Trends-in-Medicine

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by Lynne Peterson

SUMMARY

The DREAM trial found diabetes can be prevented in pre-diabetics with **Glaxo-SmithKline's Avandia**, but not with **Sanofi-Aventis/King's** ACE inhibitor ramipril. However, Avandia increased the risk of heart failure 7-fold. ♦ European doctors are excited about **Amylin/Lilly's Byetta**, but experts are watching the pancreatitis cases in the U.S. to see if they are background noise or a real problem. ♦ **Pfizer's Exubera** inhaled insulin has gotten off to a slow start in Europe. Doctors are interested but concerned about cost and the device size. ♦ A trial found **Novartis's Galvus** (vildagliptin) boosts the efficacy of metformin while cutting the GI side effects nearly in half. ♦ A study found **Novo Nordisk's liraglutide** produces more weight loss than Amylin/Lilly's Byetta, though this wasn't a head-to-head study. ♦ **Merck's Januvia** (sitagliptin) has been launched in Mexico, making it the first DPP-4 on the market. ♦ There were reports on interesting new non-invasive glucose monitors from two Israeli companies.

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EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD)

Copenhagen, Denmark
September 13-17, 2006

EASD, the premier diabetes meeting in Europe, was attended by more than 13,000 people this year. The hot topic was new drugs to treat the disease – and there are several newer therapies either being introduced or expected soon.

At the end of the meeting, 16 doctors were asked what they found the most interesting or exciting at the meeting. They most frequently pointed to DPP-4 inhibitors, the DREAM trial results, and the role of mitochondria in diabetes. Other topics that were mentioned included GLP-1 analogs, Type 1 autoimmunity, advances in an artificial pancreas, lack of effect on sexual activity of insulin pumps, advances in the genetics of diabetes, and TCF7L2 transcription factor.

Asked which of the new drugs appears the most promising, these doctors were almost equally excited about

- GLP-1 analogs – Amylin/Lilly's Byetta (exenatide) and exenatide LAR as well as Novo Nordisk's liraglutide.
- DPP-4 inhibitors – Merck's Januvia (sitagliptin) and Novartis's Galvus (vilda-gliptin).
- One doctor pointed to CB-1 receptor blockers, e.g., Sanofi-Aventis's Acomplia (rimonabant), and another was encouraged about early data on a vaccine for diabetes.

More than 230 million people worldwide may have diabetes – almost 6% of the world's adult population – and it is estimated this could increase to more than 350 million people in less than 20 years. Previously a disease of the middle aged and elderly, Type 2 diabetes has become common in all age groups and increasingly is being seen in younger patients. EASD officials expressed support for an initiative by the International Diabetes Federation (IDF) calling for a United Nations declaration on diabetes aimed at increasing awareness of the burden of diabetes and its complications.

Eight research grants from Merck Sharp & Dohme (Merck) were announced. The grants will focus on research into beta-cell function and survival. The European Foundation for the Study of Diabetes (EFSD) and Merck also announced an additional €3 million for European diabetes research, bringing the total to €4.4 million.

The EASD and the European Society of Cardiology (ESC) will soon issue new, joint guidelines for the management of diabetes, including definitions, screening for pre-diabetes, prevention, and treatment. The guidelines, which will be printed

by the end of 2006 in the ***European Heart Journal*** and ***Diabetologia***, will include 72 recommendations, such as:

- An oral glucose tolerance test is the best method to diagnose previously unknown diabetes or pre-diabetes.
- Primary screening for the potential of diabetes can be effectively done by a non-invasive risk score to define high risk.
- Therapeutic success depends on collaboration across specialities.
- Structured life-style counseling is very important and needs to be improved.
- The targets for treating blood pressure, blood glucose, and lipids are defined and stricter than in the past.
- The recommendations for treatment of Type 2 diabetes are "very, very similar if not identical" to the current guidelines, though the way they are presented and discussed may be a little different, but the message was described as essentially the same.
- Metformin remains the first-line therapy and continues to be the cornerstone for combination therapy. Doctors at EASD said they most commonly add a sulfonylurea (SU) as a second-line therapy, with thiazolidinediones (TZDs, glitazones) third-line.
- The guidelines will recommend that patients and doctors follow drug labels, and the example was given that use of insulin + an insulin sensitizer (TZD) is off-label.
- The guidelines will ***not*** incorporate DPP-4s, and an expert commented, "You need evidence-based data for guidelines, but that data are not available for either of those (DPP-4 drugs), and so it will take much more time to see if this class makes an impact on outcomes like CV disease."

Disadvantages of Current Therapies for Type 2 Diabetes

Drug	Disadvantages
Metformin	GI effects (nausea, diarrhea), lactic acidosis (rare)
SU and glinides	Hypoglycemia, weight gain, hyperinsulinemia, TID dosing, expense
TZDs	Weight gain, edema, liver toxicity, CHF
A-glucosidase inhibitors	GI effects (flatulence, diarrhea), TID dosing, expense
GLP-1s	GI effects (nausea, vomiting, diarrhea), hypoglycemia, injections

Before the results of the large DREAM trial were released, a member of the guidelines committee said that there would be an opportunity to modify the guidelines to include the findings of the DREAM trial if they warranted it. However, after the DREAM results were presented, experts generally agreed that it is doubtful that DREAM will change the recommendations on prevention, though the trial could lead to a strengthening of the warning about heart failure with the class of TZDs. An expert said, "The guidelines won't change ahead of the label for rosiglitazone…And the results won't change clinical practice because that would be an off-label use."

THIAZOLIDINEDIONES: LILLY/TAKEDA'S Actos (pioglitazone) and GLAXOSMITHKLINE'S Avandia (rosiglitazone)

Doctors had high hopes for the DREAM trial, expecting that it would show the value of TZDs in preventing diabetes, and the trial did show that – but at a cost in terms of heart failure that many experts feel is too high. The results of DREAM – a study of GlaxoSmithKline's TZD Avandia (rosiglitazone) and the ACE inhibitor ramipril (sold in Europe by Sanofi-Aventis as Tritace and in the U.S. by King Pharmaceuticals' as Altace) in the prevention of Type 2 diabetes in high risk individuals – were presented at EASD and simultaneously released in two parts in medical journals:

1. A ***Lancet*** article on the effect of Avandia on the frequency of diabetes.
2. A ***New England Journal of Medicine*** article on the effect of ramipril on diabetes prevention.

DREAM was a prospective, 3-year, randomized, double-blind trial at 191 sites in 21 countries of 5,269 patients age ≥30 with impaired glucose tolerance or impaired fasting glucose. Worldwide >8% of adults have either impaired glucose tolerance or impaired fasting glucose, and annually ~5%-10% of these people develop diabetes. Individuals with previously diagnosed CV disease were excluded. Patients received advice on diet and lifestyle but were not required to follow any particular diet. There was no difference in the use of antihypertensives in the two groups.

The design of DREAM was 2x2 factorial, with 4 different treatment arms: Avandia, Avandia+ramipril, ramipril, and placebo. This was described as "an efficient design which gives 2 answers for the price of one." An investigator said this is "a design we should use more and more." However, this design reports results in a somewhat different, and less clear, way – in 2 separate comparisons without giving the results for any one of the 4 arms by itself. Rather, the comparisons were all mixed:

a. Avandia ± ramipril *vs.* placebo ± ramipril.

b. Ramipril ± Avandia *vs.* placebo ± Avandia.

In the Avandia part of the study, researchers reported:

- Avandia met the primary endpoint, reducing the risk of diabetes or death by 60% (an absolute risk reduction of 14.4%).
- For every 7 people prescribed Avandia for 3 years, one will be prevented from developing diabetes.

- Avandia significantly increased the likelihood that glycemia would be normalized.
- The effect was present without regard to gender, geography, ethnicity, age, weight, or body-mass index.
- Avandia appears to reduce or eliminate the relation between increasing obesity and a higher risk of diabetes.
- There was no effect on a composite CV endpoint, but blood pressure was lower with Avandia.
- There was a "small excess" in non-fatal congestive heart failure with Avandia, which researchers speculated was due to fluid overload.
- In terms of risk:benefit, researchers estimated that for every 1,000 people treated with Avandia for 3 years, ~144 cases of diabetes would be prevented, with an excess of 4-5 cases of CHF. That translates to 32 cases of diabetes prevented for 1 new case of heart failure created.
- There was no effect on the Avandia results due to ACE-inhibitor use.

