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by Lynne Peterson

SUMMARY

Endocrinologists don't believe the incretin mimetics cause pancreatitis, so FDA warnings are not dampening their enthusiasm.

♦ Doctors are dubious that long-acting insulin analogs promote tumor growth. Novo Nordisk is trying to distance Levemir from Sanofi-Aventis's Lantus, suggesting that ***if*** there is a problem, it is with Lantus, not Levemir.

♦ Doctors are not convinced that Novo Nordisk's GLP-1, Victoza (liraglutide), causes thyroid cancer and dismissed C-cell hyperplasia as an animal, not human, issue.

♦ Bristol-Myers Squibb's DPP-4, Onglyza, was generating little excitement, but it is expected to expand the DPP-4 market which currently accounts for <10% of patients on oral diabetes drugs, especially in lieu of sulfonylureas, rather than taking share from Merck's Januvia. The key limitation on DPP-4s is cost. ♦ New drug "fatigue" has settled on the diabetes community, and there is no excitement about new ***classes*** of drugs. Bristol-Myers Squibb/AstraZeneca's dapagliflozin, the most advanced SGLT-2, has only modest efficacy, and doctors are very concerned about genitourinary infections, though there is no evidence they will lead to pyelonephritis. ♦ Roche's once-weekly GLP-1, taspoglutide, may be the category killer. Doctors speculated it may be as efficacious as Victoza, better than Amylin/Lilly's Byetta, and more convenient than either.

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EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD)

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Attendance at EASD was up this year compared to last year, but it wasn't due to excitement about drugs in the pipeline. If anything, there was a sense of "new drug fatigue" at the meeting, which isn't surprising given the triple whammy concerns about the risks of cardiovascular events, pancreatitis, and, most recently, cancer with anti-diabetic agents. Dr. Thomas Pieber of Austria said, "There are new and interesting developments…and some of the pathophysiology behind (the new agents) is quite convincing…but at the end of the day…we have to evaluate how good they are, and if they are really superior to what we have now."

Thus, EASD this year was dominated by three things:

- Furor over the question of a link between **insulin analogs and cancer**. At least 7,000 people attended a symposium on this issue, with nearly as many people watching from the foyer as were riveted to their seats in the 4,000-seat room.
- Discussion – and dismissal – of a concern about **pancreatitis with the incretin mimetics** (GLP-1s and DPP-4s) but recognition that all drugs in the class are likely to get similar warning labels.
- Marketing of the approved **GLP-1 and DPP-4s** and interest in newer and longer-acting versions.

Dr. David Nathan of Harvard is a self-admitted critic of some of the new agents, but he insisted at EASD that he is not a Luddite, not opposed to all things new, but he would like to see new agents judged on comparative effectiveness. He reiterated a comment he made earlier this year in the ***New England Journal of Medicine***: "In theory, newer classes of anti-diabetes medications might be welcome additions to the existing armamentarium; however, those that have been developed recently are generally no more potent, and often less effective, in lowering hyperglycemia than the three oldest classes (insulin, the sulfonylureas, and the biguanides), all of which are more than 50 years old."

The number of diabetics is continuing to grow. According to the Centers for Disease Control and Prevention (CDC), ~24 million Americans were diabetic in 2008 – 1+ million Type 1 and 22 million Type 2, of which 6 million were undiagnosed – and another 42 million have pre-diabetes. By 2030, it is estimated that more than 350 million people worldwide will be diabetic.

Dr. Nathan would like to see more individualized therapy, "With rare exceptions we treat all patients with Type 2 diabetes as if they are the same. There is an appalling lack of understanding regarding the inter-individual differences in response to therapies. There have been few head-to-head comparisons; big pharma

is not interested in doing this…And there has been inadequate phenotyping/genotyping at baseline, and even when phenotyping/genotyping is performed, it generally has not been analyzed according to differences in the population."

Dr. Nathan urged a shift in drug development targets to more focus on:

- **Prevention.**
- **Secondary interventions** – in acute control to alleviate symptoms and in chronic control to adequately reduce/ prevent development of long-term consequences.
- **Tertiary interventions** to prevent complications that have developed from becoming worse.
- **Insulin secretion**, not insulin resistance.

Less aggressive therapy for the elderly?

