Trends-in-Medicine

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by Lynne Peterson

SUMMARY

New drugs recently approved and in development were a hot topic at EASD.

♦ **DPP-4s:** Data mounted on the safety and efficacy of two DPP-4 inhibitors – Merck's Januvia, Novartis's Galvus – but questions were raised about hypertension with Bristol-Myers Squibb's Onglyza, and efficacy was unimpressive with Takeda's alogliptin.

♦ **GLP-1s:** The data on Novo Nordisk's liraglutide was very good, but positing vs. Lilly/Amylin's Byetta and once-weekly exenatide will be key. Doctors are watching the pancreatitis with Byetta but are not too concerned – yet.

♦ **Insulin:** The data on Biodel's Viaject insulin were controversial, and a study found continuous glucose monitors (CGMs) effective only in adults age ≥25.

♦ **Obesity:** Diabetes doctors feel this is now back in their realm, and they are waiting for more data on several drugs.

♦ **SGLT2 inhibitors:** Bristol-Myers Squibb and AstraZeneca have an education hurdle with dapagliflozin.

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EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD)

Rome, Italy
September 7-10, 2008

EASD was a great meeting, despite the challenge of the location and design of the new Rome convention center. It is an active time for diabetes medication development, and there were interesting findings on DPP-4s, GLP-1s, insulin, continuous glucose monitors, obesity medications, SGLT2 inhibitors, and more.

HIGHLIGHTS

BIODEL's Viaject, insulin: The company presented 2 posters – one in Type 1 diabetes and one in Type 2 diabetes. Both studies were done in the U.S., Germany, and India. The company apparently didn't like the results in India in the Type 1 trial, so they presented only the data from Germany and the U.S. in that poster. In the Type 2 trial, I guess they didn't have the same problem, so the data appear to be from all three countries. Obviously, you can't slice and dice the data this way and get away with it. My opinion: you can't put all the blame on India.

BRISTOL-MYERS SQUIBB/ASTRAZENECA's dapagliflozin, an SGLT2 inhibitor: The data look interesting, but doctors indicated they want a lot more data to convince them that this class is both effective and, even more importantly, safe. The companies have a big education hurdle, but they were working on it at EASD.

BRISTOL-MYERS SQUIBB/ASTRAZENECA's Onglyza (saxagliptin), a DPP-4: There may be a hypertension safety signal. There is a slight increase in the incidence of hypertension with all saxagliptin doses in both trials presented at EASD, though a company official insisted this was due to investigator reporting and not a problem seen across the saxagliptin program. I'm trying to get more on this.

LILLY/AMYLIN's Byetta (exenatide), a GLP-1: Experts are not convinced there is a pancreatitis problem with Byetta. Though they think the issue warrants observation, they all predicted that it will not prove to be more serious than background noise. They said it is not impacting prescribing of Byetta. However, most also predicted that the issue will cause regulators to take a tougher look at newer agents – and the newly announced FDA advisory panel (March 2, 2008) for Novo Nordisk's liraglutide was cited as one example of this.

LILLY/AMYLIN's exenatide LAR, a GLP-1: Experts predicted that this drug will face a higher hurdle – and perhaps a longer approval process – because of the pancreatitis reports with Byetta. However, company officials insisted there has been no pancreatitis in the LAR studies – at least so far. There has been some controversy at EASD over the release in ***The Lancet*** of a 30-week study in which LAR beat Byetta BID. A ***Lancet*** press release indicated this was data to be presented at EASD, though the data actually was presented at the American Diabetes Association (ADA) meeting, and EASD officials were unaware of ***The Lancet*** article or the presentation at EASD. The actual presentation at EASD was primarily the 22-week extension of that 30-week study.

MERCK's Januvia (sitagliptin), a DPP-4: The data looked good, none of the safety issues that Novartis's vildagliptin or saxagliptin face. Plus, the company is running 2 trials in insulin using diabetics that have the potential to be very important (expect data at ADA next year). Their hope is that Januvia will cut hypoglycemic events in insulin diabetics.

NOVARTIS's Galvus (vildagliptin), a DPP-4: A new pooled safety analysis found this DPP-4 safe and effective in patients with mild renal impairment. There were no differences in adverse events based on renal sufficiency status in patients taking Galvus BID. The data in moderate renal impairment patients also looked good, but the numbers were small and no firm conclusions could be drawn. The company is conducting a trial in these patients to further investigate this, but a Novartis official predicted the results will confirm the 50 mg BID dose is safe in these patients as in patients with mild renal impairment.

NOVO NORDISK's liraglutide, a GLP-1: Data were very good. It will all boil down to marketing. There is a distinct QD vs. BID advantage to liraglutide over Byetta and perhaps better efficacy. The question will be whether this is enough to get more doctors to prescribe – and more Type 2 patients to use – an injected drug.

TAKEDA's alogliptin (SYR-322), a DPP-4: The efficacy data at EASD were unimpressive. The effect on HbA1c in Type 2 diabetics not on insulin appears to be much less potent than with other gliptins (about half the effect). The safety data showed no signals. Other data in Type 2 diabetics on insulin showed the drug has an effect on HbA1c but only the high dose (25 mg QD) had an effect on fasting plasma glucose. In Germany, Takeda reportedly plans only to sell the combination of alogliptin + Actos.

OVERVIEW

The Diabetes Impact Survey, sponsored by Merck, evaluated the economic and social impact of Type 2 diabetes by polling healthcare providers and patients in France, Germany, the U.K., Canada, Mexico, and India. Full results will be presented at World Diabetes Day later this year. Preliminary results were presented at EASD from 565 healthcare practitioners and 402 Type 2 diabetics from Europe and Canada:

- 33% of patients reported diabetes-related complications, and ≤10% had been admitted to a hospital at least once in the last 12 months for diabetes or diabetes-related complications (most commonly eye problems and/or loss of sensation in the feet).
- Many patients regularly missed treatment doses. Up to 20% of patients missed at least one dose a week, and ~10% reported missing a dose 2-4 times a week. The most common reasons cited for not taking a medication as directed was having too many pills to take, fear of side effects, and lack of understanding of the importance of daily dosing.
- 40% of European and 46% of Canadian respondents were estimated to be at or below their target HbA1c level.

Dr. Anthony Barnett of the University of Birmingham, U.K., said there are several things that can and should be done:

1. Improve patient understanding of glucose measurement.
2. Ensure patients have access to key healthcare providers, with more frequent and longer consultations.
3. Help patients adhere to treatment with more QD dosing and better therapies. He said, "If I have diabetics who experience a hypoglycemic event, they are not interested in getting their HbA1c down to 6.5; they are more interested in preventing hypoglycemia."
4. Improve access to newer treatments. Almost all healthcare professionals cited restrictions on prescribing. Nearly half of healthcare professionals reported regularly prescribing their patients newer drug classes, but they said only ~4% of their patients were receiving drug treatment with these newer products.
5. Re-evaluate treatment protocols to emphasize more combination therapy and earlier therapy. "I think there are really gross limitations put on our prescribing abilities…I don't think we necessarily need to redesign protocols but they do need to include the new drugs. I think we need to put pressure on government and people who hold the purse strings to be a little more sensible on the types of limitations they put on us…I do think it is incumbent on industry to produce good pharmacoeconomic data, to show that their new drug is cost effective…Industry really has to get wise to that."

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

BRISTOL-MYERS SQUIBB/ASTRAZENECA's Onglyza (saxagliptin)

In two 24-week Phase III studies presented at EASD saxagliptin significantly reduced HbA1c, fasting plasma glucose (FPG), and postprandial glucose (PPG) when added to a sulfonylurea (SU) or a thiazolidinedione (TZD) in Type 2 diabetics when compared to placebo added to either an increased dose of SU or a stable dose of TZD. There were not enough data on renal toxicity or skin reactions to compare this to Novartis's FDA-troubled Galvus (vildagliptin).

- **Sulfonylurea study.** This was a 24-week, double-blind, placebo-controlled, three-arm, parallel-group, multicenter, international trial which compared saxagliptin (either 2.5 mg or 5 mg) plus a submaximal dose of glyburide (7.5 mg) to glyburide 10 mg alone in 768 Type 2 diabetics.
- **TZD study.** This was a 24-week, multinational, randomized, placebo-controlled, parallel-group, double-blind, three-arm study of saxagliptin in patients on a stable dose of either GlaxoSmithKline's Avandia (rosiglitazone, 4 mg or 8 mg/day) or Takeda's Actos (pioglitazone, 30 mg or 45 mg/day) in 565 Type 2 diabetics.

24-Week Results of Phase III Trials of Onglyza in Sulfonylurea Patients

Measurement	Onglyza 2.5 mg + SU 7.5 mg n=248	Onglyza 5 mg + SU 7.5 mg n=253	Placebo + SU 10 mg n=267
Primary endpoint: Change in HbA1c	-0.5% (p<0.0001)	-0.6% (p<0.0001)	+0.1%
Secondary endpoint #1: Change in FPG	-7.1 mg/dL (p≤0.00218)	-9.7 mg/dL (p≤0.00218)	+0.7 mg/dL
Secondary endpoint #2: Change in PPG	-4296 (p<0.0001)	-5000 (p<0.0001)	+1196
% of patients achieving HbA1c ≤7.0%	22.4% (p<0.0001)	22.8% (p<0.0001)	9.1%
Hypoglycemic events	13.3% (p=Nss)	14.6% (p=Nss)	10.1%
Confirmed hypoglycemia	2.4%	0.8%	0.7%
Adverse events	75.0%	72.3%	76.8%
Urinary tract infections	5.2%	10.7%	8.2%
Nasopharyngitis	5.6%	5.9%	6.7%
Upper respiratory tract infections	4.4%	6.3%	6.7%
Influenza	5.2%	4.0%	6.0%
Diarrhea	5.6%	4.0%	5.2%
Hypertension	3.6%	6.3%	2.2%

24-Week Results of Phase III Trials of Onglyza in TZD Patients

Measurement	Onglyza 2.5 mg + TZD n=195	Onglyza 5 mg + TZD n=186	Placebo + TZD n=184
Primary endpoint: Change in HbA1c	-0.7% (p<0.0007)	-0.9% (p<0.0007)	-0.3%
Secondary endpoint #1: Change in FPG	-14.3 mg/dL (p≤0.0053)	-17.3 mg/dL (p≤0.0053)	-2.8 mg/dL
Secondary endpoint #2: Change in PPG	-7849 (p<0.0001)	-9269 (p<0.0001)	-2690
% of patients achieving HbA1c ≤7.0%	42.2% (p<0.0013)	41.8% (p<0.0013)	25.6%
Hypoglycemic events	4.1%	2.7%	3.8%
Confirmed hypoglycemia	1 case	0	0
Adverse events	62.1%	74.2%	66.8%
Urinary tract infections	3.6%	6.5%	6.5%
Upper respiratory tract infections	7.7%	9.1%	7.1%
Nasopharyngitis	3.1%	4.8%	6.0%
Peripheral edema	3.1%	8.1%	4%
Hypertension	5.6%	4.3%	4.9%

Bristol-Myers Squibb submitted Onglyza to the FDA on June 30, 2008, so the PDUFA date is April 30, 2009. It was also submitted to European regulators on July 1, 2008. The filings were based on six Phase III trials of >4,000 patients (~3,000 on drug).