In the ramipril part of the study, researchers reported:

- Ramipril missed the primary endpoint of reducing the risk of DM or death. However, the curves for diabetes prevention diverged at two years, and researchers said there was a "suggestion of a possible diabetes prevention effect starting at two years."
- Ramipril met the pre-specified secondary endpoint of regression to normoglycemia, showing a modest benefit.
- Blood pressure was significantly reduced – systolic by 2.8 mmHg and diastolic by 2.4 mmHg vs. placebo.
- ALT was lowered by a small but statistically significant amount, which was described as a surprising finding.
- *Dr. Hertzel Gerstein, DREAM co-principal investigator:* "There was a small excess of edema – 7% vs. 5%. Rosiglitazone does cause fluid retention."
- *Dr. Salim Yusuf, co-principal investigator:* "At the present, we do not think ramipril can be recommended for the prevention of diabetes. However, in people in whom there is an indication for an ACE inhibitor, the favorable effects on glucose is one added reason to use ramipril…We know ramipril saves lives in a higher risk group, but not this group."
- *Dr. Yusuf:* "HOPE showed that in people with vascular disease, ramipril reduced mortality and reduced MI and stroke. On top of that, to show a favorable gluco-metabolic effect is a bonus…(With ramipril), if you treat 1,000 people, you enhance regression in 100 people. That is highly significant. The modest effect on ALT is something that may be happening at the liver level, and we need to explore that."

One thing experts did agree on is that DREAM confirms what has been shown in several other trials in recent years – that diabetes can be prevented. Dr. Gerstein said, "Now, we've demonstrated another agent can clearly prevent diabetes. We need to have in our medical arsenal a bunch of things to prevent the disease. If you are at high risk, what you can do is diet, exercise, and a number of drugs, including now rosiglitazone…We are at the beginning of an era of drugs that modify physiology."

3-Year Results of the DREAM Trial: Avandia

Measurement	Avandia 8 mg/day (± ramipril) n=2,365	Placebo (± ramipril) n=2,634	p-value
Dropouts	59 patients	46 patients	---
Key findings			
Primary endpoint: Composite of incident diabetes or all-cause death	11.6%	26.0%	<.0001
CV composite (MI, stroke, CV death, heart failure, new angina, revascularization, ventricular arrhythmia needing resuscitation)	2.9%	2.1%	Nss, 0.08
Developed heart failure	0.5%	0.1%	0.01
Developed diabetes	10.6%	25.0%	<.0001
All-cause death	1.1%	1.3%	Nss, 0.7
Normoglycemia	50.5%	30.3%	<.001
Other results			
MI	0.6%	0.3%	Nss, 0.2
Stroke	0.3%	0.2%	Nss, 0.6
CV death	0.5%	0.4%	Nss, 0.7
Composite of MI, stroke, or CV death	1.2%	0.9%	Nss, 0.2
Revascularization	1.3%	1.0%	Nss, 0.3
New angina	0.9%	0.85	Nss, 0.5
Change with Avandia vs. placebo			
Fasting plasma glucose (FPG) vs. placebo	0.5 mmol/L lower	---	<.0001
2-hour plasma glucose concentration vs. placebo	1.6 mmol/L lower	---	<.0001
Mean SBP vs. placebo	Down 1.7 mmHg	---	<.0001
Mean DBP vs. placebo	Down 1.4 mmHg	---	<.0001
Mean ALT during the first year of therapy	4.2 U/L lower	---	<.0001
Mean body weight vs. placebo	Up 2.2 kg	---	<.0001
Hip circumference	Up 1.8 cm	---	---
Waist circumference	No change	---	---
Discontinuations			
Any reason	28.5%	24.3%	---
Not taking drug at last visit	23.6%	20.2%	---
Patient refusal	18.9%	16.7%	---
Edema	4.8%	1.6%	---
Physician's advice	1.9%	1.5%	---
Weight gain	1.9%	0.6%	---
Safety			
Peripheral edema at last visit	6.8%	4.9%	0.003

Heart failure

While the effect on diabetes prevention with Avandia was dramatic, it comes at a cost – heart failure. In DREAM, Avandia had a ***7-fold increase*** in heart failure compared to placebo, though the absolute increase was small (0.5% vs. 0.1% with placebo), and 81% of the heart failure patients were hospitalized.

Dr. Yusuf suggested that the heart failure seen with Avandia may be transient and not structural, "What we don't know is if there is an effect on the function of the heart. We are doing a functional study now. If the effects are neutral (on function), it is good news. If we find no structural effect, that is good. There were no deaths from heart failure (in DREAM). That could be a play of chance, but it is reassuring. The prognosis may be very different from naturally-induced heart failure." He said, "In both trials (PROactive and DREAM), there was an excess of heart failure. We have to admit that there is heart failure with TZDs. The question is how to deal with it."

Other comments about the heart failure by experts involved in DREAM included:

- "The cloud in heart failure is the increase in heart failure. We adjudicated it carefully. It is heart failure. But there were no fatal events, and we don't know if the prognosis of this heart failure induced by rosiglitazone is any different from natural heart failure. It may be, but we don't know. It's another reason for long-term follow-up. But the absolute increase is small vs. the absolute increase in benefit. So, the benefit seems to outweigh the harm."
- "We are not calling this 'not heart failure' as some other trialists have done. The point is every drug has side effects. I don't know an effective drug that doesn't have side effects. The key is to understand and document, and then we can avoid and treat it – not suppress it."
- "Everything has a trade-off…The issue is if the trade-off is reversible."
- "This (heart failure) is not a fatal event…It is a condition that can be diagnosed and treated."
- *Dr. Gerstein:* "We don't know the prognosis of people with heart failure secondary to a drug. That may be very different from run of the mill heart failure after a heart attack or other cardiovascular event."
- *Prof. Rury Holman of Oxford, European co-chair of DREAM:* "Heart failure is a long-known effect of these (TZD) drugs…It is lower in this trial…but it is a frightening thing when people get it. When you remove the drug, it disappears. People haven't been put into irreversible heart failure. We are working to see which people might be at risk…The mechanism of the heart failure is being explored. Probably it has to do with the way the kidney excretes fluid, but a heart failure diagnosis is very worrying."

3-Year Results of the DREAM Trial: Ramipril

Measurement	Ramipril 15 mg/day (± Avandia) n=2,623	Placebo (± Avandia) n= 2,000+	p-value
Key findings			
Primary endpoint: Composite of incident diabetes or all-cause death	18.1%	18.5%	Nss, 0.15
Developed diabetes	17.1%	18.5%	Nss, 0.15
All-cause death	1.2%	1.2%	Nss, 0.93
Normoglycemia/FPG <6.1	42.6%	38.3%	0.001
Normoglycemia/FPG <5.6	31.3%	27.8%	0.002
SBP reduction vs. placebo	Down 4.3 mmHg	---	<.001
DBP reduction vs. placebo	Down 2.4 mmHg	---	<.001

Asked what he would do if a patient on Avandia developed heart failure, Dr. Yusuf said, "I would stop rosiglitazone and treat with everything I normally use for heart failure – diuretic, beta blocker, ACE inhibitors, etc., depending on the patient's circumstances…If the patient were in the diabetes range, I would use something like metformin."

Outside experts not involved in the trial were more concerned about this side effect. These cardiologists described heart failure as a more serious disease than diabetes. They agreed that 100-150 cases of diabetes would need to be prevented to justify ***one*** case of heart failure. That is far more than the 32:1 reported in DREAM. The vice president of EASD, Dr. Eberhard Standl, said, "It's nice to prevent diabetes, but that's only important if you also prevent the cardiovascular effects, particularly heart failure." Another cardiologist said, "The annual cardiovascular event rate with diabetes is 3%, compared to 7%-10% in mild heart failure and 45% death in severe heart failure…And the edema could be incumbent (future) heart failure." Dr. Klas Malmberg of Karolinska Institute in Sweden said, "DREAM dealt with a very low risk population; it excluded people with previous cardiovascular risk. In that population, you should have an extremely low risk of heart failure." Another cardiologist commented, "Heart failure is the equivalent of cancer."

To put this data in additional perspective, it might be helpful to review the results of the failed PROactive trial which was presented at EASD last year. PROactive compared Lilly's Actos (pioglitazone) to placebo in 5,238 diabetics. Actos did not meet the primary endpoint of ≥20% reduction in any CV 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). The trial found a small (10%) but not statistically significant improvement in the CV event rate with Actos, and Actos also decreased progression to permanent insulin use by 50% vs. placebo. Importantly, the incidence of heart failure with Actos was ***twice as high*** as the reduction in CV events.

The critique

Dr. Nick Wareham, a Cambridge (U.K.) epidemiologist, offered the independent commentary on DREAM. An investigator called his comments "harsher than the data deserved." His comments included:

- The trial made patients out of participants. He said, "They were found by screening and would be unlikely to consult a doctor. We need a high level of evidence that the benefits of screening outweigh the costs…because we are offering treatment to people who didn't ask for help."
- He suggested that the impact of Avandia on progression to diabetes was simply the glucose-lowering effect of a TZD.
- DREAM investigators in 2004 said that the promise of any diabetes prevention strategy lies in the assumption that it will also prevent CV events, but DREAM was underpowered to detect a CV impact. His epidemiological analysis suggested that ***at least*** 554 people would have to be treated with Avandia for 3 years to prevent one CV event.
- He criticized the lack of washout data, though that will be presented in the future.
- The weight gain with TZDs sends a mixed health message to patients, and increased weight predicts a decline in physical activity, affects quality of life, and raises the longer term risk of CV and other health problems.
- There is a high cost to drug therapy, which he estimated at $1,128/year per patient, ***plus*** the cost of monitoring them, whether or not they progress to diabetes. He said, "I think it is likely rosiglitazone would not be a cost-effective intervention if prescribed to the patients in this trial."
- He said the ramipril results should be taken "with a pinch of salt," adding, "If there is an effect of ramipril on glucose regulation, it is not large and does not justify its use for this reason."