Like Dr. Nathan, Dr. Edwin Gale, editor-in-chief of the EASD journal, ***Diabetologia***, challenged doctors to start thinking differently about oral treatment of diabetes – to focus on individualized therapy – particularly in the elderly. He questioned the value of aggressive HbA_{1c} lowering (to ≤7.0%) in the elderly (those >age 65) and even more so in those over age 75. He said, "You have to recognize that there is a cost to the individual…Our patients have the right to know what the benefits are…I think we have been perhaps too sensitive in leaving age out."

He noted that one-third of people with Type 2 diabetes are over age 60 when diagnosed, only one-third of these will achieve a target HbA_{1c} <7.0%, and a "disproportionate" number of those who do meet that goal are relatively early in treatment. He said that people over age 65 who don't already have retinopathy or nephropathy are very unlikely to develop it to the point of disability.

Dr. Gale asked, rhetorically, why diabetes doctors are so "obsessed with glucose control." He contended that targeting HbA_{1c} <7% in people over age 65:

- Does not improve quality of life.
- Does not improve mortality.
- Does not reduce cardiovascular events other than MI.
- Has been unsuccessful at a public health level.
- Is not cost-effective.
- Has negative consequences for some patients.
- Distracts from other health priorities.

Before treating these elderly patients aggressively, Dr. Gale suggested asking:

- *Will they feel better?* They may have more hypoglycemia, and symptomatically they may not see any improvement.
- *Will they live longer?* Insulin increases survival when introduced in young patients, but there is only a marginal benefit on mortality in the elderly. He pointed out that Type 2 diabetics on insulin have not, on average, lowered their HbA_{1c} very much (from 8.5% to 8.4%) despite a "heavy" investment in long-acting insulin analogs.
- *Will patients experience fewer complications?* Dr. Gale said it has been estimated that:
  - 30 people would have to be treated to a goal of HbA_{1c} 7% for five years to prevent one coronary (which the patient will survive).
  - Over age 65, 1,000 patients would have to be treated to prevent one episode of blindness, and after age 75 there is no blindness prevention benefit at all.
  - After age 65, 1,000 patients would have to be treated to prevent one end stage renal failure.
- *Is it cost-effective?* Targeting <7% is very effective for people age 25-35 but not for people over age 65. In contrast, blood pressure treatment is cost-effective across all ages.

One suggestion Dr. Gale had: pay-for-performance (P4P) for glucose control. He said that P4P has been very successful in cardiology with cholesterol lowering, "I think historically our approach to diabetes has been the belief that we can eliminate it. I think that is garbage...The future of humanity is learning how to live with diabetes…The only thing that will change the percentage of diabetics is lifestyle changes, war, or a depression…We should not treat diabetes as a medical problem but as something that affects everyone in the community."

Outcomes Treating Elderly Diabetics with Insulin

Measurement	Intensive insulin therapy	Conventional insulin therapy
Outcomes per 1,000 patient years/~5 years		
MI	51	59
CVA	26	29
Heart failure	32	35
CV death	34	35
All deaths	68	69

Value of Intensive Insulin Therapy by Age

Measurement	Age 45	Age 55	Age 65	Age 75
Lifetime risk of blindness				
HbA_{1c} 7%	~ 4%	~ 1.5%	~ 1%	~ 1%
HbA_{1c} 8%	~ 11%	~ 5%	~ 2%	~ 1%
HbA_{1c} 9%	~ 26%	~ 12%	~ 5%	~1%
Cost-effectiveness by age				
	26-34	**45-64**	**65-74**	**75-84**
Intensive glucose control	$10,000	$37,000	$154,000	$401,000
Cholesterol reduction	$141,000	$53,000	$40,000	$110,000

PANCREATITIS AND THE INCRETIN MIMETICS

Just days before EASD, the FDA announced it is revising the label for Merck's Januvia (sitagliptin) and Janumet (sitagliptin/metformin) to include information on 88 reported post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis. The new labeling will (1) include information on these cases, (2) recommend that healthcare professionals monitor patients carefully for the development of pancreatitis after initiation or after dose increases and discontinue the drug if pancreatitis is suspected while using these products, and (3) note that sitagliptin has not been studied in patients with a history of pancreatitis.

In May 2008, the FDA warned it had received reports on 89 cases of pancreatitis (1 of which was fatal) in patients taking Amylin/Lilly's Byetta (exenatide). Then, in August 2008 a new warning was issued for Byetta after the Agency received reports of 6 cases of hemorrhagic or necrotizing pancreatitis in patients taking the drug. Two of those patients died.