Dr. Roland Chen of Bristol-Myers Squibb also presented data on a third Phase III trial, this time a randomized, double-blind, active-controlled study of Onglyza ± metformin in 1,306 Type 2 diabetics with baseline HbA1c ≥8% and ≤12%. He said, "We saw changes in HbA1c at Week 4 – the earliest measurement – and in the two monotherapy arms which persisted… There was no evidence of escape of efficacy over the study period."

Dr. Chen insisted there was no signal of renal safety in this study or across the saxagliptin program, "We didn't see any clinically meaningful or significant (liver toxicity) issues or any drug-induced liver injury across our program – and no evidence of clinically meaningful effects on platelet count."

On the hypertension issue, he said, "These were investigator-reported events. We examined not only the adverse events, but we also looked at blood pressure across the study...but in all treatment arms, we saw a small decrease in blood pressure means for the 24-week study period. The events of hypertension in this study were all mild or moderate, and none led to treatment discontinuation."

24-Week Results of Onglyza ± Metformin

Measurement	Saxagliptin 5 mg + metformin 500 mg n=316	Saxagliptin 10 mg + metformin 500 mg n=315	Saxagliptin 10 mg n=317	Metformin 500 mg n=313
Primary endpoint: Change in HbA1c	-2.5% (p<0.0001)	-2.5% (p<0.0001)	-1.7%	-2.0%
Secondary endpoint #1: Patients achieving HbA1c ≤6.5%	45.3% (p<0.0001)	40.6% (p<0.0001)	20.3%	29.0%
Secondary endpoint #2: Patients achieving HbA1c <7.0%	60.3% (p≤0.0026)	59.7% (p≤0.0026)	32.2%	41.1%
Secondary endpoint #3: FPG change	-60 mg/dL (p≤0.0002)	-62 mg/dL (p≤0.0002)	-31 mg/dL	-47 mg/dL
Body weight change	-1.8 kg	-1.4 kg	-1.1 kg	- 1.6 kg
Adverse events				
Any adverse event	55.3%	57.3%	53.4%	58.5%
Hypertension	4.7%	5.3%	4.5%	3.4%
Reported hypoglycemia	3.4%	5.0%	1.5%	4.0%
Confirmed hypoglycemia	0	0.6%	0	0.3%
Nasopharyngitis	6.9%	2.5%	4.2%	4.0%
Headache	7.5%	9.9%	6.3%	5.2%
Diarrhea	6.9%	9.6%	3.0%	7.3%

MERCK's Januvia (sitagliptin) and Janumet (sitagliptin + metformin)

More than 6 million prescriptions have been written for Januvia since it was launched in 2006. Merck was busy at EASD emphasizing the safety and efficacy of Januvia and Janumet. Data are expected by the end of 2008 on Januvia + insulin, and those results are likely to be presented at the American Diabetes Association in June 2009.

There was no evidence in the data presented at EASD or in discussions with experts or company officials that any concerning side effects have arisen with sitagliptin. Dr. Barry Goldstein of Merck said, "The skin lesions seen in preclinical studies have not been seen in the sitagliptin clinical program… We know there is a dose reduction if there is renal impairment." Asked specifically about atrial fibrillation or chest issues, Dr. Goldstein said, "In the overall safety database, that hasn't emerged as a signal for concern."

Asked if there is an attenuation of the metformin side effects with the addition of sitagliptin, Dr. Anthony Barnett of the University of Birmingham, U.K., said, "It is not clear from the clinical study results, but many investigators say that." Dr. Bernard Charbonnel of Hotel Dieu (University Hospital of Nantes), France, said, "There are some trials that suggest fewer side effects with metformin – not just with this gliptin but other gliptins that show slightly fewer side effects when you combine the two."

Asked if there are any advantages of adding a DPP-4 to a GLP-1, Dr. Tina Vilsbøll of the University of Copenhagen, Denmark, said, "That has never been done…The study has to be done, but I don't expect major differences (benefits) from that."

Asked if sitagliptin lowers blood pressure, Dr. Vilsbøll said, "Generally, DPP-4s are overall neutral on blood pressure… GLP-1 agonists seem to lower blood pressure a little. Some say that is due to a weight decrease, but it is seen before they lose weight. It is not seen with DPP-4s, but they don't increase blood pressure."

Asked if sitagliptin will work with insulin and whether that will be investigated, Dr. Barnett said, "Yes and yes. I think there is a good likelihood it will work with insulin…What is fascinating is the reduction in the hypoglycemia rate…If that is shown in proper trials, it will be a major, major issue…To have an oral agent that combines with insulin and at the same time reduces hypoglycemia is very, very positive…The reason it may reduce hypoglycemia relates to the mechanism of action…As sugar levels fall, you get this recovery, which is protective against hypoglycemia…The company really needs to…get a license (label) for it." A Merck official added, "That study is ongoing. We do have a trial of combination of Januvia and insulin."

There were five major datasets on Januvia presented at EASD:

1. **Triple therapy.** In a multinational, randomized, placebo-controlled, double-blind, parallel-group, 54-week study in 262 patients with Type 2 diabetes, the addition of Januvia to combination therapy with metformin + a TZD (Avandia) showed significant improvement in glucose, and the tolerability was described as "placebo-like."

Addition of Januvia to Metformin/Avandia Combination at Week 54

Measurement	Metformin/ Avandia n=170	Januvia + metformin/ Avandia n=92	p-value
HbA1c change from baseline at Week 54	---	Down 0.8% more	<0.001
Primary endpoint: HbA1c change from baseline at Week 18	---	Down 0.7% more	<0.001
Patients achieving HbA1c <7.0% at Week 18	9%	22%	0.003
Patients achieving HbA1c <7.0% at Week 54	14%	26%	---
Adverse events			
Any adverse event	71%	75%	---
Drug-related adverse event	11%	15%	---
Hypoglycemia	1%	4%	---
Nausea	3%	1%	---
Peripheral edema	5%	9%	---
Upper respiratory tract infection	7%	17%	---
Headache	4%	6%	---

2. **Combination therapy with metformin at 2 years.** The one-year data was previously presented, and the two-year findings from an extension study showed what a researcher called "powerful" glycemic control and a small reduction in body weight with the higher dose combination. The lower dose combo was weight neutral. The safety profile was similar to metformin monotherapy.

2-Year Data on Januvia ± Metformin

Measurement	Januvia 100 mg QD	Metformin 500 mg BID	Metformin 1000 mg BID	Januvia 50 mg BID/ metformin 500 mg BID	Januvia 50 mg BID/ metformin 1000 mg BID
Primary endpoint: Change in HbA1c at Week 54 (previously presented)	-0.8%	-1.0%	-1.3%	-1.4%	-1.8%
Change in HbA1c at Week 104	-1.1%	-1.1%	-1.3%	-1.4%	-1.7%
Patients with HbA1c ≤7.0 at Week 104	3.2%	2.8%	4.5%	4.5%	6.0%
Any adverse event Weeks 54-104	37%	34%	55%	53%	55%

3. **Pooled safety analysis.** In this meta-analysis of 6,139 patients, Januvia 100 mg was well tolerated out to 2 years. There were no signals of hepatotoxicity, cardiac events, or skin problems with Januvia in excess of the comparator.

Pooled Safety Analysis of Januvia

Measurement	Januvia 100 mg n=3,415	Placebo or active comparator n=2,724
One or more adverse events	63.0%	62.8%
Drug-related adverse events	12.5%	17.7%
Serious adverse events	6.7%	6.8%
Deaths	0.3%	0.6%

4. **Japanese study.** This 52-week study of Januvia + a TZD (Actos) showed significant and durable improvement in glucose and no safety issues.

5. **Subgroup analysis.** A pooled analysis of two randomized, placebo-controlled, double-blind, Phase III trials of Januvia added to metformin in Type 2 diabetics found Januvia effective, with consistent glycemic control, regardless of baseline age, gender, BMI, HOMA-β, or P/I ratio.

NOVARTIS's Galvus (vildagliptin)

An expert said there are three problems with this DPP-4:

1. Initially, skin toxicity in monkeys – which affected all the DPP-4s except Merck's Januvia (sitagliptin).
2. FDA concern with the renal impairment data.
3. A license (label) change in Europe due to ALT (liver) elevations with the QD dose.

Novartis officials insisted there are no signs of any hypertension or edema problems (at therapeutic doses) with Galvus. An official said, "We have seen no signal of increased blood pressure, and no preclinical or clinical indications for any increase in blood pressure…I think this gives us reassurance we don't have a safety concern with blood pressure. It certainly is neutral, and it may have a favorable effect."

But Galvus does have its problems, including questions about liver elevation with the 100 mg QD dose and safety in patients with renal impairment. Galvus is approved in Europe at the 50 mg BID and 50 mg QD doses; the company voluntarily withdrew the 100 mg QD dose after it saw an elevation in liver enzymes in an early meta-analysis. Novartis officials claim newer data indicate that neither of these issues are a problem, but officials would not say:

1. **If it plans to resubmit the 100 mg QD dose in Europe.** A Novartis official said, "Everything is open for discussion… We'll keep a close eye on the safety profile for that dose…We voluntarily withdrew that dose due to a slight imbalance in hepatic enzymes seen at that dose but not other doses. We felt this was reasonable since we had the 50 mg dose available and more safety data on the 50 mg dose…We have 7,400 more patients since that decision was made showing no enzyme imbalance or hepatic safety risk…It was the right decision at the time, but we didn't have this much data…Now, we are not seeing the signal developing further…We are continuing to keep a very close eye on this issue, but right now we are very comfortable and very confident with the safety profile as it is emerging."