Physician reaction

Doctors generally were disappointed in the results of DREAM. They were impressed with the efficacy in preventing diabetes, but they thought the heart failure was too high a price. Very few sources said the results would change their use of TZDs in general or Avandia in particular. Comments included:

- *Canada #1:* "I'm impressed that rosiglitazone prevents diabetes, but that doesn't mean I will use it to do that. It won't be used en masse. And that isn't just because of the heart failure, which is way lower than expected in terms of absolute risk. A 32:1 trade-off is okay."
- *U.S.:* "DREAM adds impetus to using a TZD as second-line or even first-line, to use it early. I disagree that the participants weren't patients. They may not be cognizant that they have a real problem, but they are patients, and the UKPDS (U.K. Prospective Diabetes Study) showed that by the time of formal diagnosis, people have lost 50% of beta-cell function, so pre-diabetics are really diabetics …We need to monitor for heart failure and watch for hints – to look for a sprinkle before it becomes a down-pour."
- *Caribbean:* "I won't change my TZD use. The benefit is quite small to translate into widespread use, and the initial effect is too short-lived."
- *U.K. #1:* "We need to see the washout data…And the heart failure was high given the tight selection criteria…If the diabetes bounces back (when the drug is discontinued), then it just treats diabetes early. But if the effect lasts, then it may be more useful…You could say it incontrovertibly delays diabetes at a cost of weight gain, a small but worrisome increase in heart failure, and an expense."
- *U.K. #2:* "DREAM will not change my practice. The heart failure is concerning. Once you have it, you 'scar' the patient forever."
- *Spain:* "DREAM was not conclusive, so it won't change my practice (in pre-diabetes), but my TZD use will go up in diabetic patients."
- *Canada #2:* "DREAM won't change my practice because pre-diabetics are not sick, but it gives me more assurance using a TZD in Type 2 diabetics or to use a TZD early in treatment. It may, in fact, reduce the possibility of progression to complete failure of the pancreas."
- *Greece:* "We need more data on heart failure, but I strongly believe prevention is the best way. I will prescribe Avandia if a lifestyle change is not possible."
- *U.K. #3:* "DREAM confirmed that a TZD can prevent diabetes, but I won't use it in pre-diabetics because I don't screen for that. Primary care doctors will ***never*** use it, given the heart failure, which is a major concern."

Other studies

Further analyses are underway that may shed more light on the DREAM results:

- **A three-month post-trial washout period.** This is expected to tell whether the positive effects are sustainable. These results will be presented at the International Diabetes Foundation (IDF) meeting in Capetown, South Africa, December 3-7, 2006.
- **A heart failure study** with echocardiograms and neurohormonal tests of the patients who got heart failure on DREAM plus a meta-analysis of the literature. Dr. Yusuf admitted that if the heart failure is found to be structural, the risk:benefit analysis would be worse for Avandia. The results from this are expected at the American College of Cardiology 2007. Dr. Yusuf said, "If the effects are neutral, it is good news. If we find no

structural effect, that is good…The fact that we have not seen a death could be a play of chance, but it is reassuring. The prognosis (for these heart failure patients) may be very different from naturally-induced heart failure." Prof. Holman added, "When heart failure appears out of the blue, it is usually bad news…but here it may be reversible…It is a worrying issue because it is potentially damaging…but with follow-up studies, perhaps we could finesse the management of the drug."

- **A subset of participants who were evaluated for the reduced risk of atherosclerosis.** Data from this analysis will be presented later this year, but it was not announced where.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGS

AMYLIN/LILLY'S Byetta (exenatide)

The good news is that Byetta has gotten off to a great start in the U.S., and European doctors are impressed with its results. Cost will be an issue for use in Europe, but most sources said they plan to use it.

The bad news is that questions have been raised recently about two things: (1) rash and (2) a small number (~22) cases of pancreatitis that have been reported to the FDA in Byetta patients. An Amylin official denied there was any rash but another source confirmed that there have been a few cases of rash that improved with discontinuation of the drug. At least one patient got it again on re-challenge, and a couple of patients have systemic rashes but no Stevens-Johnson Syndrome (SJS).

Amylin and Lilly officials insisted there is no signal of a problem with the pancreatitis, that it is the same as the background rate. According to several articles on the history of Byetta, the victims of Gila monster bites can develop pancreatitis due to over-stimulation of the pancreas. It is the gila monster venom from which exenatide (exendin-4) was discovered. Is there a link here? A U.S. doctor speculated that the pancreatitis could be gallbladder-related "since gallbladder disease is a relatively common side effect with sudden weight loss." European regulators reportedly have asked the companies to watch/monitor pancreatitis, but do not intend to hold up approval over the issue.

The typical doctor at EASD did not appear aware of the pancreatitis issue, but **most experts had heard about it**, and several had comments, including:

- *U.S.:* "We are seeing an odd case of pancreatitis here and there. I'm not sure if it is related. The community is not discussing it yet. If it is a problem, think what that means for exenatide LAR!"
- *Denmark #1:* "In one case the patient was given a provocation (re-challenge) test, and it was found the pancreatitis was truly from the treatment (Byetta). We have to assume it is causal, but I think it was an idiosyncratic reaction. I can't see the link…It could be the effect of exendin instead of GLP-1, but I think that is unlikely. People do develop pancreatitis."
- *U.K.:* "The regulators are watching this closely. The number of cases of abdominal pain also needs to be considered. If we expand the definition of pancreatitis to include abdominal pain, there are more cases. We can't dismiss it as noise. We need to continue to watch it, but it hasn't risen to the level where we need to take action about it."
- *Denmark #2:* "It's just noise. It has nothing to do with Byetta."
- *Sweden:* "We are watching it. It will delay European approval of Byetta."
- *South America:* "It is not noise…But it could be idiosyncratic, though I'm not saying that is the case. Trial patients are carefully selected and the numbers are small, so something that comes up in clinical practice has to be watched."

Among physician comments about Byetta were:

- *California:* "Patients who don't lose weight quit Byetta, but I haven't seen many patients quit yet."
- *Greece:* "In one year, I could see 20%-30% of my Type 2 patients being on Byetta, mostly my obese patients."
- *Italy #1:* "The pancreatitis was totally unexpected and quite surprising. It could be a coincidence or perhaps it is from improper use."
- *France:* "Byetta will be for very obese Type 2 diabetics who are failing oral agents."
- *Italy #2:* "I think the pancreatitis cases need to be carefully examined."

AMYLIN'S exenatide LAR

This long-acting form (once weekly) of Byetta has been in development for a while, but the company insists it is making significant progress.

Asked about injection site reactions, an Amylin official said, "There were not many (in a 15-week trial in Type 2 patients), but it was a small trial, so we can't project too far in the future how safe and robust this platform is…but in 30 patients treated with LAR, there were no ulcerations or skin breakdown…There was some mild pruritis and bruising in 1-2 individuals, but that was equally across the three treatment groups. Unfortunately, we need a large trial with more patients to get a true sense of the skin reaction with this type of platform."

Asked about the size of the LAR needle that will be used in the Phase III trials, a company official declined to answer. Asked if there are supply issues, he said, "It is difficult to

manufacture, but we can make enough for the Phase III trials, and I think we have solved the issue for manufacturing a commercial batch." The Phase III trial in Europe is expected to start by the end of 2006.

NOVO NORDISK'S liraglutide

Novo Nordisk claims once-daily injections of liraglutide have better weight-lowering ability than BID or TID Byetta, and the weight loss with liraglutide is ***not*** a function of any nausea side effect, though there are no head-to-head studies of the two drugs. In fact, Novartis showed data from a 14-week study of 165 patients indicating that patients without nausea actually lose more weight than patients who do get nausea or vomiting.

Novo Nordisk sources also pointed out that liraglutide showed very little hypoglycemia in a meta-analysis of three trials.

