed on the skin and remains active about two weeks, then it degrades and disappears in the body. While it is active, it provides continuous glucose monitoring. The sensor is composed of a polymer membrane that allows glucose to diffuse in and out. No adjustments need to be made to the device during the two-week period.

INSULIN PUMPS

Sources agreed that the pump market is growing, but slowly. Currently, only about 10% of American Type 1 diabetics use a pump, and the numbers are smaller outside the U.S.

Several insulin pumps are on the market, including devices by:

- **ANIMAS.** One of the key advantages of this device, according to sources, is that it is waterproof. An Israeli doctor said, "Animas' service (sales rep) is better than Medtronic's because Medtronic sales reps are over-loaded and have too many patients. Animas also is the only pump in Hebrew." An Animas source estimated that 40%-45% of the company's

business is in pediatric patients. Animas has 52 sales reps and 80 diabetes educators; three of the sales reps are former Disetronics sales reps, but Animas has no former Medtronic sales reps.

- **DANA.** This Korean firm is waiting for its first FDA approval. The advantages of the U.S. product were described as ease of use and affordability.

- **INSULET.** This company didn't have a booth at EASD, but a source said it has a disposable pump (iXL) in development that bears watching, particularly because of the price. The source explained, "With the other pumps, it costs payors $6,000 to start a patient on a pump, so a patient can't just try one out, and that makes the threshold high. With the Insulet pump, you can try a pump for less than $1,000. Payors will love it."

- **MEDTRONIC/MINIMED.**

- **ROCHE/DISETRONICS.** Roche sources said the company is still waiting for a decision by the FDA on whether or not manufacturing issues with its Disetronics pump have been resolved. One source said, "We haven't heard anything negative, and we can launch almost immediately (in the U.S.) when it is cleared. The FDA is on its own timetable; it doesn't necessarily respond in 30 days." A competitor said, "When Roche is back on the U.S. market, it will be a formidable competitor. They understand diabetics, but not the pump market." Another source predicted Roche will take market share primarily from Medtronic.

Roche was showing its new Spirit pumps at its EASD booth. There is no built-in bolus calculator, so a separate Pocket Compass hand-held device is needed to send instructions to the pump, to retrieve information, and do a bolus.

- **SMITHS MEDICAL'S Deltec Cozmo.** The Cozmo is the newest pump on the market. Users only need one hand to access features, and, like the Animas pump, it is waterproof.

Why do doctors choose a particular pump? A Danish doctor said, "The Roche device is cheaper, but the Medtronic device has a longer duration. Supply and cost are the same, and so is service. I've had a good experience with Roche, and now I'd like to try Medtronic."

Sources cited several reasons for their choice:

- **Features.** Among the options in higher-end pumps are carbohydrate calculation systems, alarms, etc. A Greek doctor said, "I used Medtronic and Roche pumps. The Medtronic advantage is you can fine-tune the dose with more precision. I don't want to go to a stripped down device."

- **Service.** This can be a huge issue, and the quality of the toll-free patient-assistance reportedly varies greatly among the companies. Is the person who answers the patient phone call at midnight a certified diabetes educator, a nurse, an operator, or a sales rep? A source said, "Roche's key is connectivity with its suite of products, and Animas doesn't have that." A Finnish doctor said, "All the companies have about the same services. There are only small differences." Another source said, "Roche care of doctors has fallen off…Medtronic doesn't do the service that MiniMed did."

- **Reimbursement.** Some insurers specify a particular brand that is covered, and there are geographic differences within the U.S. on coverage.

- **Relationships** – with the company and the sales reps.

- **Cost** – not just for the pump itself but also for supply costs and maintenance. This is more an issue outside the U.S. than in the U.S.

- **Reliability.**

- **Patient preference.** Some doctors said they (or their nurse or diabetes educator) show patients the available pumps and let the patient choose. Others said they make the choice because they have to know the device in case the patient has questions, and they don't want to have to become knowledgeable about too many pumps. A Swedish doctor said, "I need to know the pump well, so I tend to use just one or two products."

OTHER AGENTS AND COMPANIES WORTH WATCHING

ACON LABORATORIES. The company expects to have a CE Mark for its **blood glucose measuring system,** On-Call, by March 2006, but it will not be on the U.S. market until 2009 because of patent issues. The device was described as the lowest price meter, perhaps because it is manufactured in China. Outside the U.S. the devices are sold through distributors.

AGAMATRIX. This company, founded by MIT researchers, has a pending 510K application for a low cost but high-tech **glucose monitor** and is hoping to begin shipping in November 2005. AgaMatrix has an exclusive distribution agreement with Liberty Medical in the U.S. and is looking for a partner in Europe. However, the company's key product (in development) is a no-strip/no-lancet glucose monitor that can be used for 25 tests and then thrown away.

OSI PHARMACEUTICALS' PSN-9301. This is a **subcutaneous DDP-4** being tested in combination with metformin for obese Type 2 diabetics. In rats, monotherapy improved glucose as well or better than metformin, and in combination with metformin, it accelerated glucose clearance. PSN-9301 also was either weight neutral or showed some weight reduction.

SUMITOMO PHARMACEUTICALS. This Japanese company has a **dual PPAR-α/γ agonist** in preclinical development. It is more balanced between the alpha and gamma than Pargluva, which has more gamma activity than alpha activity.

TAISHO'S SGL-0010. SGL-0010 is an **oral sodium-dependent glucose cotransporter** that – in a mouse study – inhibited SGL-T1 and SGL-T2 that enhances urinary glucose excretion by inhibiting glucose reabsorption in renal proximal tubules. In a rat study, SGL-0010 improved hyperglycemia in a dose-dependent manner. SGL-0010 is currently in Phase I development in Japan.

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