Questions about a link between incretin mimetics and pancreatitis had been circulating long before any of these FDA warnings, and U.S. and European endocrinologists generally have contended that the risk with the mimetics is no worse than the background rate in the diabetic population. That hasn't changed; doctors as well as industry sources questioned at EASD continued to believe that this is a non-issue. However, they also believe that all DPP-4s and GLP-1s are likely to wind up with a similar class warning.

Dr. John Buse, chief of endocrinology at the University of North Carolina School of Medicine and a past president of the American Diabetes Association, said, "The recent statement from the FDA was that there were a moderate number of cases reported with DPP-4s…The problem with this post-market surveillance is you have a very hard time knowing whether that pancreatitis is related to the drug or just because pancreatitis happens in people, particularly overweight people and people with diabetes. My personal view is the risk of pancreatitis with DPP-4s is probably vanishingly low, not zero but vanishingly low. There is increased risk of pancreatitis in diabetics in general, and it is something patients should be aware of, so if they have the symptoms, they should hold off taking the next tablet until they speak with their physician."

A European endocrinologist added a slightly more cautionary note, "What Dr. Buse said is correct, but there are one or two shadows on the horizon which are causing some concern. As you know, exenatide has been associated with pancreatitis… When the GLP-1s and DPP-4s came in, there started to be a little concern the effects seen with exenatide might be generic. And there have been some highly controversial animal studies …showing that with exposure to various different GLP therapies, you get proliferation of pancreatic duct cells. A study to be published (soon) in ***Diabetologia***…shows that if you compare pancreatic duct cell profiles in human post mortems from lean non-diabetics, lean diabetics, obese non-diabetics, and obese diabetics, there is an increased rate of ductal proliferation with (a) obesity and (b) diabetic obesity… So, Dr. Buse is correct…but there is a longer term concern."

Other comments about pancreatitis included:

- *Germany #1:* "My position is there is no proof that there is an increased risk of pancreatitis with exenatide or another diabetes medication."
- *Germany #2:* "Pancreatitis is not a high concern. Things like that happen often…There is no evidence of an increased risk. Some cases are terrible for the individual, but there is no evidence the drug causes it…I try not to induce fear in patients. I don't point it out to patients, but if they ask, I give a lot of information, and this is on our information sheet."
- *Netherlands:* "The data don't support a concern, but that's the FDA."
- *U.K.:* "If you look at the number of reports of pancreatitis on (diabetes) drugs vs. the number of diabetics with pancreatitis, you are in the same ballpark. Normally, things are under-reported. These reports of symptoms of pancreatitis resolved when the drug was stopped, but the pancreatitis was treated at the same time. And not all cases were confirmed, which makes it very difficult. I haven't seen any evidence that any of these drugs cause pancreatitis. You can't make a causal conclusion…I guess we need several years to be absolutely sure."

AMYLIN/LILLY's Byetta (exenatide)

Dr. Gary Bloomgren of Amylin provided new data at EASD which showed Byetta was not associated with an increased rate of pancreatitis. Dr. Bloomgren's study was a 9-month, retrospective, cohort review of claims made to a major insurer (with >14 million covered lives) from September 2004 to December 2007, looking for acute pancreatitis in patients initiating Byetta vs. other anti-diabetic drugs (OADs). He insisted there is "no biologic mechanism for exenatide-induced pancreatitis."

Retrospective Review of Pancreatitis with Byetta

Time period	Byetta n=25,719	Other anti-diabetic drugs n=234,536
Crude pancreatitis incidence per 100,000 patient years		
Current users	220	227
Recent users	321	326
Past users	355	218
By ITT analysis	273	228
Adjusted rate of pancreatitis per 100,000 patient years for Byetta vs. other OADs		
Current users	0.9	
Recent users	0.9	
Past users	1.4	
ITT analysis	1.1	

Interestingly, Dr. Bloomgren said Byetta initiators are more likely to be female, age 45-64, with comorbidities, and a "little further along" in the continuum of their disease. He also reported that 40% of Byetta pancreatitis cases and 33% of OADs were confirmed by chart review, so the positive predictive value of an ICD-9 577.0 chart entry is only 50% in any position and 58% in the primary position.