2. **When or if they planned to resubmit Galvus to the FDA.** All a Novartis official would say about the Galvus status with the FDA is, "We are continuing discussions about resubmission in the U.S.…There are no immediate plans, but those discussions are ongoing…The FDA is interested in further data in patients at increased risk of drug exposure, including patients with renal impairment." "Resubmit" was an odd choice of wording since approvable letters generally do not require resubmission of the drug, just submission of additional data.

Renal impairment appears to be a key issue – but perhaps not the only issue – with the FDA, and European regulators (the EMEA) did not approve Galvus for patients with moderate or severe renal impairment (only for patients with mild renal impairment). Renal dysfunction is common in Type 2 diabetics; the prevalence of kidney disease in Type 2 diabetes is 20%-40%.

In February 2007, the FDA issued an approvable letter for Galvus, at least in part due to concerns about patients with renal impairment. Novartis has two ongoing, 6-month U.S. – and one non-U.S. – studies in patients with moderate-to-severe renal failure (with a total of 300 patients getting Galvus) to answer the FDA and EMEA concerns, but officials would not discuss the status of those trials – not when they started and not when they are expected to be completed.

According to Novartis, more than 22,000 patients have been studied in vildagliptin trials so far, including >19,800 patients in completed studies. About 3,700 patients have been treated for more than one year, and ~1,800 patients for more than two years. The advantages of Galvus, according to a Novartis official, are: "As effective as other oral anti-diabetic drugs, with fewer side effects – equivalent HbA1c lowering to a TZD without weight gain and a lower risk of edema, similar efficacy to an SU with 14-times less hypoglycemia…and a favorable cardiovascular and tolerability profile…We believe that prescribing options, particularly a single pill, offer compliance and adherence advantages."

Novartis made a concerted effort at EASD to promote the efficacy and safety of vildagliptin. Dr. Martin Fitchet, vice president and global brand manager at Novartis, said, "We feel quite strongly that there is a dose response between 50 mg QD and 50 mg BID, especially in combination with metformin… We think the most important use right now is in patients failing on metformin."

However, European doctors were not completely convinced. Most of those questioned have started to use vildagliptin, but Merck's Januvia remains the preferred DPP-4. One said, "I'm using Januvia, and I'll start using Galvus. I don't see a big difference between them. Januvia is better for us because it was first to market. The big interest in DPP-4s is as a third addition (to metformin and SU). That is not the label, but it is more the way I use them." Another said, "I will use both sitagliptin and vildagliptin. Until now, it's been all sitagliptin, and I need to study vildagliptin to see where to use it instead."

Among the new data released by Novartis at EASD on vildagliptin were:

- **Comparison to TZDs.** The results of the 2,478-patient GALIANT community-based study, conducted by primary care doctors in the U.S., showed that vildagliptin was better tolerated and equally effective in Type 2 diabetics as a TZD when either was added to metformin. GALIANT was originally intended to be a larger study, but it was amended to a smaller trial which Novartis said was to get quicker results.

12-Week Results of GALIANT Trial in Type 2 Diabetes

Measurement	Vildagliptin 100 mg QD n=1,653	TZD n=825	p-value
Primary endpoint: Change in HbA1c	-0.8%	-0.57%	0.001
Weight change	-0.58 kg	+0.33 kg	<0.05

- **Cardiac safety.** A pooled safety analysis of 6,063 patients showed vildagliptin has a "favorable" cardiovascular (CV) profile, with a lower overall incidence of CV and cerebrovascular events (MI, stroke) vs. placebo. Dr. Fitchet said this is important because of CV safety concerns that have been raised recently over TZDs and SU.

Pooled Analysis of Cardiovascular Safety of Vildagliptin

Vildagliptin dose	Number of patients	Hazard ratio vs. placebo	Hazard ratio vs. all comparators n=4,357
50 mg QD	1,469	0.77	0.69
50 mg BID	4,594	0.89	0.79

- **Islet cell function.** In a 4-week crossover study, vildagliptin 100 mg QD demonstrated improvement in alpha cell function as well as beta cell function. Dr. Fitchet said, "Diabetes is not just a disease of insulin resistance and deficiency; it is also inappropriate glucagon elevation. In combination with insulin, we see a potential protective effect – much lower hypoglycemia compared to insulin alone…This is something that merits further investigation…This (study) confirms the positive effects of vildagliptin on the alpha cell as well as the beta cell." Dr. Bo Ahren of Sweden said, "Improved glucose sensing may explain the very low hypoglycemia potential of vildagliptin that has been observed in other studies."

- **Renal impairment.** A pooled safety analysis of >1,400 patients found vildagliptin safe and effective in patients with mild renal impairment over ≤24 weeks. There were no differences in adverse events based on renal sufficiency status in patients taking Galvus 50 mg BID long-term (6 months plus a 6-month extension). Efficacy was similar for patients with mild renal insufficiency (GFR 50-80 mL/min/1.7m^2) and for patients with normal renal function (GFR >80 mL/min/1.7m^2). The data in moderate renal impairment patients also looked good, but the numbers were small, and no firm conclusions could be drawn for those patients. The company is conducting trials in renal impairment patients to further investigate this, but a Novartis official predicted the results will confirm the 50 mg BID dose is safe in these patients as in patients with mild renal impairment.

  Dr. Tom Thuren of Novartis said, "We do not see any increased risk down to a GFR of 30…We see a robust effect in mild, moderate, and normal patients…There are no safety signals of concern with moderate renal impairment, but the experience is limited in this patient group. Therefore, the use of vildagliptin is not recommended in these patients, so that is in the European label. We are doing studies in these patients, but so far there is nothing to suggest there would be any safety concerns... and efficacy seems to be in line with normal GFR patients …50 mg BID is the recommended dose in patients with mild renal insufficiency, and if I predict, that will be the dose for the other renal insufficiency patients."

Pooled Analysis of Galvus Safety/Efficacy in Renal Impairment Patients

Measurement	Galvus 50 mg BID n=4,594	Placebo n=1,304	All comparators n=4,357
Normal renal function	69.1%	61.8%	67.6%
Mild impairment	29.4%	5.8%	31.1%
Moderate renal impairment	1.3%	2.4%	1.3%
Serious adverse events (per 100 patient years)			
Normal GFR patients	~ 5%	~ 12%	~ 10%
Mild renal insufficiency patients	~ 10%	~ 17%	~ 15%
Serious adverse events resulting in discontinuations			
Normal GFR patients	~ 6%	~ 7%	~ 9%
Mild renal insufficiency patients	~ 9%	~ 6%	~ 14%
Any adverse event			
Normal GFR patients	~ 130 (65%)	~ 165	~ 155
Mild renal insufficiency patients	~ 140	~ 170	~ 160
Specific adverse events			
Renal and urinary disorders	6.13%	7.30%	7.41%
Skin and subcutaneous tissue disorders	19.41%	30.46%	22.81%
Hepatobiliary disorders	2.72%	2.37%	2.28%
Efficacy: Change in HbA1c			
Normal GFR patients	-0.07%	---	---
Mild renal insufficiency patients	- 1.06%	---	---

TAKEDA's alogliptin

Dr. Richard Pratley of the University of Vermont presented data on this oral, once-daily DPP-4 in Type 2 diabetes. Like Merck's Januvia, it appears to be weight neutral, and lowers HbA1c, but the efficacy did not look impressive in comparison to other gliptins, and it failed to show a benefit on FPG. Interestingly, a Takeda official said that in Germany the company only plans to offer a combination of alogliptin + pioglitazone (Takeda's Actos), not alogliptin alone.

Alogliptin has a half-life of ~21 hours. It is ~60% excreted renally, and PK studies indicate it is not affected by food. Dr. Pratley said it showed "no significant effects on FPG, weight, lipids, or beta cell function," but he defended the efficacy, saying, "The magnitude of the reduction on HbA1c was proportional to baseline HbA1c."

Dr. Penny Fleck from Takeda presented 26-week data on alogliptin in Type 2 diabetics taking insulin (15-100 units/day) either alone or with metformin. The drug met the primary endpoint for both doses tested (12.5 mg QD and 25 mg QD), and was weight neutral, but only the high dose showed a benefit on FPG, and neither dose reduced hypoglycemic events.

26-Week Results of Alogliptin in Type 2 Diabetics Not on Insulin

Measurement	Placebo n=99	Alogliptin 12.5 mg QD n=153	Alogliptin 25 mg QD n=199	p-value
Primary endpoint: HbA1c change from baseline	+0.01%	-0.38%	-0.52%	<0.001 both doses
FPG change	+0.12	-0.26	-0.46	Nss both doses
Body weight change	-0.02 kg	+0.6 kg	+0.7 kg	Nss both doses
Any adverse event	53.5%	63.5%	63.1%	---
Any drug-related adverse event	10.1%	15.3%	17.7%	---
Upper respiratory tract infection	N/A	2.0%	2.5%	---
Hypoglycemic events	11.1%	15.8%	9.6%	---

26-Week Results of Alogliptin in Insulin-Dependent Type 2 Diabetics

Measurement	Placebo n=130	Alogliptin 12.5 mg QD n=11	Alogliptin 25 mg QD n=129	p-value
Discontinued	17.7%	16.0%	20.9%	---
On insulin + metformin	60.8%	58.8%	55.8%	---
Hyperglycemic rescue	40.0%	20.6%	19.4%	---
Primary endpoint: HbA1c change from baseline	-0.13%	-0.63%	-0.71%	<0.001 for both doses
HbA1c in patients with insulin alone	-0.18%	-1.05%	-0.95%	---
Secondary endpoint #1: FPG change from baseline	+0.32	+0.13	+0.65	<0.05 only for high dose
Secondary endpoint #2: Body weight change	+0.63 kg	+0.68 kg	+0.6 kg	Nss for both doses
Hypoglycemic events	24%	27%	27%	Nss for both doses
Mild-moderate hypoglycemia	16%	21%	23%	---
Severe hypoglycemia	2 patients	0	1 patient	---
Any adverse event	73.6%	67.9%	66.7%	---
Any drug-related adverse event	12.4%	10.7%	13.2%	---
Death	0	1 patient (CV-related)	0	---
Urinary tract infection	7.8%	6.1%	7.0%	---
Arthralgia	2.3%	6.9%	3.1%	---
Headache	4.7%	5.3%	3.1%	---
Nasopharyngitis	4.7%	3.8%	6.2%	---
Diarrhea	5.4%	0.8%	6.2%	---