Liraglutide and Weight Loss

Measurement	Placebo	Liraglutide 0.65 mg QD	Liraglutide 1.25 mg QD	Liraglutide 1.90 mg QD
Change in weight from baseline in all patients	-1.8 kg	-1.7 kg	-2.6 kg	-3.0 kg (p<.05 vs. placebo)
Change in weight from baseline in patients ***without*** nausea or vomiting	-1.4 kg	-1.6 kg	-2.5 kg	-3.2 kg (p<.01 vs. placebo)

Liraglutide and Hypoglycemia

% of patients with hypoglycemia	Liraglutide n=347	Glimepiride n=26	Metformin n=70	Liraglutide + metformin n=30
Minor events	0	2.8%	0	2.8%
Major events	0	0	0	0
Overall	0	8.3%	0	2.8%
Symptoms only	0	5.6%	0	2.8%

Effect of 14 Weeks of Liraglutide on Blood Pressure and Biomarkers of CV Risk in Type 2 Diabetics

Measurement	Placebo	Liraglutide 0.65 mg QD	Liraglutide 1.25 mg QD	Liraglutide 1.90 mg QD
Mean DM duration	5.5 years	6.9 years	6.8 years	5.7 years
BMI	30.4	28.9	31.2	N/A
Primary endpoint: HbA1c	N/A	Down ~1.2 (p<.001)	Down ~1.6 (p<.001)	Down ~1.7 (p<.001)
Weight loss	---	---	---	Down 1.2 kg vs. placebo
HOMA insulin resistance	Down ~10	Down ~13	Down ~17	Down ~24
TGL vs. placebo	---	-19% (p=.03)	-15% (p=.09)	-22% (p=.01)
CRP vs. placebo	---	-3% Nss	-12% Nss	-20% Nss
PAI-1 vs. placebo	---	-14% (p=0.29)	-29% (p=0.02)	-25% (p=0.05)
SBP change	Up ~1.5 mmHg	Down ~6 mmHg	Down ~4 mmHg	Down ~6 mmHg
BNP vs. placebo	---	-26% (p=0.1)	-30% (p=0.05)	-38% (p=0.01)

A Novo Nordisk official explained that the 1.25 mg and 1.9 mg doses have equal efficacy on glucose, but there is more effect on weight with the 1.9 mg dose. He declined to discuss the injector that will be used for this product but commented, "We are good with injection devices."

There has been no hint of pancreatitis with liraglutide, but the number of patients is relatively small.

A Phase IIIa liraglutide trial has either started or is about to get underway.

Asked what the role will be for liraglutide in Type 2 diabetes, a speaker said, "With liraglutide, we have for the first time proven that a GLP-1 analog significantly increases maximal beta-cell secretory capacity…(Use) depends on the long-term effect on weight. A crucial point of interest is the effect on beta-cell mass. If you can prove that – and I think it will take 1-2 years to show that – then it would be the drug of choice …If you compare 1 week with 14 weeks, the beta-cell increase will be exactly the same."

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

On the positive side, DPP-4s are oral agents with few side effects, and doctors generally agree they are effective. On the negative side, they are weight neutral and do not yet have a clear niche.

While doctors are very interested in this class of agents, which work by increasing incretin levels, many doctors have no idea yet where to use them. Sources said they plan to use them second-, third-, or even fourth-line – after metformin, SUs, and perhaps TZDs. However, by the end of the meeting several doctors were suggesting they may replace SUs in combination therapy with metformin. Comments were:

- *U.S. #1:* "We need prevention trials for DPP-4s…But they won't capture 20% market share the first year because there are so many new drugs coming at the same time…And a big re-education effort is needed."
- *U.S. #2:* "I would use a DPP-4 for Type 2 patients who are thinking about insulin before I use Byetta."

- *Denmark #1:* "I will recommend a DPP-4 plus metformin from the beginning for Type 2 patients…The data we still don't have is metformin + sitagliptin from the beginning of the disease. If that were available, it would be easy to convince general practitioners to use it."
- *Denmark #2:* "A DPP-4 in combination with a GLP-1 would be very interesting, but there aren't data on that. They target the same mechanism, but DPP-4s are neutral on weight, and weight is extremely important for cardiovascular endpoints."
- *U.K.:* "I'm not sure where it would fit, but probably third-line. No one will take away metformin, but it could replace SU, but SU has few side effects, works quickly, and is cheap…DPP-4s will be primarily a primary care drug."
- *Germany:* "Use in one year could be more than 10%. But the companies need to do outcomes studies to get better use in Germany. Long-term the fate of DPP-4s will depend on whether they show an effect on beta-cell mass."
- *U.S. #3:* "The beta-cell protection gives them a role, and they may replace SU second-line, but because of the weight loss, Byetta may get used before a DPP-4…DPP-4s need to carve out more of a niche. They drop blood sugar, but I'm not convinced they have the muscle of SU. They need better product definition. However, 10%-15% of patients could be on one in a year."

MERCK'S Januvia (sitagliptin)

A Merck official described Januvia as a first-in-class agent, saying the drug has been registered and is being sold in Mexico. The company declined to say what the price is in Mexico, but one Mexican pharmacy said it is charging 542 pesos for a 28-day supply, which translates to $1.77/day, and another said it has three doses (25 mg, 50 mg, and 100 mg) all for the same 28-day price of $80 (or $2.86/day). Of course, this doesn't mean that either of these will be the price in Europe or in the U.S.

Januvia 100 mg QD has been submitted to the FDA and has a mid-October 2006 PDUFA date. Currently, 43 Januvia studies have either been completed or are underway, with four more due to begin later this year. About 1,100 patients have been treated with Januvia ≤1 year, but officials would not say how many have been treated ≥1 year.

In addition, a BID combination tablet, MK-0431a, has been submitted to the FDA in 2 doses, and the PDUFA date for that is March 2007:

- Januvia 50 mg + metformin 500 mg.
- Januvia 50 mg + metformin 1000 mg.

Comments that Januvia speakers and European doctors made included:

- "Ultimately you may require as many as four different agents to achieve the kinds of glucose levels you want."
- Januvia is renally eliminated, so a dose reduction is suggested in renally-impaired patients.
- "We all need to become more aggressive in the management (of diabetes). Many patients will require two- or three-drug therapy. Many patients with Type 2 diabetes will see this as an option…It works well with metformin, and it is quite well tolerated…Certainly, as a choice of monotherapy, this provides some important benefits, but many patients will be on combination therapy."
- *U.S.:* "This will give us a choice…This will be a new alternative…This won't be the choice for all doctors for monotherapy, but it is another drug…It has weight neutrality, which may be important in some patients…TZDs may have aspects that make them No. 1 or metformin No. 1…This has a different profile and is another option to consider for monotherapy or combination therapy."
- *U.K.:* "All the guidelines say to start with metformin unless there is a problem…so many of us who follow the guidelines will use metformin first-line…and the question then is what we add on after metformin."
- "In a subgroup analysis on response, and in some studies, particularly monotherapy studies, patients with <5 years (since diagnosis of diabetes) had a somewhat better response than patients with longer duration (disease), but across the duration…we still saw a very nice response… When we started, we actually expected a loss of effect with longer duration (of disease)…but even patients with fairly long duration of diabetes (up to 20 years), duration is not a very strong predictor of response."
- *Germany:* "It will be more a general practitioner drug than a specialist drug. Uptake will be rapid because we aren't happy with our current options, but people will be reluctant to pay $3 a day for it."

Asked where Januvia will or should be used, a researcher said, "I wouldn't be able to answer yet. It is an addition to our armamentarium…I believe it will have a role as early as (pre-diabetes) because of the potential beta-cell effect…Certainly it has a role as add-on therapy…If the results hold up, it may have a place even in most severe cases before you switch to insulin. I'm not afraid to start insulin, but certainly there is reluctance to do it among patients…Every family physician without real expertise and backup can use it (Januvia)…For (cardiologists) to treat patients with more complex regimens is a problem…so really every physician can treat (with Januvia) in most settings." Another researcher said, "It is obvious that we are moving in a direction that probably we won't stop with one drug when we make a diagnosis of Type 2 diabetes…I am

very impressed with these results…with metformin…and in patients no longer well-controlled with metformin, and then you add it to the metformin. And maybe it will be good in patients who can't watch for hypoglycemia, like the elderly."

Asked if Januvia reduces the side effects of metformin when given in combination with that drug, a researcher said, "There was no statistically significant improvement in GI side effects – no worsening, but not improvement."

Asked how Januvia differs from other DPP-4s (e.g., Novartis's Galvus), a researcher said, "The more obvious things look very similar to me, but there might be differences in specificity…And there might be differences in how they penetrate into different tissues…We think it is very important to block DPP-4 in the intestines."

The new data at EASD were:

1. **Study P020 SU data:** Januvia vs. placebo for 24 weeks followed by 24 weeks of Januvia vs. SU. In the SU phase (which were the new data), researchers reported:
   - As expected, the SU patients gained weight, while Januvia patients lost weight (a difference of 2.4 kg).
   - There was substantially less hypoglycemia with Januvia (0.8% vs. 18.3%).

2. **Study P024:** Januvia vs. SU for 54 weeks, in a per-protocol analysis.