NOVARTIS's Galvus (vildagliptin)

Novartis presented a poster at EASD, claiming that Galvus is not associated with an increase in pancreatitis. The conclusion came from a pooled meta-analysis of 33 Galvus randomized clinical trials comparing Galvus to "all comparators."

Meta-Analysis of Pancreatitis in Galvus Trials

Time period	Galvus 50 mg QD n=2,003	Galvus 50 mg BID n=5,601	Comparator n=5,667
Any pancreatitis-related adverse event	0.1% (SYE 0.24)	0.1% (SYE 0.10)	0.2% (SYE 0.15)
Pancreatitis	0 (SYE 0)	0.1% (SYE 0.04)	0.1% (SYE 0.08)
Acute pancreatitis	0.1% (SYE 0.16)	0.1% (SYE 0.06)	0.1% (SYE 0.05)
Lipase increased	0 (SYE 0.09)	0 (SYE 0.08)	0 (SYE 0.02)
Odds ratio	0.90	0.78	---

CANCER AND INSULIN ANALOGS

The question of cancer and insulin arose from a study from Germany which found an increased cancer risk with Sanofi-Aventis's long-acting insulin analog Lantus (insulin glargine). It was submitted to ***Diabetologia*** for publication, and editor-in-chief Dr. Gale said that before he would publish this "highly controversial study," he asked Sweden and Scotland to do national studies to see if there was anything to the German report, "We expected the two (new) studies to be entirely negative, and we thought we could publish them simultaneously with the German study…Instead, what worried us was that the Swedish study showed a significant increase in breast cancer with glargine alone, and in one analysis, the Scotland study showed a significant effect for breast cancer, though in another analysis there was a non-significant trend…The message we published is that there is a question about breast cancer because if there is any cancer, it is that one…We decided this needed further consideration."

The message at EASD

Cancer and insulin was a front and center topic at EASD, and it was ***very*** controversial. There was only a little bit of new data presented at the meeting, but it actually reconfirmed the association between insulin and cancer. Yet, experts were emphasizing that this is an ***association***, not proof of causation. Most experts said they were not going home and warning patients about any potential cancer risk from insulin – not even patients at higher risk of breast, pancreatic, or colorectal cancer (the three cancers with the highest incidence among Type 2 diabetics).

However, the European Foundation for the Study of Diabetes, the research foundation of EASD, is committing €3 million to support basic and clinical research on this issue. And the EASD executive director declared, "All diabetes textbooks from now on will have a diabetes and cancer discussion."

The bottom line was:

- **Diabetics have an increased risk of cancer**, regardless of the medication they are on. Having diabetes raises the risk of mortality from cancer. A meta-analysis of cancer incidence in men based on body mass index (BMI) found that the risk ratio increased for most cancers as BMI went up. Cancer mortality also is strongly associated with obesity, and obesity is linked to diabetes.
- **Metformin and perhaps TZDs, but not sulfonylureas (SUs) appear to be somewhat protective** against cancer and are starting to be explored by the oncology community.
  - *Dr. Jeffrey Johnson of the University of Alberta, Canada*, said metformin may have a special effect on the body that modulates the cancer risk, "Using a health database from Canada, we saw ~25% reduction in cancer mortality in patients using both metformin and a TZD…What is very interesting to me is that both these drugs are now being studied in clinical trials in cancer patients…Epidemiologic evidence suggests a negative role for SUs and a positive role for TZDs...but we are awaiting more definitive clinical trials."
  - *Dr. Ulf Smith of Sweden* said, "What really comes out as a very important conclusion is that metformin and also TZDs may reduce the cancer risk. Basically, we do not for sure know the mode of action of metformin. We have some idea, but we don't know for sure how it reduces the risk of cancer…The story with metformin is extremely exciting…(According to a recent paper) the pathogenesis of cancer and metastasis is linked to cancer stem cells which remain even after chemotherapy...and metformin (appears) able to target cancer stem cells. This is a conclusion which is extremely important and interesting."
  - *Dr. Jay Skyler of the University of Miami, a Sanofi-Aventis consultant*, said, "I think…in the analysis…it was evident that sulfonylurea has increased risk as well. What was more remarkable was the decreased risk with metformin. The metformin thing may turn out to be the most interesting aspect of all of this."
- **Insulin may promote tumor growth**, but it doesn't *cause* a person to develop an initial cancer.