GLP-1 MIMETICS

The six deaths with Lilly/Amylin's Byetta (exenatide) hovered over the EASD meeting and over all the GLP-1 mimetics in development. Expert comments in the pre-EASD period included:

- *Canada:* "We didn't look for pancreatitis with (GlaxoSmithKline/Human Genome Sciences') albiglutide in animal studies…We have no evidence of it, but we didn't look for it…We're currently working on that in the lab."
- *Denmark:* "We simply don't know if it (pancreatitis risk with GLP-1 mimetics) is real or not real…And there is no way of telling right now…There is a weak effect (of these drugs on the pancreas)…Whether that should lead to pancreatitis is completely unresolved…And there is no indication right now that one (drug) vs. the other should be more likely to produce pancreatitis. We simply don't know if the problem is real."
- *Sweden:* "Pancreatitis is a very rare phenomena. It is seen in diabetics already. There is no difference in the incidence with GLP-1s vs. placebo. I don't know if the (risk) is real, but you have to take it seriously. I don't think it will delay the long-acting GLP-1s, but doctors should get a warning until we know more."
- *Belgium:* "I believe in long-acting GLP-1s. It (pancreatitis) is a side effect that is there. Being on Byetta blames Byetta as the cause of the pancreatitis, and that may be exaggerated."
- *U.K.:* "(In the Novo Nordisk liraglutide studies) there were a small number of people who developed it, both on liraglutide and the comparators. It was not thought to be above the background level of a Type 2 diabetic population, and the total numbers were very small."

Comparison of GLP-1 Receptor Agonists

Drug	Approximate half-life	Dosing	Binding	Approximate decrease in HbA1c
Lilly/Amylin's Byetta (exenatide)	6-10 hours	10 µg BID	N/A	Down 1.5% at 30 weeks
Lilly/Amylin's exenatide LAR	5-7 days	2 mg QW	N/A	N/A
Conjuchem's CJC-114	N/A	QW	Covalent link to recombinant human albumin	Down 0.6% at 4 weeks
GlaxoSmithKline/Human Genome Sciences' albiglutide	5 days	16-32 mg QW	Genetically fused to human albumin	Unknown yet
Novo Nordisk's liraglutide	16-20 hours	1.8 mg QD	Non-covalent link to human albumin	Down 1.9% at 30 weeks
Roche's taspoglutide	1-2 weeks	20 mg QW	Aminoisobutyric acid	Down 1.2% at 8 weeks
Sanofi-Aventis's AVE-0010	N/A	20 µg QD	Exendin-4 coupled with lysine	Down 0.6% at 4 weeks

At a symposium sponsored by GlaxoSmithKline (GSK), Dr. Bo Ahren of Lund University in Sweden compared and contrasted the various GLP-1 mimetics. Among the points he made were:

- Novo Nordisk's liraglutide decreases HbA1c more than Lilly/Amylin's Byetta (exenatide) and has shown a trend to slightly better glycemic control. He said, "We might conclude that the longer the duration, the better the glycemic effect."
- At 26-30 weeks, there is no clear difference in weight loss between Byetta and exenatide LAR.
- Safety and tolerability is better with liraglutide than with Byetta.
- Liraglutide and Byetta appear to increase islet cell size equivalently (in animals).
- The different mimetics may have different receptor site binding characteristics and, thus, different non-islet cell effects.

Dr. Ahren's Comparison of Byetta and Liraglutide

Measurement	Byetta 10 µg BID	Liraglutide 1.8 mg QD
Nausea with metformin	45%	12%
Nausea with SU	51%	11%
Nausea with metformin + SU	20%	4%
Minor hypoglycemia with metformin	5%	N/A
Minor hypoglycemia with SU	3%	8%
Minor hypoglycemia with metformin + SU	13%	16%
Antibodies with metformin	43%	4%
Antibodies with SU	41%	12%
Antibodies with metformin + SU	49%	10%
Increase in islet size in mice	Comparable	

GlaxoSmithKline/Human Genome Sciences' albiglutide

Three trials have been completed recently but not yet presented, so watch for these results soon:

- A Phase II dose-ranging study in Type 2 diabetics.
- A scintillographic study of gastric emptying.
- A Japanese study.

Dr. Philip Home of the U.K. said that Phase II studies of albiglutide have shown nausea in 9%-12% but no hypoglycemia and no lab or ECG abnormalities. He said what's known right now is:

- At the higher doses tested, it has shown useful glucose lowering efficacy.
- The long half-life (4-6 days) should allow QW or less frequent dosing.
- Nausea and vomiting occurred as with other GLP-1 mimetics. "The tolerability issues in Phase I and Phase IIa are as anticipated, but medium duration clinical studies are not needed."
- Hypoglycemia was not found even at the highest doses.

A Phase IIb trial is underway looking at both once-weekly and once-monthly administration as well as various doses. The results may be published in a major medical journal in March or April 2009 and presented at the American Diabetes Association meeting in June 2009. A researcher pointed out these advantages to albiglutide vs. other GLP-1s:

- Water soluble so can be administered with a very, very small needle (29 g).
- Once-weekly dosing.
- Less immunogenicity (no neutralizing antibodies).
- No microspheres involved.

Lilly/Amylin's Byetta (exenatide BID)

A study by researchers at the University of Ohio State University concluded that Byetta is an effective *in vivo* anti-rejection therapy for islet cell allo-transplantation in non-human primates. Other immunosuppressants used in transplant patients, such as cyclosporine (CsA), have been shown to be beta cell toxic. Adding Byetta to CsA is not enough to overcome the diabetogenic effects of CsA.

Asked about the impact of the pancreatitis deaths on use of Byetta, doctors offered these comments:

- *Canada:* "It doesn't appear to be more than the background rate."

- *Novo Nordisk official:* "Today, there is no evidence of an association of pancreatitis and any GLP-1 – only uncontrolled spontaneous reports. And the number of cases is low…There really seem to be good explanations for the Byetta cases…The Byetta label is being revised, and there probably will be wording about more caution in our (liraglutide) label."
- *Netherlands:* "I was not seeing a big role for it before (these deaths) because it is an injection. There is no reimbursement…The pancreatitis is an additional reason to hold back. It's a little smoke. I'm not sure if there is a fire…I also have serious concern about the nausea with Byetta."
- *Italy:* "The pancreatitis is a problem. I think the company should do an observational study of patients just to understand the risk factors to avoid…It is quite physiologic that a drug like this could cause pancreatitis."
- *U.K.:* "I use Byetta, but I'm concerned with the pancreatitis. I've gotten my fingers burned because I had a case of pancreatitis. It was exactly as the FDA cautioned – with gallstones. I told the patient it wasn't the drug, but now I'm sure it was."

LILLY/AMYLIN's exenatide LAR

Lilly and Amylin attempted to distract attention at EASD from the six pancreatitis deaths in Byetta patients with, first, data in ***The Lancet***, that once-weekly exenatide is more effective than Byetta BID and, second, data that Byetta BID is more effective than Merck's Januvia. Both presentations proved somewhat controversial.

The 30-week DURATION-1 results on exenatide once-weekly (LAR) vs. Byetta BID that ***The Lancet*** indicated would be presented at EASD actually were never presented there after all. In his presentation of the 22-week extension study of that trial, Dr. John Buse of the University of North Carolina School of Medicine, president/Medicine and Science of the American Diabetes Association, made reference to top-line results from the 30-week DURATION-1 study, but he did not present it in any detail.

In fact, the data in ***The Lancet*** had previously been presented at the American Diabetes Association meeting in June 2008, but this was the first publication of that data. The results showed that, besides being more convenient, a once-weekly formulation of Byetta gives better glucose control than the currently-approved BID formulation while also leading to weight loss.

Dr. Daniel Drucker of Mount Sinai Hospital and the University of Toronto, Canada, and colleagues reported on the results of the randomized, 30-week, comparator-controlled, open-label DURATION-1 non-inferiority trial of 2 mg exenatide LAR vs. Byetta 10 µg BID in 259 patients with Type 2 diabetes.

The researchers reported:

- HbA1c reduction was significantly greater with exenatide QW by 10 weeks, a difference that persisted throughout the rest of the trial.
- HbA1c reductions were consistent regardless of background therapy.
- Similar weight loss with the 2 drugs.

30-Week Results of DURATION-1 Trial of Exenatide QW vs. BID

Measurement	Exenatide LAR 2 mg QW n=129	Byetta 10 µg BID n=130	p-value
Primary endpoint: Change in HbA1c	Down 1.9% to 6.4%	Down 1.5% to 6.8%	0.0023
Achieved target HbA1c ≤7.0%	77%	61%	0.0039
Achieved target HbA1c ≤6.5%	49%	42%	Nss
Achieved target HbA1c ≤6.0%	25%	18%	Nss
Patients losing weight	79%	76%	---
Patients with reduction in HbA1c and in weight	73%	74%	---
Change in body weight (overall)	-3.6%	-3.7%	Nss
Change in body weight in patients with nausea	-5.4 kg	-4.1 kg	---
Change in body weight in patients without nausea	-3.1 kg	-3.4 kg	---
Antibody formation	Higher	---	0.0002
FPG	-2.3	-1.4	<0.0001
Adverse events			
Nausea	26.4%	34.5%	---
Vomiting	10.8%	18.6%	---
Major hypoglycemia	0	0	Nss
Serious adverse events	5.4%	3.4%	---
Withdrawals due to adverse events	6.1%	4.8%	---

In an accompanying commentary in ***The Lancet***, Dr. André Scheen of the University of Liège in Belgium wrote, "Compared with the twice-a-day exenatide (Byetta) regimen, the once-a-week formulation (LAR), besides obvious improved ease of use, provided the remarkable advantage of both improved efficacy on glucose control and good gastrointestinal tolerability." If confirmed, he suggested that exenatide LAR might "substantially change the management of Type 2 diabetes." However, he also noted that a head-to-head study comparing exenatide LAR and liraglutide "would be useful" and "interesting."