Januvia in Study P024

Measurement	Januvia 100 mg + metformin	Glipizide ≤20 mg + metformin
HbA1c change	-0.67	-0.67
HbA1c <7% at Week 52	62.8%	58.9%
HbA1c change in patients with baseline HbA1c 9%-10%	Up to -1.7%	N/A
Body weight	Down 1.5 kg	Up 1.1 kg
Hypoglycemia	4.9% (p<.001)	32%

3. **P036:** Initial therapy with Januvia co-administered with metformin for 52 weeks. Partial results from this 24-week, randomized, 1,056-patient Phase III trial were presented at EASD, and the full results (including p-values) will be released at the IDF meeting in December 2006. Eligible patients had an HbA1c from 7.5%-11%. Patients with HbA1c >11% were enrolled in an open-label cohort.

NOVARTIS'S Galvus (vildagliptin)

The key news about Galvus at EASD was the ***suggestion*** that adding it to metformin adds to the efficacy of metformin while cutting metformin's GI side effects nearly in half. Novartis officials were careful to call this a possible signal, not a confirmed finding, but they said they are going back to study it. Experts and clinicians agreed that if the finding is born out in a prospective trial, it would make Galvus very attractive as a replacement for SUs, would move its use earlier, and would help differentiate it from Merck's Januvia.

That result came from a 24-week, multicenter, double-blind, randomized, 416-patient, parallel-group, Phase III study. Galvus was added to patients on a stable dose of metformin (average 2109 mg/day).

Novartis officials also were excited about data that when Galvus is dosed for a month (chronically), it increases GLP-1 but also increases fasting GLP-1 and GLP levels, and they are differentially affected in naïve and metformin-using patients.

Asked why Galvus might have this effect in combination with metformin, a Novartis official said, "We have some theories that we aren't ready to share right now because we want to investigate if that is a unique phenomenon or not. We clearly have some ideas and believe this is probably a true finding, and we will continue to examine that." Asked if the effect might be due to gut motility, he said that was a reasonable hypothesis.

A Novartis official said, "In real life, patients rarely get to a maximum metformin dose. People are not pushing metformin as high as they could because of tolerability That is one of the limitations of metformin, so having an alternative that has a beneficial effect would be great…Metformin is foundation therapy. It is an extremely well-established and cheap treatment. Our role with this (Galvus), given its mode of action and the need for more than one drug, is to find another complementary drug to be used with metformin." Another expert said Galvus failed to demonstrate non-inferiority in a head-to-head study with metformin but agreed Galvus is a good add-on therapy to metformin.

Novartis also announced the start of the GLORIUS trial program, a large series of outcomes-focused studies in Type 2 diabetics.

Januvia in Study P036

Measurement	Placebo n=165	Januvia 100 mg QD n=175	Metformin 500 mg BID n=178	Metformin 1000 mg BID n=177	Januvia 50 mg + metformin 500 mg BID n=183	Januvia 50 mg + metformin 1000 mg BID n=178	Open-label cohort: Januvia 50 mg + metformin 1000 mg BID n=117
Change in HbA1c	+0.2%	-0.7%	-0.8%	-1.1%	-1.4%	-1.8%	-2.94%
Achieve HbA1c <6.5%	---	---	---	---	---	~50%	---
Achieve HbA1c <7%	---	---	23%	38%	43%	66%	---

Galvus has been filed with the FDA for both monotherapy and add-on therapy, and the PDUFA date is in November 2006. It was filed with European regulators in July 2006.

Novartis officials declined to discuss any plans for a combination pill with Galvus or to say when outcomes data will be available but suggested that details like these may be available at Novartis's R&D Day on November 28, 2006. An official did say that the company is interested in exploring the use of Galvus in prevention, adding, "I think we can keep patients on treatment without tolerability issues, whether as monotherapy or combination therapy, and that is something we are willing to explore." The company also is studying the drug in elderly patients in many of its studies.

Galvus as Add-On Therapy to Metformin

Measurement	Galvus 50 mg QD n=143	Galvus 100 mg QD n=143	Placebo n=130
Any GI side effect	9.6%	14.8%	18.2%
Any adverse event	63.3%	65.0%	63.5%
Serious adverse events	2.3%	2.7%	4.4%
Primary endpoint: Change in HbA1c	-0.7 (p<.001)	-1.1 (p<.001)	N/A
Change in FPG	-0.2 (p<.005)	-1.0 (p<.001)	+0.7
Weight change	+0.4	+0.2	-1.0
Nausea	2.8%	4.4%	5.0%
Diarrhea	1.1%	4.4%	5.5%

Galvus Monotherapy in Drug-Naïve Type 2 Diabetics

Measurement	Galvus 50 mg QD n=104	Galvus 50 mg BID n=90	Galvus 100 mg QD n=92	Placebo n=94
Baseline BMI	32.9	33.3	32.4	32.6
Baseline HbA1c	8.2	8.6	8.4	8.4
Disease duration	2.1 years	2.1 years	2.4 years	1.6 years
Primary endpoint: Change in HbA1c	-0.8 (p=0.006)	-0.8 (p=0.006)	-0.9 (p=0.001)	-0.3 *
Change in HbA1c in patients diagnosed ≥3 months before enrollment	-0.7	-0.5	-0.7	+0.2
Change in HbA1c in patients with HbA1c >8.0 at baseline *(pre-specified analysis)*	-0.8	-1.3	-1.4	N/A
Change in FPG	-1.0	-0.8	-0.8	+0.1
Change in total cholesterol	Nss	-4.5 (p=0.048)	Nss	Nss
Change in weight	-0.3 kg to -1.8 kg			---
Adverse events				
Serious adverse events	4.9%	4.0%	1.9%	3.2%
Adverse events leading to discontinuation	1.9%	1.3%	3.9%	4.5%
Hypoglycemia	2 patients	0	1 patient	0
Nausea	1.9%	1.3%	4.0%	3.8%
Diarrhea	2.6%	1.9%	1.3%	3.2%
Nasopharyngitis	8% - 9%			8%
Headache	5% - 6%			6%
Dizziness	4.9% - 8.6%			5.1%
URI	1.9% - 6.6%			3.8%

*** This was driven largely by the 16% of patients enrolled within two weeks of diagnosis.**

Asked how Galvus differs from Merck's Januvia, Novartis sources suggested:

- A better reduction in HbA1c from baseline, not just from placebo, in naïve patients and as add-on therapy, though these were not head-to-head studies.
- No uric acid issues have been seen with Galvus.

Asked about long-term data on Galvus, a researcher said, "We have data out to two years, and the tolerability looks the same. It remains excellent."

Other benefits of Galvus were cited as:

- 3%-5% increase in HDL.
- Reduction is LDL and triglycerides, but this is an indirect effect.
- Lack of drug-drug interaction.
- Less edema in combination with Lilly/ Takeda's Actos (pioglitazone) than for Actos alone. A speaker said, "We are investigating this…It is not a delay phenomenon, and we hope it is true."

New data from a 24-week, randomized, multicenter, double-blind, 380-patient, parallel-group study was presented on Galvus as monotherapy in drug-naïve Type 2 diabetics.

Other DPP-4s. There was no news at EASD on any of these:

- **TAKEDA'S SYR-322.**
- **GLAXOSMITHKLINE'S denagliptin.**
- **BRISTOL-MYERS SQUIBB'S saxagliptin (BMS-477118),** which is in Phase III trials.
- **PROSIDION'S PSN-9301.**

INHALED INSULIN: PFIZER'S Exubera

There was a lot of traffic at Pfizer's Exubera booth at EASD. Doctors wanted to see the device and learn more about it, but they were not optimistic about use. The U.K. and Germany are the first European countries to get two new drugs – Pfizer's Exubera inhaled insulin, but financial issues in both those healthcare systems make it difficult to use it as a guide to how drugs will do in the rest of Europe. Sources pointed out that just before EASD the German government basically banned insulin analogs, and doctors were very upset about that.

Pfizer sales reps confirmed that sales have gotten off to a very, very slow start in Germany and in the U.K., the first European countries to approve Exubera. One said, "Doctors are allowed to give it to Type 1 diabetics, but I think it is better for Type 2s…I've worked for Pfizer for many years, and I've never seen the physician and government resistance to a drug that I've seen with Exubera in Germany. The doctors there are anti, anti, anti. And if a doctor writes too many prescriptions, he may personally have to repay the insurance agency. Doctors don't see a real need for it at all."