- There is an **association between insulin and cancer**, but it is an ***association***, not a cause. However, one speaker noted a dose-response association between insulin and cancer in Type 2 diabetes that could support causality. Another speaker said, "No one has ever suggested that glargine or any other insulin causes cancer. That has never been brought up. What we are worried about is the potential that already existing cancers, small cancers, can grow faster – growth promoting effect – but no one has ever suggested that insulin causes cancer."
- The **cancers most associated with diabetes** – and insulin – appear to be breast, pancreas, and colorectal. Prostate cancer actually is associated with a lower risk of cancer in men, which may be due to hormonal factors.
- There is **a possible mechanistic explanation** for how insulin could be associated with cancer. Dr. David Russell-Jones of the University of Surrey, U.K., said there are two possible mechanisms:
  1. Increased duration of action of the insulin receptor – but none of current insulin analogs have a problem with this. They are all the same as human insulin.
  2. Differential binding to the IGF-1 receptor. On this, Dr. Russell-Jones said the insulin analogs do differ.
- **Insulin resistance** is associated with both an increased cancer risk and an increased cancer mortality in Type 2 diabetes.
- This topic is now **going to be researched** to death, so it will stay in the news. Among the topics EASD believes need to be explored are: The links between metabolism, cell turnover, and cancer; possible non-diabetic use of metformin and TZDs; understanding the link between insulin resistance and cancer; targeted screening of high-risk groups; and understanding why people with diabetes have a higher mortality from cancer.
- There is **no statistically significant difference between Sanofi-Aventis's Lantus (insulin glargine) and Novo Nordisk's Levemir (insulin detemir)** on cancer.

The problem

Dr. Gale, the editor-in-chief of ***Diabetologia***, said, "What has emerged in the past few months is a whole new area – diabetes and cancer…Breast cancer is a leading cause of death in non-diabetic women under age 55…In diabetes, cardiovascular (CV) disease is the leading cause of death of women of all ages…(Diabetic women) are not only at risk for CV disease but also death from breast cancer. If they develop breast cancer, they are ~5% more likely to die from it than women without diabetes."

Dr. Craig Currie, an epidemiologist from the U.K., presented a large observational study done in the U.K. that compared insulin alone to insulin plus metformin, looking for a recorded diagnosis of a first solid tumor. He concluded, "There was a dose-response association between insulin and cancer incidence in Type 2 diabetes, supporting the principle of causality. Metformin attenuated cancer risk in all but the highest insulin dose, with variability by tumor site."

Asked if these data are definitive, Dr. Currie said, "They are not definitive. As an epidemiologist, they alert us to the strong possibility that there is (an association)…but there is a distinct possibility that if this is reported improperly, some people will be hospitalized…So, it has to be reported with care…There is an epidemiologic association between high dose insulin in Type 2 diabetes and increased risk of cancer. We need to look further to see if that is the case, and if that is the case, my clinical colleagues will advise doctors how to handle this."

Cancer and Diabetes

Treatment	Odds ratio for cancer among diabetics
Case control analysis for pancreatic cancer	
No treatment	1.0
Metformin	0.38
Sulfonylurea (SU)	2.52
Insulin	4.99
Published studies on cancer risk with Lantus vs. other insulins*	
Germany	0.86
Sweden	1.07
Scotland	1.02
UK THIN	0.81
Meta-analyses of diabetes and cancer risk 2005-2007	
Breast	1.20
Pancreas	1.82
Bladder	1.24
Colorectal	1.30
Endometrial	2.10
Prostate	0.84
Canadian retrospective cohort study of cancer risk	
SU	1.30 (cancer mortality)
SU + metformin	0.96
Metformin monotherapy	0.81
Metformin + TZD	0.74
Insulin <12 years	1.67
Insulin ≥12 years	6.9

*Confidence intervals all cross 1

Cancer and Insulin

Time on insulin	Events per 1,000 patient years *(compared to a rate of 10 for metformin alone)*	
	Insulin + metformin	Insulin only
Crude rates		
<7 years	9	15
7-10 years	12	15
11-15 years	11	19
>15 years	34	60
Hazard ratio adjusted for age, sex, and smoking status		
<7 years	0.87	1.05
7-10 years	1.12	1.21
11-15 years	1.07	1.92
>15 years	3.20	5.73

Lantus and Levemir

The day before EASD started, Sanofi-Aventis announced a plan to do a methodical and robust study of this issue. Novo Nordisk officials said they do not plan to do a similar study. Rather, they held their own briefings and tried to distance their drug from Lantus, saying basically that they don't believe any of the long-acting insulin analogs promote cancer, but if any of them does, it is Lantus, not Levemir.