However, the results of the extension study presented by Dr. Buse did look good. In that study, all patients were treated with LAR to assess safety, efficacy, and switching effects. Byetta patients experienced a "transient loss of glycemic control" when switched to LAR, but then they responded well to LAR. Vomiting was less with switching than with initial therapy, which Dr. Buse said was "likely due to patient acclimation to exenatide." There was some minor hypoglycemia, but only in patients on SU. He concluded, "The

safety profile of once-weekly exenatide was consistent with the current BID formulation with somewhat less nausea and a new, but modest, problem of injection site reaction. The transition from BID to once-weekly exenatide was not associated with more adverse events."

22-Week Extension of Exenatide LAR in DURATION-1 Trial

Measurement	Continuous LAR n=120	Byetta switched to LAR n=121
Withdrawals during Weeks 30-52	4.1%	6.1%
HbA1c change at Week 52	-2.0%	-2.0%
Patients achieving HbA1c <7.0%	72%	75%
Patients achieving HbA1c ≤6.5%	54%	53%
Mean HbA1c at Week 52	6.6%	N/A
FPG change	-0.6	-2.4
Weight loss	-4.1 kg	-4.5 kg
HbA1c change in patients with a baseline >9%	-2.8%	-2.6%
SBP change from baseline	-6.2 mmHg	-3.8 mmHg
DBP change from baseline	-2.8 mmHg	-1.8 mmHg
Adverse events in Weeks 30-52		
Diarrhea	8.6%	6.9%
Nausea	7.0%	7.7%
Injection site bruising	0	5.4%
Injection site pruritis	0.8%	4.6%
Vomiting	6.3%	4.6%
Major hypoglycemia	0	0

The audience had questions for Dr. Buse about:

- **Antibodies.** Dr. Buse said, "There was a greater percentage of patients who had antibodies with the once-weekly formulation than the BID formulation reported in ***The Lancet***. With 52 weeks of follow-up, the patients with the highest antibody count had a bit of a lower HbA1c response, but not an absence of response…and some patients with the highest titer had a HbA1c response of >1%, though some had no response at all…So antibodies were higher with once-weekly than twice-daily…The group that switched had a slight increase (in antibodies) and then a reduction in antibodies, but it didn't seem to predict response."
- **Size of the LAR dose –** about 15 times the Byetta BID dose. Dr. Buse said, "The absorption of exenatide (LAR) is extremely prolonged. Within individuals there is substantial variation in the level of exenatide circulating that is achieved with the 2 mg (LAR) dose, but, in general, the area under the curve (AUC) over 24 hours when once-weekly is administered is substantially higher than the 24-hour AUC with twice-daily (Byetta). In general, the levels of exenatide when delivered once-weekly through 24 hours of the day are similar to the near peak levels of exenatide administered BID...So, this (LAR) formulation really allows for the delivery of more exenatide than the current formulation because of the peaks and troughs (with Byetta BID)."
- **Similar weight change in the 2 groups.** Dr. Buse said, "The weight loss with BID was somewhat greater than we've seen with similar trials of similar duration…There were fewer withdrawals…BID patients knew if they continued (in the first 30 weeks), they would get the once-weekly formulation (in the extension)…Other than that, there is no explanation for not seeing a greater weight loss. For BID we got the sense of a long and prolonged use that was required to get to 5% body weight loss…Here we saw weight loss came on more quickly but did not exceed that level."

Byetta (exenatide) vs. Januvia (sitagliptin)

Researchers presented data at EASD which showed that Byetta may be more effective than Januvia at reducing glucose levels in Type 2 diabetics, but it was a very short trial (just 2 weeks before crossover), and the endpoint was PPG. Criticisms of this trial included:

- **2-week length.** Dr. Vilsbøll said, "While the trial was interesting, it was not a true head-to-head comparison because for that you need a trial to last at least 12 weeks."
- **PPG endpoint.** Dr. Vilsbøll said, "You need a clinically meaningful endpoint – HbA1c…It is well known that two-hour PPG does not decrease with sitagliptin treatment."
- **Higher Byetta adverse events.** Nausea and vomiting were much higher with Byetta than Januvia (34% vs. 12% and 25% vs. 3%, respectively).
- **Peak effect.** Another expert argued that the study looks at the peak in the Byetta effect, while Januvia has a more steady effect.

Novo Nordisk's liraglutide

The company announced that the FDA will take liraglutide to an advisory panel in March 2009, which means at least a two month delay in approval. Company officials suggested that all new oral diabetes drugs may need to go to panel for the foreseeable future, given the FDA's caution since the Avandia safety issues arose.

At a Novo Nordisk-sponsored symposium, speakers reviewed data that have already been presented or published on liraglutide. Among the points they made were:

- **Nausea.** The percent of patients who get nausea is similar to that with Byetta, but over time it disappears.
- **Pancreatitis.** There have been liraglutide patients who got pancreatitis, but the level is not thought to be above a background level for Type 2 diabetics – and the numbers were "very small."
- **Hypoglycemia.** There is a low risk of minor hypoglycemia (<1.5 events/per subject year).

Asked where GLP-1 agonists fit in the management of Type 2 diabetes, Dr. Lawrence Blonde of the Ochsner Clinic in New Orleans said, "Treatment earlier might be beneficial, though we need more information on long-term durability. And the data on beta cell mass and beta cell function suggest that earlier treatment would be effective. This clearly would be a very effective add-on treatment to metformin in people who don't achieve goal on metformin plus life-style adjustment."

Asked how incretin mimetics and DPP-4 inhibitors compare, Dr. David Russell-Jones of the U.K. said, "Glycemic reductions are greater with the analogs (mimetics). I think there is weight reduction that you don't see with DPP-4 inhibitors, and I personally would rather give an (incretin) agonist than blanket inhibition of an enzyme process (DPP-4), some of which we know how to work and others we don't know. I think it (an incretin mimetic) is cleaner and appears to have a greater effect. But there is the disadvantage of the injection." Dr. Bernard Zinman of Canada added, "There isn't one solution, and it is useful to have multiple agents…We don't need another agent that drops HbA1c a little bit…We need more robust decreases…and the GLP-1-based therapies result in significant and sustained reductions…None of our patients like the fact that we give them pills to control their glucose and tell them they may gain some weight…Any agent that has the properties of reducing glycemia and doesn't result in weight gain will be extremely important."

Novo Nordisk has a long-acting GLP-1 in Phase II development (NN-9535) which is expected to be a once-weekly injection.

Researchers insisted that the weight loss with liraglutide is not just in the most responsive quartile, that it is not driven by the "super-responders." They also said the weight loss is not related to nausea because the nausea patients are not the ones who lose weight.

Other data presented at EASD on liraglutide included:

➢ **Compared to insulin.** The 26-week results from the LEAD-5 trial of liraglutide vs. insulin glargine in Type 2 diabetics on metformin/SU were presented at EASD. In the trial, the baseline HbA1c was 8.3%. Researchers reported that liraglutide reduced HbA1c better than insulin, with comparable minor hypoglycemia, significant and substantial weight reduction, a reduction in systolic blood pressure, a low rate of serious adverse events, and a declining incidence of nausea.

Dr. Russell-Jones, who presented the data, said the observation that liraglutide appears to lower systolic blood pressure starting at about 2 weeks, "This appears to be an intrinsic effect and not due to weight loss…This is at a level that may convey a cardiovascular risk reduction." Asked about the possible mechanism for this, he said, "It is a consistent finding in the LEAD-5 trial, and I'm sure it is an intrinsic property of liraglutide. There are a number of people who put forward hypotheses, but the true mechanism is unknown at this time."

➢ **Program overview.** In another presentation, Dr. Allan Vaag of Denmark presented data from across the five LEAD trials, concluding that liraglutide reduced HbA1c in Type 2 diabetics, irrespective of baseline HbA1c. He reported that:

- In each trial liraglutide exceeded or equaled the comparator on HbA1c reduction.
- Liraglutide added to oral anti-diabetic (OAD) agents showed a clinically meaningfully reduction in HbA1c across all baseline HbA1c quartiles.
- The reduction in HbA1c was greatest in patients with a high baseline HbA1c and highest when liraglutide was combined with metformin and Avandia.

26-Week Results of LEAD-5 Trial of Liraglutide vs. Insulin in Type 2 Diabetics

Measurement	Liraglutide 1.8 mg QD n=232	Insulin glargine n=234	Placebo n=115	p-value vs. insulin glargine	p-value vs. placebo
Primary endpoint: Change in HbA1c	-1.33%	-1.09%	-0.24%	0.0015	<0.0001
Secondary endpoint: Change in FPG	-28 mg/dL	-29 mg/dL	+10 mg/dL	Nss	<0.0001
Patients achieving HbA1c ≤7.0%	52%	44%	15%	0.0139	<0.0001
Patients achieving HbA1c ≤6.5%	36%	23%	11%	<0.0001	<0.0001
Weight change	-1.81 kg	+1.6 kg	-0.432 kg	<0.0001	0.0001
Adverse events					
Major hypoglycemia	2.2%	0	0	---	---
Minor hypoglycemia	27%	29%	17%	---	---
Nocturnal minor hypoglycemia	5.7%	8.2%	6.1%	---	---
Minor hypoglycemic events per patient per year	~1.2%	~0.9%	~1.3%	---	---
Nausea	14% *	N/A	N/A	---	---
Any adverse event	66%	56%	55%	---	---
Serious adverse events *	3.5%	7.8%	6.1%	---	---

*** Initially 5%-7% of patients, but dropped to 2%-4% after the first 12 weeks; 2 withdrawals due to nausea.**

Overview of Liraglutide LEAD Trials

Measurement	LEAD-3 n=746	LEAD-2 n=725	LEAD-1 n=695	LEAD-4 n=54	LEAD-5 n=22
Type of trial	Monotherapy	+ metformin	+ SU	± metformin/ TZD	+ metformin/SU vs. insulin
HbA1c reduction at 1.8 mg dose from a mean baseline HbA1c >8%	-1.5%	-1.3%	-1.4%	-1.5%	-1.3%
HbA1c reduction in patients with the lowest quartile baseline HbA1c	~0.5%	~0.7%	~0.4%	N/A	N/A

- Body weight loss was greatest in quartile 1 (~7 kg).
- Reduction of HbA1c is not explained by weight loss per se. Patients with the greatest weight loss had the same reduction in HbA1c as those who did not have any weight loss during the trials.