Physicians complained about the size and cost of the device. Among their comments were:

- *U.K. #1:* "A new NICE review of inhaled insulin is due this fall. In the meantime, there is little use except at very specialized teaching and research-based centers…The device is bulky. Patients ask about Exubera, but I tell them the problems with it, and that ends it."
- *Spain #1:* "I don't think it is very innovative. The dispenser is very big, and it is expensive. Patients don't have a problem with injections – and it doesn't avoid injections entirely."
- *Australia:* "I think it will be years before it ever gets listed (approved) in Australia."
- *Spain #2:* "Exubera could get 30%-50% use in one year."
- *Germany:* "Exubera is very costly, and there is still uncertainty on reimbursement…And doctors have different expectations than patients. In a year it will be used by fewer than 10% of Type 1 diabetics…In Germany it is not a big deal."
- *France:* "In one year, it could be 10%-20% of the insulin market. The question is that patients don't eliminate injections."
- *U.K. #2:* "Inhaled insulin is fine, the issue is the device. It is complicated, too large, and cleanliness is an issue."
- *U.K. #3:* "NICE said inhaled insulin can't be used for Type 2 diabetics, even those on insulin because of the cost. But I'm not in favor of it anyway because the device is cumbersome, and I worry about the accuracy and what happens when a patient gets a cold or has asthma. There are loads of people who can't use it."
- *U.K. #4:* "I'm not using Exubera yet. I want to see more data first."
- *New York:* "The device needs to get smaller. In one year, 3%-4% of patients could be on it."

Pfizer also presented some additional efficacy data on Exubera which indicated that users can maintain good blood glucose control when exposed to second-hand smoke or when they develop a respiratory infection. In an open-label, randomized, crossover study, 28 non-smoking non-diabetic subjects received 3 mg Exubera. Then, a commercial smoking machine was used to simulate levels of passive smoking in a social setting.

Effect of Second-Hand Smoke on Exubera Efficacy

Measurement	Exubera	Exubera after exposure to passive smoke
Mean insulin area under the curve	5,703 µUmin/mL	4,718 µUmin/mL
Mean maximum insulin concentration	41.0 µU/mL	28.9 µU/mL
Hypoglycemic events	1 patient	N/A

A retrospective, pooled analysis of 14 Phase II and Phase III trials in both Type 1 and Type 2 diabetics looked at the effect of respiratory infections on the efficacy of Exubera. The study found the rates of intercurrent respiratory tract infections (iRTIs) were similar whether the patient was on Exubera, subcutaneous insulin, or oral anti-diabetic agents. There were no changes in hemoglobin levels or overall hypoglycemic rates in any treatment group. In Type 1 diabetics, mean FPG and severe hypoglycemia rates increased during iRTIs in both Exubera and SC insulin, but no changes were seen in Type 2 patients. The principal investigator said, "The studies showed that patients taking Exubera are no more likely to develop a respiratory infection than patients using injectable insulin."

OBESITY TREATMENTS

SANOFI-AVENTIS'S Acomplia (rimonabant)

Acomplia which is approved in Europe, is a first-in-class selective cannabinoid-1 (CB-1) receptor blocker. The FDA turned Acomplia down for smoking cessation but issued an approvable letter for it as a weight loss drug. The company has suggested that the FDA wants some form of risk management plan before approving Acomplia, but no details on this have been available. An Acomplia researcher speculated that this will involve ensuring that patients with ongoing psychiatric problems (especially depression or anxiety) or a history of those problems do not get the drug. An Italian doctor thought any risk management program would be aimed at avoiding widespread use. An investigator said, "I was not aware of the need for a U.S. risk management program, but my speculation would be that it has to do with the depression…The company, rightly or wrongly, wants to position Acomplia as a cardiovascular drug."

Asked how long patients can or should take Acomplia, a speaker said, "You can use it forever but…probably you need to discontinue it for two to four weeks every year to see if there is relapse or if it is still working."

Acomplia is already approved in Europe, but it is only on the market in Germany, Denmark, and the U.K. so far. Very few of the doctors from those countries who were asked about Acomplia have started to use it yet, and few had any comments about it or plans to start using it. A U.K. sales rep said most of the interest in the drug has come from doctors treating diabetes, "Mostly diabetologists have shown an interest. Many diabetologists run diet clinics." A U.K. diabetes educator said, "We are using Acomplia for patients with and without diabetes, especially pre-diabetes patients, who are obese – that is, a BMI >30. The drug has been widely publicized, but only a few patients have asked about it. There is a lot of company support for patients taking it. There are help lines, and patients can register and get company support. Acomplia will be more widely used than Xenical (Roche, orlistat) because of Xenical's side effects, but I think fewer than 5% of our patients will be on it in a year."

Other comments included:

- *Germany:* "I'm positive about it because 6 kg of weight loss makes a difference to patients and to the disease."
- *Canada:* "I would use it in mostly obese diabetic patients until I see more effect in Type 2 patients. What we have now – Xenical – is pretty ineffective."
- *Denmark:* "Acomplia has only been out in Denmark for two weeks. I'm using it for patients not responding to intensive dietary treatment. We are trying to see how it works in clinical practice…For me it is a kind of drug for patients who are not happy on, or can't tolerate, other drugs. The only problem is the depression issue, where I'm still a little concerned, so I'm only using it in patients with no history of depression, and I'm also asking patients if they have had any depressed moods or felt any change in mood…I think the depression is a class effect of CB-1 receptor blockers."
- *Greece:* "Acomplia will be big. Obesity is very important in diabetic patients. If we can treat the diabetes and the obesity at the same time, it would be good."
- *Italy:* "When it is available in Italy, it should be used in obese patients, but it is easy to predict that people who only need to lose a little weight will ask to use it. It is a good drug and quite effective…I predict there will be great public demand."
- *U.K.:* "I'm not using Acomplia, and there is no excitement about it – no patient demand. I would only use it in a patient with a BMI >30, but I will use it for those patients. In a year, it could be used by 25% of my diabetic patients."
- *U.S.:* "Acomplia is generating a lot of excitement because it targets obesity. But if it doesn't deliver what is expected, which is a pound a week, it won't take off. It can't be another Meridia (Abbott, sibutramine)."

Bariatric surgery

A large, long-term study, the Swedish Obese Subjects (SOS) Study, looked at the effect of bariatric surgery – gastric banding, gastric bypass, vertical banded gastroplasty (VBG) – on total mortality. The study is following 4,047 patients for up to 20 years. SOS researchers found:

- Markedly reduced incidence of diabetes.
- Marketed increased recovery from existing diabetes.

Swedish Obesity Subjects (SOS) Study

Measurement	Year 2	Year 10	Year 15	Year 20
Surgical patients evaluated	93%	80%	59%	---
Control patients evaluated	83%	72%	73%	---
Number of patients	4,047	3,058	1,963	0
Incidence of diabetes	8%	---	---	---
Recovery from diabetes	20%	15%	---	---

SOS Study Results at 10 Years

Measurement	Surgery n=2,010	Non-surgical controls n=2,037	p-value
Average age	47	46	Nss
Smokers	20%	28%	<.05
Weight loss			
Gastric bypass	-28 kg	Almost no change	---
Gastric banding	-20 kg		---
VBG	-18 kg		---
Safety			
Stroke	79 patients	67 patients	Nss, HR 1.155
Cerebral infarction	42 patients	43 patients	0.8142
Intercerebral hemorrhage	9 patients	9 patients	Nss
TIA	20 patients	18 patients	0.8021
Unspecified stroke	5 patients	3 patients	0.5167
MI	64 patients	87 patients	0.0411, HR 0.715 28.5% risk reduction
Primary endpoint: Overall mortality	101 patients ~10%	129 patients ~14.5%	<.05 23.7% risk reduction
Post-op deaths in first 90 days	5 patients 0.25%	2 patients 0.10%	---
CV deaths	43 patients	53 patients	---
Non-CV deaths	58 patients	76 patients	---
Cancer deaths	28 patients	48 patients	---

- No effect on total stroke incidence.
- 43% (29% unadjusted) reduction in MI.
- 31% (24% unadjusted) reduction in overall mortality, the primary endpoint of the trial, but it took a long time to show the mortality advantage. Dr. Lars Sjostrom of Sweden said, "It took 13 years before it was possible to prove the favorable effect of bariatric surgery. It takes a long time until the effects of obesity treatment show up favorably."
- A reduction in all cancer. The finding was intriguing, but the import will depend on further analysis which is ongoing. An investigator said he was surprised that it isn't primarily breast and/or colorectal cancer, but a reduction in all cancer, "About half the mortality benefit with bariatric surgery could be due to the lower cancer rate."

Dr. Sjostrom said that, in his opinion, as long as other 10-20-year studies have not proven that <15% average weight loss is enough to significantly reduce the incidence of hard endpoints, bariatric surgery should be ***ideally*** considered for:

- All pre-diabetes and a majority of obese Type 2 diabetics.
- Many obese patients with other high risk conditions, such as visceral obesity, lipid disturbances, previous MI, and previous cancer.
- The many, many obese patients with psychosocial dysfunction.