Liraglutide vs. Byetta or exenatide LAR

Doctors asked how they would choose between liraglutide and Byetta (either BID or QW) said:

- *U.K.:* "LAR has quite a rate of high injection site reactions, uses a bigger needle, and antibodies are a significant problem. I think initially there will be a role for both."
- *Netherlands doctor who is not a fan of Byetta:* "I might change my mind if LAR (exenatide once-weekly) is approved. I'd like to do a study with LAR in 75+ elderly patients. The key market for LAR will be the elderly and nursing home patients…I would use LAR on patients with normal triglyceride levels only, and I'll forewarn them about abdominal pain. I'll use it (LAR), but I won't be the first."
- *Italy:* "I need to analyze them both more when I get home from the meeting."

ROCHE's taspoglutide (R-1583)

The results of an 8-week, double-blind, placebo-controlled, dose-ranging Phase II study in 188 Type 2 diabetics found that once-weekly taspoglutide plus metformin improved glycemia, beta cell function, insulin secretion rates, and beta cell glucose sensitivity.

SANOFI-AVENTIS's AVE-0010

Nothing jumps out about this potential once-daily GLP-1 that makes it stand out other than the QD dosing. Phase II data presented at EASD appear to justify the company's decision to take QD dosing – at 20 µg and possibly 10 µg – into Phase III trials. Dr. Julio Rosenstock, who presented the data, said, "We want to use the highest dose possible for the greatest effects…This study carefully assessed every potential dose… There do not appear to be any obvious differences giving it twice a day on efficacy, and twice a day may increase the side effects, so the dose picked for Phase III was 20 µg QD and presumably 10 µg QD may also have some potential."

The 13-week, multicenter, multinational, parallel-group, placebo-controlled Phase II trial looked at 4 doses of AVE-0010 given either BID or QD, finding:

- Dose-dependent effects for both formulations, with similar results for QD and BID.
- HbA1c changes from 0.5%-0.9%, which were considered a good reduction since the average baseline HbA1c in this study was 7.5%.
- 47%-69% of patients achieved target HbA1c of <7%, and 51%-77% achieved target HbA1c ≤6.5%.
- FPG and PPG were improved.
- Weight reduction ranged from ~2-4 kg.
- Vomiting was 5%-9%, but spiked at ~30% with the highest QD dose. Nausea was 11%-25% and described as "mostly mild." Diarrhea ranged from 7% to 11%.

12-Week Results of AVE-0010 in Type 2 Diabetics

Measurement	Placebo	AVE-0010 QD				AVE-0010 BID			
	n=109	5 µg n=55	10 µg n=52	20 µg n=55	30 µg n=54	5 µg n=53	10 µg n=56	20 µg n=54	30 µg n=54
Discontinuations	5.5%	3.6%	9.6%	16.4%	16.7%	3.8%	8.9%	14.8%	13.0%
Discontinuations due to adverse events	1.8%	1.8%	N/A	5.5%	11.1%	0	3.6%	14.8%	9.3%
HbA1c change achieved	N/A	-6.8%				-6.6%			
Primary endpoint: HbA1c change (%)	-0.2	-0.5 *	-0.5 *	-0.7 *	-0.8 *	-0.7 *	-0.8 *	-0.8 *	-0.9 *
Secondary endpoint #1: Patients reaching HbA1c <7% target	32%	47% *	52% *	68% *	69% *	51% *	65% *	62% *	77% *
Secondary endpoint #2: Patients reaching HbA1c <6.5% target	8%	18% *	18%	34% *	N/A *	31% *	35% *	N/A *	43% *
Secondary endpoint #3: FPG change	-4	-11	-10	-14	-18 *	-3	-18 *	-20*	-26 *
Secondary endpoint #4: PPG change	-7	-38 *	-64 *	-66 *	-78 *	-36 *	-63 *	-74 *	-83 *
Any adverse event	60%	56%	50%	67%	78%	57%	57%	70%	74%
Serious adverse event	2.8%	0	1.9%	1.8%	5.6%	0	1.8%	3.7%	0

* p<0.05

INSULIN

BIODEL's Viaject (ultra-rapid acting regular human insulin)

The company presented two posters at EASD, but they prompted more questions than they answered because Biodel used different methods to analyze the data from two open-label, parallel group, randomized, 6-month, non-inferiority trials, both of which were conducted in the U.S., Germany, and India. Both trials compared Viaject to recombinant human soluble insulin (RHSI). Both trials showed non-inferiority of Viaject to RHSI, with less weight gain and fewer severe and non-severe hypoglycemic events. However, the excess of injection site pain raises questions about potential patient acceptance of this therapy, and the exclusion of some of the patients in the Type 1 diabetes trial raises questions about the validity of the findings.

1. **Type 2 diabetics.** For this trial, Biodel included ***all*** the patients from all three countries in the analysis.

6-Month Results of Viaject in Type 2 Diabetics

Measurement	Viaject n=186	RHSI n=205	p-value
Primary endpoint: HbA1c change from baseline by LOCF	-0.3%	-0.5%	Met non-inferiority
Patients achieving HbA1c <7.0% by LOCF	30.6%	33.2%	Nss
Weight change	+0.6 kg	+1.8 kg	0.007
Adverse events			
Hypoglycemia	67.2%	71.7%	---
Severe hypoglycemia	2 patients	2 patients	---
Injection site pain at Week 2	23.4%	1.8%	---
Injection site pain at Week 26	10%	0.5%	---

2. **Type 1 diabetics.** For this trial, Biodel ***excluded the patients from India***, claiming that this was due to "a significant interaction of treatment" associated with the data from India (p=0.007).

6-Month Results of Viaject in Type 1 Diabetics

Measurement	Viaject n=131	RHSI n=140	p-value
Primary endpoint: HbA1c change from baseline by LOCF	-0.1%	-0.3%	Met non-inferiority
Patients achieving HbA1c <7.0% by LOCF	28.2%	27.9%	Nss
Weight change	-0.3 kg	+1.8 kg	0.007
Adverse events			
Hypoglycemia	9.6 events/month	9.9 events/month	---
Severe hypoglycemia	6.1%	14.3%	---
Injection site pain at Week 2	23.7%	1.8%	---
Injection site pain at Week 26	12.3%	3.2%	---

Continuous glucose monitoring devices (CGM)

Data published in the ***New England Journal of Medicine*** and presented at EASD found that CGM devices showed a significant improvement in glycemic control only in adults (≥25), not adolescents (15-24) or young children (<15). The 322-patient, 26-week, multicenter trial compared CGM devices to home glucose meter monitoring. Patients were provided with one of these devices: DexCom's DexCom Seven, Medtronic's MiniMed Paradigm Real-Time, or Abbott's FreeStyle Navigator. The study was powered to determine the value of therapy in each age group independently.

An industry source estimated that ~60% of CGM device users are adults, ~10% are adolescents, and ~30% are kids.

Key findings in this trial included:

- In adults (≥25 years): CGM lead to significant decreases in HbA1c, in the percent of patients decreasing HbA1c by 10%, and in patients achieving the goal of HbA1c 7.0%. Investigators suggested that this benefit over other age groups may be due to greater use of sensors.
- In adolescents (age 15-24), CGM failed to show any significant benefit on HbA1c.
- In kids (age 8-14), CGM failed to meet the primary endpoint, but showed some good benefits on secondary endpoints, which investigators suggested could be attributed to parental oversight.

The investigators concluded the results "do not shed light on the use of such devices in a less well controlled, less motivated population of patients with Type 1 diabetes." Dr. Laurie Laffel of the Joslin Diabetes Center in Boston speculated on why she thinks adults did better on HbA1c reduction than the other age group: "I suspect it is related to a larger percentage of patients in the youngest age groups showing worsening HbA1c. One in five (young) patients randomized to CGM had worsening HbA1c. I suggest that may be parents' efforts to eradicate low blood sugar first."

At a special session on the results of the Juvenile Diabetes Research Foundation (JDRF) study published in ***The Lancet*** which found CGM devices effective at lowering HbA1c only in adults, not adolescents or kids, experts discussed the implications of the findings. One expert said, "It seems that the best patients benefit when followed by the best teams." A JDRF official said, "We selected motivated patients. This device helps people who want to do better with their diabetes. Obviously, there is a population of kids who do not want to wear this device…We need smaller devices that are semi- and fully-automated systems."

Dr. Irl Hirsch of the University of Washington School of Medicine said, "The patients who do the best with the technology are those who show change in their behavior based on real-time administration. Successful use of RT-CGM (real-time CGM) requires more, not less, attention to diabetes

management…Clinicians are not jumping up and down right now to do this…There is a disincentive right now because of the time involved…(And) there is an additional cost with RT-CGM…Successful management of Type 1 diabetes continues to require a large amount of effort from patients and their families. No approach is ideal. CGM can add a tremendous benefit for the management of Type 1 diabetes and should now be considered standard of care for appropriate adults already practicing state-of-the-art intensive therapy."

Dr. Hirsch said patient acceptance of the devices was good, at least at his center, "Almost all patients (n=60) at our center wished to continue their sensor after the study ended."

Dr. Laffel said the adolescents in the trial had lower baseline HbA1c (by ~1%) and significantly more DKA (diabetic ketoacidosis) than adults at entry. She offered these comments on the trial: "Youth expect devices to make management easier. They have unrealistic expectations for 'cure' with the artificial pancreas…8-24-year-old males tend to have less frequent sensor use – to check their blood sugar less often …so it appears that behavior predicts behavior."

Dr. Laffel said that in the 8-14 age group CGM tends to be used least by the older children, and in the 15-24-year-olds it is used least by the youngest, "The picture is that ages 11-17 were the least likely to use CGM…There may be predictors of CGM use in youth that we can use to identify youth who may have barriers to CGM use to help us develop interventions to enhance application of CGM in pediatric patients and families …Imperfections in the current devices and in behavior should not preclude opportunities for improvement in control."

Asked about the lack of a consistent benefit across age groups in prevention of hypoglycemic events, Dr. Hirsch said, "The rate of severe hypoglycemia is drastically lower than in (landmark) trials, but hypoglycemia is still the rate-limiting aspect of this treatment."

Asked how the various devices compared in the study, a speaker said, "We specifically designed the study not to compare the devices, but we don't think there was a statistically significant difference among the devices."

Asked if payors are likely to use this trial to restrict reimbursement of CGM devices to adults, a speaker doubted that would happen, "We talked to most of the plans in the U.S. We plan a grassroots effort to ensure this powerful technology gets into the hands of people with diabetes. We think these devices can add value for all (age) patients…The consensus of the JDRF study group is that this is a powerful tool for kids as well as adults."

Most of the European doctors questioned at EASD about this study and its potential impact predicted that their CGM use would remain flat over the next year. The problem is not the study results, they said, but, rather, reimbursement difficulties and the desire for a closed loop system. Comments included:

- *Netherlands:* "Use is not going up because a closed loop system is still not there. I tend to use CGM just for diagnostics about once a year in ~5% of my (Type 1) patients. It usually gives me a lot of information when I use it. Cost is not the issue. It is mainly for patients on four-times-a-day insulin…I haven't used it in the hospital yet except in a research setting."
- *Italy #1:* "The devices are still experimental. My use is steady at about 5% of patients."
- *U.K.:* "Fewer than 10% of my patients use a CGM device, and that is not changing. It is expensive equipment…I don't use it in the hospital."
- *Italy #2:* "Adults need to think about that (trial) data. It is useful to use and maybe it does help with compliance …I use a CGM device for less than 1% of my patients, but that is increasing. When there are more reliable and less expensive meters, they will become the rule in younger diabetics.

26-Week Results of CGM Trial

Measurement	Patients ≥25 (adults)		Patients 15-24 (adolescents)		Patients 8-14 (children)	
	CGM n=52	Control n=46	CGM n=57	Control n=53	CGM n=56	Control n=58
Primary endpoint: Change in HbA1c	-0.50% **(p<0.001)**	+0.02%	-0.18% (p=Nss,0.52)	-0.21%	-0.37% (p=Nss, 0.29)	-0.22%
Secondary endpoint #1: Patients achieving HbA1c ≤7.0%	34% **(p=0.005)**	9%	14% (p=Nss,0.67)	18%	25% **(p=0.02)**	10%
Secondary endpoint #2: Patients achieving 10% drop in HbA1c	26% **(p=0.003)**	4%	14% (p=Nss, 0.46)	10%	29% **(p=0.04)**	12%
Hypoglycemic events	5 patients	4 patients	3 patients	5 patients	4 patients	6 patients
Rate of severe hypoglycemic events	43.4%*	26.3%	17.9%	23.9%	17.9%	24.4%
Use of CGM monitoring 6.0 days per week	8%	---	30%	---	50%	---
No severe hypoglycemia	90%	91%	95%	91%	93%	90%
Hypoglycemic events per 100 person years	43.4% (p=Nss, 0.66)	26.3%	17.9% (p=Nss, 0.64)	23.9%	17.9% (p=Nss, 0.664)	24.4%

*** Driven by one patient who had 6 severe hypoglycemic events on days when the patient had taken no insulin or no long-acting insulin for long periods. Without this patient the event rate for this group was 20.0%.**

What device is most popular? Among the doctors questioned at EASD, there was no clear favorite, and none of the doctors indicated any real share shifts were going on among the manufacturers. One doctor commented, "I have two patients on DexCom, and they are very enthusiastic. The Medtronic device works well, but the sensor only lasts three days, which is an issue because of cost. But I use the Medtronic device in the hospital." Another said, "We use Medtronic because we have a good relationship with the company."

Insulin pumps

Doctors interviewed at EASD estimated that an average of <5% of their insulin patients are on a pump, and they generally predicted that this would remain unchanged over the next year. Usually, they said, their staff or patients choose the device, without their input. Among the comments were:

- *Netherlands:* "Usually, the diabetes nurse shows patients all the devices and lets them choose the one they prefer."
- *U.K.:* "Fewer than 5% of my patients are on pumps because of funding. Use is up a little because reimbursement has relaxed a little, but over the next year I don't see any real increase…We use Medtronic and Roche pumps mostly because we are comfortable with those machines."
- *Italy:* "About 2% of my Type 1 diabetics are on a pump, and that is an increase over six months ago. Over the next year, I expect it to increase to about 5% of my patients… All the devices are pretty much the same."

INSULET's OmniPod

Finding OmniPod users was more difficult than pump or CGM users. The few doctors who commented were generally impressed with it. A U.K. doctor said customer service is okay, and he was unaware of any competitors on the horizon, "I start OmniPod if a patient has tried and been unsuccessful with all conventional means to control blood sugar, but the patient has to be motivated. I never start new insulin patients on OmniPod, only switching patients on a pump or injected insulin." An Italian doctor said, "I just saw OmniPod. I haven't used it yet, but it is wonderful! It will be very popular. I hope it is available to us quite soon."

MANNKIND's Technosphere inhaled insulin

Inhaled insulin didn't generate much attention at EASD this year, but Mannkind researchers remain optimistic that their product will succeed where others have failed. One researcher pointed out that Technosphere has a "unique" PK profile and a "less intimidating" inhaler. He also said that Mannkind is aiming at specific patients, not a broad switch from injected to inhaled insulin, "(Pfizer's) Exubera didn't offer anything beyond rapid-acting insulin, but ours is faster." He said Mannkind is completing Phase III trials now and intends to submit an NDA for Technosphere by the end of 2008. Asked about bioavailability, he said that he didn't know how much is absorbed in the lungs and that no bioavailability studies have been done yet. The company has done a two-year safety study in ~2,000 patients with high resolution CT scans and has not seen any pulmonary fibrosis.

Mannkind also has an inhaled GLP-1 in first-in-man studies.

ORAMED PHARMACEUTICALS' oral insulin

A researcher said this Israeli company has finished PK studies in Type 1 diabetes and is finishing a PK study in Type 2 diabetes. A six-week Phase II trial is expected to start in the next couple of months. The researcher said this oral insulin uses a GRAS (generally recognized as safe) material, not a new molecular entity (NME), as a carrier. Bioavailability is 5%-10%, but the researcher said they don't know yet the variability of the bioavailability.

OBESITY

"I'm glad to see obesity is now back where I believe it belongs – in the diabetes community," commented Dr. Nick Finer of Cambridge University in the U.K. Speaking at a Merck-sponsored symposium on obesity, he predicted that by 2050, 50%-60% of the U.K. population will be obese. He added that the chances of becoming obese increase by 57% if a friend becomes obese, by 40% if another adult sibling becomes obese, and by 37% if a spouse is obese. And he noted that 80%-90% of Type 2 diabetes is due to obesity.

The limitations cited for current and future drug therapy were:

- Weight loss is almost always ~8%-10%.
- There are no long-term effects and/or outcome studies.
- Ancillary therapy is insufficient.
- Cost.
- Concern about CNS-linked mechanisms of action.
- Side effects – valvular problems, suicidality, depression, memory loss, GI discomfort, blood pressure issues, mood disturbances, etc.

At the same Merck-sponsored symposium, Dr. Luc Van Gaal of Belgium reviewed current weight loss interventions:

- **ABBOTT's Meridia (sibutramine)** – works at 11 kg over 12 months which is maintained. Dr. Van Gaal said, "Authorities should more and more emphasize weight maintenance. The question remains to what extent weight loss will translate to outcomes. The first outcome trial is ongoing – SCOUT in 10,000 patients. No pulmonary hypertension has, to my knowledge, been reported with sibutramine."
- **ROCHE's Xenical (orlistat)** – newer data indicated it not only reduces weight but also reduces the incidence of Type 2 diabetes, probably due to improved insulin sensitivity.

- **SANOFI-AVENTIS's Acomplia (rimonabant)** – approved in Europe but not the U.S. Newer data show that stimulation of the endocannabinoid system increases weight and perhaps visceral fat and may contribute to Type 2 diabetes. It is too early to say that a CB1 blocker is able to reduce visceral fat; further studies are needed. There is a signal that CB1 blockade may, to some extent, contribute to the overall cardiovascular profile.

Other drugs in development or used off-label for obesity include:

- **NEUROSEARCH's tesofensine** – Data from a 24-week trial of tesofensine is in press in ***The Lancet***. That data reportedly shows a reduction of up to 12.5 kg in obese subjects but with an elevation of heart rate observed (~8 bpm at the high dose, which was the effective dose).
- **JOHNSON & JOHNSON's Topamax (topiramate)** – has not been studied extensively in obesity. An obesity trial was stopped due to side effects, but the drug is still used off-label. Dr. Van Gaal said, "In Europe what we do is if patients are under valproate for epilepsy, which gives weight gain, and if the neurologist can confirm topiramate is equivalent for that patient, then a shift to topiramate may help the patient in weight loss efforts."
- **Peptides** – more and more these are considered an option for obese patients.
  - **AMYLIN's pramlintide** (off-label) – Dr. Van Gaal said that data published in ***Diabetes Care*** showed good weight loss, and the weight loss was sustained at ~8 kg at the end of 12 months. He said it is associated with transient nausea in the beginning of treatment.
  - **AMYLIN's pramlintide + metreleptin** – Dr. Van Gaal said, "By itself leptin is not that effective in weight loss, but patients put on combination therapy, after initiation of pramlintide therapy, had additional weight loss. What is very interesting for the future is that the combination of pramlintide/metreleptin is not just giving you an additive effect, but it gives you a synergistic effect, and that, for me, is one of the interesting approaches for the future."
- **MERCK's taranabant** – a CB-1R inverse agonist has shown "interesting" reduction in body weight. Dr. Steven Heymsfield, global director of scientific affairs/obesity at Merck, reviewed the taranabant findings so far.
  - In Phase II, doses from 0.5 mg to 6 mg/day produced dose-dependent weight loss after 12 weeks of treatment.
  - In the first 52 weeks of a 104-week, double-blind Phase III study (Protocol 15) in 2,502 obese patients, taranabant led to durable and clinically meaningful weight loss. This study has not been formally presented or published yet. The highest doses tested – 4 mg and 6 mg – were associated with more weight loss than the low dose (2 mg), but with an increased incidence of adverse events. The 6 mg dose was discontinued near the end of the trial by the DSMB because of an excess of adverse events. Patients with a significant psychiatric diagnosis or who were taking >1 psychiatric medication were excluded.