GLUCOSE MONITORS AND METERS AND INSULIN PUMPS

Medicare

An August 2006 meeting of the Medicare Coverage Advisory Committee (MCAC) raised questions about the future of reimbursement for either finger stick strips or continuous monitors in Type 2 diabetics over age 65. Medicare currently pays for as many as 100 glucose test strips a month for insulin-using diabetics and up to 100 strips every 3 months for diabetics not on insulin. The key concerns appear to be:

- Inappropriate use of strips by:
  - Skilled nursing facilities.
  - Home health agencies.
- Inappropriate marketing to Medicare beneficiaries.
- Whether finger stick monitoring was changing treatment.

The panel also discussed continuous glucose monitoring systems (CGMS), and an industry source described that discussion as "fairly negative." He said CMS wants more data and is trying to get companies to do outcome studies. He added, "Companies sometimes think they did their job getting a device covered (by Medicare), but doctors need to get reimbursed (for their time), too."

Non-invasive glucose monitoring

Two Israeli companies presented data on their non-invasive glucose monitors, and both looked very interesting.

- **INTEGRITY APPLICATIONS' GlucoTrack.** This device, which clips on the ear, uses ultrasound, conductivity, and heat capacity to measure glucose levels. So far, the device has been tested in 71 patients. Initially, it will be a spot measure, but the company plans to have a continuous monitor in the future. It needs to be re-calibrated once a month and takes about 1.5 minutes for the display to report the glucose value, though the company is working to get this down to 30 seconds.

Clinical trials are expected to start by the end of this year in Israel and Spain and in 1H07 in the U.S., where it will require a PMA. About 150 patients will be enrolled in each country, and studies will be done simultaneously in three environments by two groups (one group for a week and another for 45 days):

- At a clinic with the measurement done by clinic staff.
- At a clinic with the patient doing the measurements.
- At home with patients doing measurements with Gluco-Track and an FDA-approved meter.

A company official said their first goal is the European market, and they hope to launch there in 2H07 through distributors. Pricing was not announced, but he said, "Life-cycle costs will be less than current devices."

- **ORSENSE'S NBM-100.** This device, which clips on the thumb, is based on the company's proprietary "occlusion spectroscopy, which uses optical signals across the finger. The device overcomes, according to company claims, the low signal-to-noise ratio and non-specificity. Analysis of the signal reportedly provides the sensitivity necessary to measure blood glucose and other analyte concentrations. Phase I trials are complete, and new trials are expected to start in Denmark in 4Q06, with U.S. trials to start soon after that. So far, it has been tested in about 400 patients.

The company presented a poster on the results of a 24-hour, 27-patient, multicenter trial of:

- A simulated home-use study (in an outpatient ward) vs. measurements with Abbott's FreeStyle meter.
- In-patient use at a medical center vs. venous blood glucose.

Based on a total of 4,111 measurements, the company reported that 94.7% fell within Clark error zones A and B. The mean relative absolute difference in glucose levels was 19.5%.

Continuous glucose monitoring systems (CGMS) and insulin pumps

European doctors were far less interested in or enthusiastic about either continuous glucose monitors or insulin pumps

than American doctors. Most cited the cost of both types of devices as the key deterrent to use.

In Italy, only 3.5% of Type 1 diabetics are on an insulin pump, compared to >20% in the U.S. An Italian doctor said the two top reasons for a Type 1 diabetic to go on a pump are active glycemic control and pregnancy. In the U.K., NICE a few years ago issued a preliminary ruling that pumps are appropriate for only about 2% of the population, but a final decision is not expected until spring 2007. An industry official said, "NICE has taken a glass house ceiling view…We are working with experts and NICE to revise this." Another industry source said, "Use is still small because of the reimbursement issue. Each device has to be handled on a case-by-case basis." Another industry source said, "We have more data now, and doctors are speaking out (in favor of the devices)." A U.K. doctor said, "I don't use CGMS because it is too expensive."

A closed loop system is considered almost the holy grail of insulin pumps, but perfecting one has proven very difficult for all companies. Andres Joehle, Vice President of Diabetes for Medtronic Western Europe, said Medtronic is currently working on an external system, "That is most reasonable and cost-effective at this point…But we are working on closing the loop – a semi-closed loop at night while patients sleep. It is not there yet…Think about liability. We want to be 100% sure the system works as needed."

Asked why the uptake of insulin pumps has been so slow, especially in Europe, an Italian diabetologist said, "I think it is the spread of knowledge. I believe if physicians were more exposed (to pumps) and more educated about them, probably the penetration would increase. Sixty percent of patients at my center are on a pump…We need to overcome the problem that sensors are not reimbursed by the health system. This is an important problem, and I think it is also the reason why we have low percentage of patients treated with an insulin pump…I think over the next year and in the near future, the number of patients will increase…but we have this problem to get the sensor to be reimbursed by the health system."

Asked how many patients stay on insulin pumps, a speaker said, "Very few pediatric patients return the pump. In my center, 1 in 500 has returned it. But among adults, especially the elderly, the return rate is ~10%. Those are the patients the insurance companies love." Another speaker said, "In young patients, very few decline a pump. It is like a mobile phone – fancy – and they don't have to give injections…Young people are usually very happy."

Asked if more patients are opting for a pump with the introduction of CGMS devices, a speaker said, "There are no data, but my view is probably yes because patients measuring blood glucose four times a day are suddenly very happy…Pre-prandial glucose is usually fine, but they see that, especially after meals, they are extremely high, and they didn't know or didn't want to know it before. Now that they are faced with the fact that it is very high, they may decide to use an insulin pump." An industry source said, "CGMS will increase pump use because success begets success…Pump users test more, and they like the positive feedback of good numbers. And they like the ability to change things (with a bolus) if the numbers are bad."

Among the remaining questions about CGMS devices are:

- Analytical performance and clinical accuracy.
- Indications and patient selection.
- Cost-effectiveness and reimbursement.
- Hypoglycemia warnings and prevention (optimum settings of glucose threshold).
- Period and mode of monitoring (continuous or periodically). Most doctors said they don't believe that most patients will wear these devices continuously. Rather, they suggested that they are more likely to be used intermittently, and one source referred to CGMS as a kind of "Holter monitor" for diabetes. An industry source said, "I'm not convinced people will see this as a lifetime use device until they get one level better, but intermittent use – say 20 days to understand patterns – will be very helpful…Typically, people wear them now for a few weeks a few times a year."

Three CGMS devices are currently available:

➢ **DEXCOM'S STS.**

➢ **ABBOTT'S FreeStyle Navigator.** One of the key features of this device is its alarms, but there were a number of unanswered questions about the alarms, particularly false alarms, at the American Diabetes Association meeting in June, and Abbott officials sought to provide the data at EASD that they didn't have then.

Navigator has two types of alarms:

1. **Threshold glucose alarm,** which alerts the user when the glucose is below a set low glucose threshold value or above a set high glucose threshold value. This can be set from 60-139 mg/dL (default 65 mg/dL).
2. **Projected glucose alarm,** which alerts the wearer before reaching a low or high glucose threshold value. The projected alarm provides a warning that hypoglycemia or hyperglycemia will occur if the current trend continues. It can be set from 140-300 mg/dL (default 300 mg/dL). It uses the current glucose and the rate of glucose change over the previous 15 minutes to calculate the trend.

There are also three ways the alarms can be provided: visual, sensory (short, medium, or long vibration), or audible (high, medium, or low beep). All alarms continue until the user acknowledges the alarm. When acknowledged, alarms will reassert themselves if the conditions continue. Audible alarms may be muted for 1 hour (except low alarms), but the user will

continue to get vibratory alarms. Alarms may be switched off individually.

In the alarm study, there were:

- 173 glucose reference events were observed, the equivalent of an average of 5.2 events per week per subject. That translates to ~1 occasion per week when the system fails to detect glucose falling <70 mg/dL.
- 167 Navigator alarms were observed, the equivalent of an average of 5.0 alarms per week per subject. That translates to ~1 occasion per week when the device falsely alarms subjects at the 70 mg/dL level.

Asked if BMI has much influence on where the sensor was placed, an expert said, "Not really…There didn't seem to be much difference in terms of insertion. It really was patient specific on what they liked, not their body make-up or composition. Some preferred the abdomen, and others liked doing it in the arm. It is really more a preference than any make-up or composition issue." An Abbott official said, "We did see a little relationship (between BMI and accuracy). The higher the BMI, the better the performance…(But) performance overall was the same on the arm as the abdomen."