Asked about the CNS side effects with taranabant, Dr. Heymsfield said, "It became clear the CNS side effects were of concern…So, we implemented a rigorous psychiatric protocol in our studies. If patients develop depressed mood, in certain situations they are referred to a mental health practitioner, so we are getting more detail on the psychiatric side effects…And we have added extension studies to all our studies, to gather as much data as possible."

Asked about the regulatory status of taranabant, Dr. Heymsfield said doses above 2 mg have been discontinued. The 6 mg dose is definitely "off the table," and the 4 mg dose was stopped, but a final decision on that for the future has not yet been made. He added, "The program is still ongoing, and a decision on when to file has not been made...We've done a

52-Week Taranabant Results in the Phase III (Protocol 15) Trial

Measurement	Placebo	Taranabant		
		2.0 mg n=417	4.0 mg n=414	6.0 mg n=415
Completers	65%	67%	65%	60%
Primary endpoint #1: ≥5% weight loss	37%	57%	64%	N/A
Primary endpoint #2: ≥10% weight loss	8%	26%	36%	N/A
Primary endpoint #3: Absolute change from baseline in body weight	-2.6 kg	-6.6 kg	-8.1 kg	N/A
Any adverse events	67%	85%	91%	88%
Drug-related adverse events	37%	45%	57%	55%
Serious adverse events	6%	8%	7%	7%
Drug-related serious adverse events	10%	13%	20%	21%
Discontinuation due to drug-related adverse events	7%	10%	16%	17%
Discontinued due to serious adverse events	1%	1%	1%	1%
Nervous system disorders	25%	23%	33%	29%
GI	29%	42%	47%	46%
Flushing	1%	3%	6%	5%
Psychiatric disorders	20%	26%	40%	36%
Depression	7%	9% *	11% *	11% *
Depressed moods/symptoms	4%	6%	7%	7% *
Suicidal ideation	0	0	0	<1%
Suicide attempt/completion	0	0	0	0

* p<0.05

large wave of studies of 2 mg to 6 mg, and now we are in a second wave of studies of 0.5 mg to 2 mg…Then the decision will be made."

Asked how taranabant differs from Sanofi-Aventis's rimonabant, which gained European but not FDA approval, Dr. Heymsfield said, "Until there is a head-to-head study, it is hard to know clinically. The additional answer is they are different drugs. Taranabant is more selective, has fewer off-target effects, and is more potent, so you can give lower doses…The half-life of taranabant is shorter."

Asked about the use of taranabant in diabetics, Dr. Heymsfield said, "We have done and are doing Protocol 11 in naïve diabetics and diabetics on metformin, and those results will be finished and presented at the North American Association for the Study of Obesity (NAASO) meeting in Phoenix October 3-7, 2008."

Asked if Merck has plans for a full cardiovascular outcomes trial with taranabant, Dr. Heymsfield said, "Not at the moment…The company is still thinking hard about how to position the drug."

Asked about the type of psychiatric patients excluded from the trial, Dr. Heymsfield said, "Patients with real depression (were excluded) – real depression as defined by DSM-III criteria and people on >1 psychiatric medication. In the study we captured a large population of patients who might come for obesity treatment…Having a drug class that affects mood in people brings forth how much depression there is in the general population…So, I think we are in a new frontier in unraveling all this." Dr. Van Gaal added that the depression and mood disturbances with Acomplia are "definitely drug-mediated, and the endocannabinoid system is involved."

Asked which drug he would choose for which patients, Dr. Nick Finer of Cambridge University, U.K., said that, except for a situation where a particular drug is contraindicated, he would:

- Not give Xenical to patients with inflammatory bowel disease, diverticulitis, etc.
- Use Acomplia for patients complaining of hunger.
- Give Xenical to organized patients who are doing well adhering to a low fat diet.
- Use sibutramine for snackers, but he would not give it or Acomplia to people on an antidepressant.
- Reserve Acomplia and taranabant for patients with cardioembolic risk factors.

SGLT2 Inhibitors

Concerns and Advantages of SGLT2 Inhibitors

Concerns	Advantages
Polyuria	Glucose effect independent of insulin
Upper respiratory tract infections	Weight loss expected
Electrolyte disturbances	Low risk of hypoglycemia
Genitourinary infections	

At a session sponsored by Bristol-Myers Squibb and AstraZeneca, the audience – two-thirds of whom were European doctors – was questioned about its thoughts on this class of drugs. Among the findings were:

- 46% said the results of ACCORD/ADVANCE/VADT have affected their view on the importance of glycemic control for selected patients only, and 35% said those trials have made them think quite differently.
- 39% said the most important problem in treating hyperglycemia is failure to achieve HbA1c targets, followed by weight gain (21%) and hypoglycemic events (21%).
- The most important potential advantage of SGLT2 inhibitors is their novel mechanism of action, much more than their lack of weight gain, lack of hypoglycemia, or blood pressure lowering.
- The most important potential side effects of SGLT2 inhibitors are genitourinary infections, followed by electrolyte disturbances.
- The greatest barrier to physician use of SGLT2 inhibitors will be concern about potential mechanism-related adverse events and lack of hard endpoint data.

SGLT2 Inhibitors in Development

Company	Drug	Status
Astellas	ASP-1941	Phase II
Astellas/Kotobuki	YM-543	Phase II
Boehringer Ingelheim	BI-10773	Phase I/II
Boehringer Ingelheim/Ajinomoto	BI-44847	Phase I/II
Bristol-Myers Squibb/AstraZeneca	Dapagliflozin	Phase III
Dainippon Sumitomo/Kissei	DSP-3235	Phase I
GlaxoSmithKline/Kissei	Remogliflozin	Phase II
GlaxoSmithKline/Kissei	Sergliflozin	Phase II
ISIS	ISIS-388626	Preclinical
Johnson & Johnson/Mitsubishi Tanabe	TA-7284 (JNJ-28431754)	Phase II
Roche/Chugai	R-7201	Phase II
Sanofi-Aventis	AVE-2268	Phase II
Sanofi-Aventis	SAR-7226	Phase I
Taisho	TS-033	Phase II
Tanabe	T-1095	Phase II (discontinued)

How might SGLT2 inhibitors be used if they were approved? Dr. John Wilding of the U.K. said, "These agents have the potential to be used anywhere in the treatment algorithm…I think metformin will remain the first-line diabetes treatment for some time to come…but once you need to add a second agent, then choosing an agent which doesn't cause weight gain or which causes weight loss is good…and may improve compliance…but I also see use for these agents later on in the course of diabetes. I think we all have many patients on multiple agents who are still struggling to achieve control and don't wish to go onto insulin. There may be a role there. And there may be a role in patients on insulin where weight gain is a problem." Another expert said, "If the safety profile is reassured, I think you can place this agent anywhere. I would like to use it on Day 1 of diagnosis, even in untreated people because this could help stop progression from IGT (impaired glucose tolerance) to overt diabetes…The risk would be dehydration."

How serious is the polyuria side effect? The estimate was that it would increase daily urine by 200-400 ml, which was described as one additional bladderful of urine per day. An expert said most patients wouldn't consider that a major problem.

Could this be a purely weight loss drug? Dr. Wilding said, "Obviously, it has crossed my mind that this could be a possible use of these agents…The effect would likely be similar to orlistat (Roche's obesity drug Xenical)...It may not produce the dramatic weight loss patients might expect."

Are these agents safe in the elderly? Dr. Wilding said, "One would have to be cautious in that group…but there may be potential advantages in terms of the number of patients who might require insulin treatment."

BRISTOL-MYERS SQUIBB/ASTRAZENECA's dapagliflozin

Dr. Wilding said dapaglifozin may differentiate itself because of a long half-life in humans (16 hours) and renal excretion (~75% is recovered in the urine, primarily as glucuronide). In Phase I and Phase IIa trials, no serious adverse events were observed, and safety looks good; the most frequent side effects were constipation, nausea, and diarrhea. There is also a low risk of weight gain or hypoglycemia.

MISCELLANEOUS DRUGS TO WATCH

INTEKRIN THERAPEUTICS' INT-131 (formerly AMG-131) – a non-TZD selective PPAR-γ modulator (SPPARM). In a six-month safety study in cynomoglus monkeys and in rats, the typical TZD effects of weight gain, fluid retention, hepatic toxicity, and cardiovascular pathology were not seen with INT-131 at 70 times the highest dose being used in an ongoing Phase IIb study in Type 2 diabetics.

ROCHE's RO-489620 – A Roche researcher said Roche has discontinued development of this glucokinase activator due to elevated ALT (liver enzymes). However, he said Roche has a back-up compound in Phase I which will soon start Phase II.

SANWA KAGAKU KENKYUSHO's SKL-14959 – *In vitro* and *in vivo* studies of this low molecular weight antagonist of glucose-dependent insulinotropic polypeptide (GIP) suggest it (1) reduces weight without a decrease in food intake and (2) improves insulin resistance.

VEROSCIENCE's Cycloset (oral, quick-release bromo-criptine mesylate) – This agent has been around for a very long time, but there appeared to be renewed interest in it at EASD. A company official said the FDA approvable letter required a large safety trial, and a 3,000-patient trial has been completed and filed with the FDA. Dr. Anthony Cincotta presented data from this trial. Compared to placebo, Cycloset reduced the pre-specified cardiovascular outcome (MI, stroke, hospitalization for unstable angina, CHF, or revascularization) by 42% at one year (HR 0.58) and reduced MACE (death, MI, stroke) by 55% (HR 0.45). He said, "Daily morning pulsatile delivery via the Cycloset formulation improves glycemic control after 24 weeks of therapy. Morning Cycloset therapy for Type 2 diabetes is a potential new approach for treating the microvascular and macrovascular complications of this disease."

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