Navigator Alarms in Home Use

Alarm reading	Specificity
Hypoglycemia at 65 mg/dL alarm threshold	
Alarm confirmed by blood glucose monitor	84.4%
False alert rate	15.6%
Hyperglycemia at 300 mg/dL alarm threshold	
Alarm confirmed by blood glucose monitor	99%
False alert rate	0.2%

Navigator Alarms

Alarm reading	Sensitivity n=167 events	Hypoglycemic event sensitivity
Threshold alarm only, true alert	28.3%	53.5%
Threshold projected alarm, true alert	32.9%	22.3%
Projected alarm only, true alert	18.5%	3.5%
No alarm, accurate glucose	16.2%	20.5%
No alarm, missed alert	4.0%	0.2%
Alarm reading	**Night time sensitivity**	
Projected for threshold, true alert	79.8%	
No alarm, missed alert	20.2%	
Alarm reading	**Specificity n=173 events**	**Hypoglycemic event specificity**
Threshold alarm, true alert	79.0%	87.2%
Alarm, accurate glucose	13.8%	11.9%
Alarm, false alert	7.2%	1.1%

Asked about the need for a 10-hour calibration every five days when the sensor is changed, Joe Bugler, Director of Clinical Affairs for Abbott Diabetes Care, said, "In theory, someone could wear two systems, and overlap that 10-hour period, but I'm not sure that is very practical. In practice, we find a lot of people insert it in the evening, and then calibrate in the morning, so they miss one night in five in that context."

Asked if the accuracy improves if the number of calibrations is increased, Bugler said, "There is a law of diminishing returns. The number of calibrations is fairly optimized for five-day wear. Further calibrations don't really benefit." A Navigator investigator added, "If people pick a time to calibrate where glucose is changing rapidly, that could diminish accuracy."

Asked if the device can be used in a hospital intensive care unit, Bugler said, "That is an avenue we are starting to explore. The initial device is designed for home use, but the potential in the acute environment is high. We just started some very provisional feasibility studies to understand the performance in those environments. It is our plan in the future to extend the product." Abbott also is planning outcomes studies.

One interesting difference between Navigator and the other devices on the market: Navigator is seeking approval for 5-day wear, while the others are 3-day wear. However, the others generally can be stretched to five days by resetting the monitor. While Navigator is designed to last the full five days, it cannot be stretched beyond that; the screen goes blank at five days (122 hours).

➢ **MEDTRONIC'S Guardian RT** (and the MiniMed Paradigm Real-Time system which integrates Guardian and Medtronic's insulin pump). A German doctor said, "I have Guardian myself, but there are too many false alarms. We use it for inpatient training. It is a very good education tool, but no patients have bought it for themselves." A U.K. doctor said, "I've started Guardian on select patients, particularly 'brittle' diabetics, pregnant women, pump patients, and patients with frequent hypoglycemia. It's too early to say whether use will be intermittent. In a year <5% of my Type 1 patients will be on it. It's a niche product – a nice idea – but there are a lot of expensive products that are a good idea."

Asked about the outlook for CGMS devices like Guardian, a U.K. sales rep said, "Hospitals prefer (Medtronic's) CGMS Gold so patients can't see and respond to the read-out, but they get an idea of what the patient does. A few patients are getting Guardian, and they generally use it intermittently, perhaps one or two weeks or when they are ill or change medications. Cost is a big issue." A Medtronic official said, "We have no assessment yet on where users are coming from, but once patients try it, they fight to keep it. We are targeting Type 1 diabetics – both pump users who may upgrade (to Paradigm) and patients on multiple daily injections. About 60% of Guardian users are pump users…I think Guardian will boost pump usage…Guardian sales have been pretty good in the Netherlands because of private insurance, which covers it when patients request the device…In the future, we may see a

co-payment for coverage, where the pump would be covered but not the sensor or meter."

Medtronic has three outcomes trials – STAR-1, STAR-2, and STAR-3 – that the company hopes will aid in obtaining European reimbursement. The results of STAR-1 should be available by the end of this year. STAR-2 is an interim trial, and STAR-3, a large, two-year, randomized trial, is starting now. The primary endpoint in STAR-3 is change in HbA1c and it compares multiple daily injections to a Paradigm (a sensor-augmented pump).

JOHNSON & JOHNSON/ANIMAS

Animas reportedly has four different projects underway. An official said, "I think CGMS is great, but people need realistic expectations. They think this is the end of finger sticks, and it isn't. I think of it as the 'Holter monitor' of diabetes. We will be in clinical trials with a device by the American Diabetes Association (ADA) meeting in 2007, with data probably at ADA 2008."

What would she like to be different from current devices?

- Labeling that it could replace a meter – that is, not require calibration and be reliable.
- Accuracy in hypoglycemia readings, which she said is where current devices fail.
- Short warm-up time so it will be useful the first night.
- Tissue sparing so spots don't get used up on the body.

MISCELLANEOUS

HOME DIAGNOSTICS' private label strips

A knowledgeable source predicted that competitive bidding will have little effect on the meter/strip business in the U.S. because it is "only volume pricing."

He thought Home Diagnostics could do well in the private label market if it can sell to channels like Wal-Mart, "Is it the best strip? No. And the market is a little crowded. Home Diagnostics is trying different distribution channels (from the big companies). The Big 4 won't sell through Wal-Mart because that would hurt their business with the big drug store (pharmacy) chains…J&J strips use a photometric method for the hospital and electrochemistry for home use. Bayer, Abbott, and Roche all use electrochemistry. Home Diagnostics' technology is comparable. All of it is comparable."

NOVARTIS'S FTY-720

A poster from Japan reported on a cell-line study into the role of fingolimod – an oral S1P receptor modulator which is being developed as an oral therapy for multiple sclerosis – on focal adhesion and adherens junction remodeling associated with actin redistribution under both normoglycemic and hyperglycemic conditions. The researchers concluded that fingolimod may play a pivotal role in ameliorating endothelial barrier function disturbed by hyperglycemic challenge, implying the possibility of fingolimod as a therapeutic treatment for diabetic vascular disorder.

ROCHE'S CERA (continuous erythropoietin receptor activator)

New data on this potential competitor to Amgen's Epogen and Aranesp (darbepoetin) and Johnson & Johnson's Eprex/Procrit was presented at EASD in three posters. Roche submitted a Biological License Application (BLA) to the FDA in April 2006 for the treatment of anemia associated with chronic kidney disease (CKD), including patients both on and off dialysis.

- A subgroup analysis of the 673-patient Phase III MAXIMA Phase III trial of IV CERA (Q2W or Q4W) in dialysis patients. The subgroup analysis compared ESRD patients with diabetes to those without diabetes and found no difference in efficacy (stable hemoglobin) or adverse events with CERA.
- A subgroup analysis of the 572-patient Phase III PROTOS trial, looking at the efficacy of CERA by diabetic status. The analysis found subcutaneous CERA was equally effective in maintaining stable hemoglobin following conversion from 1-2/week epoetin in diabetics as in non-diabetics.
- A pooled analysis of the MAXIMA and PROTOS studies, looking at efficacy and safety based on diabetic status. In this analysis, both IV and subcutaneous CERA had the same efficacy (stable hemoglobin levels) in diabetics as in non-diabetics.

Among other points presenters made were:

- The subcutaneous dose of CERA is the same as for the IV dose, which is not true of other EPOs.
- The starting dose for CERA is equivalent to 200-400 U of EPO, but the conversion factor has not been finalized. An expert said, "Roche still has to pull all the trials together and come up with a dose and conversion factor."

VALERITAS' h-Patch

This daily, disposable micro-infusion transdermal patch delivers both selected bolus doses and 24-hour basal insulin through a small, hidden needle. It is designed to be worn for one day and then replaced. The company has 510K approval and is planning to launch in 2007. A source at EASD said sales at first will be to hospitals and long-term care facilities.

An industry source thought this device – or another patch – might be useful as a "tester" for patients to use before buying an insulin pump, but he doubted there would be much long-term use because of skin irritation and cost. Another industry

source said, "No one has been able to deliver insulin intra-dermally."

Among the questions sources had about this product and the technology were:

- What safeguard is there against an accidental bolus? If the device is jarred or punched by mistake, will a bolus be delivered?
- Can it be titrated?
- Will patients use up sites with daily patch changes?
- Is it reliable?
- How much skin irritation is there? This is a common patch issue.
- What is the variability from punch to punch in the bolus?
- Will a constant needle be painful or uncomfortable for the patient? What is the size of the needle?
- What are the intra-individual and inter-individual variations?

Other sources suggested that a patch could capture a good share of the overall insulin-using diabetes market if it was truly shown to work, but they were dubious about patches for several reasons:

- "Patients care more about eliminating finger sticks than the insulin needle, especially with pens."
- *Canada:* "A patch would be very popular with patients …Truck drivers on injected insulin can't drive a truck into the U.S., and maybe a patch or inhaled insulin will be accepted."
- *Greece:* "It is a more physiological way to administer insulin, and it would be very good for children. I'm in favor of patches. I would see it taking 10%-15% market share in a year."
- *Australia:* "It is interesting. I think acceptance would be pretty slow unless it is as reliable as injectable insulin."
- *Germany:* "It will be difficult. PK and absorption will be issues."
- *U.S.:* "I'm not impressed. If there is local irritation, people won't like it. And there is the hassle factor. It is less attractive with the growth in use of pen injectors."

♦