Dr. Skyler, the Sanofi-Aventis consultant, made a case that news stories implying that Lantus causes cancer were "unwarranted" and "unsubstantiated." He said a meta-analysis of the Sanofi-Aventis randomized clinical trials database looking at Lantus vs. human insulin found an adjusted hazard ratio for cancer of 0.63 – definitely not an increased risk. An analysis of cancer rates in 26 uncontrolled Lantus trials found the risk of all cancers generally – and breast cancer specifically – was not increased with Lantus vs. comparators. Dr. Skyler said, "My conclusion: Insulin glargine does not cause cancer."

Risk of Cancer with Lantus vs. Comparators

Cancer	Lantus	Comparator	Relative risk
All cancers	0.80	0.88	0.90
Skin	0.20	0.11	1.85
Colorectal	0.11	0.19	0.55
Breast	0.07	0.11	0.62
Gastrointestinal	0.11	0.08	1.38
Analyses of cancer rates			
Controlled studies (31)	0.63	---	---
Uncontrolled studies (26)	5.00	4.63	---

Dr. Russell-Jones, U.K., tried to make a case that Novo Nordisk's Levemir has a lower cancer risk than Lantus. He presented soon-to-be-published data from the Levemir database, and the event rate per 100 patient years was higher with Lantus than Levemir, but the difference was not statistically significant. He said, "There is no indication in the papers of any problem with insulin detemir…There is no potential cause for concern (with Levemir)."

Risk of Cancer with Levemir vs. NPH Insulin

Cancer	Event rate per 100 patient years	
	Levemir n=3,983	NPH n=2,661
All cancers	0.36 (p<0.05, OR 2.53)	0.92
Breast	0.04	0
Colorectal	0	0
Pancreas	0.04	0.28
Skin	0.09	0.14

Novo Nordisk officials insisted there is no evidence of a cancer signal with Levemir and "no *a priori* reason to believe that detemir carries a risk for increasing mitogenicity." Without ever specifically saying it, Novo Nordisk officials suggested that – if there is any link between cancer and long-acting insulin analogs – the problem is with Lantus, not Levemir. And they laid out some reasons why this might be the case, pointing out that Lantus is very similar to another long-acting insulin analog that they were developing (called X10) but dropped because of tumorgenicity in female Sprague-Dawley rats.

Peter Kurtzhals, senior vice president of diabetes research for Novo Nordisk, said that regulatory bodies are now asking that all insulin analogs be tested on a panel of cell lines, "Across all cell lines, detemir has reduced mitogenicity vs. human insulin…Detemir is equivalent to human insulin for molecular assay parameters…Novo Nordisk analogs have been rationally designed with molecular safety as a key endpoint…There is a standardized program required by regulatory bodies on safety. EMEA and FDA request testing of analogs in cells, receptor models, and animals for 2 weeks. There is no request for two-year carcinogenicity studies unless there is a cause for concern, and cells and preclinical SIBA and SIAC are both clear. Detemir has very low affinity for the IGF receptor… There is no cause for concern with SIBA and SIAC, so the expectation was that we would do 52-week toxicology studies, and those are completed and completely safe."

Comparison of Various Insulin Analogs *

Measurement	Human insulin	Novo Nordisk's X10	Novo Nordisk's Novolog	Lilly's Humalog	Sanofi-Aventis's Lantus	Novo Nordisk's Levemir
Mitogenic potency						
Insulin receptor affinity	=100	205	92	84	86	72
IGF-1R affinity	=100	587	81	156	641	64
Insulin receptor off rate	=100	14	81	100	152	204
Metabolic potency	=100	207	101	82	60	108
Mitogenic potency	=100	975	58	66	783	44
Mitogenicity in various cell lines						
Saos/B10	=100	975	---	---	783	44
MCV-7	=100	425	---	---	656	60
CHO-K1	=100	---	---	---	---	36
HMEC	=100	426	---	---	650	68
L6-hIR	=100	246	---	---	49	37

* Source: Novo Nordisk

Another Novo Nordisk official said, "There are no plans to run (cancer or database) studies because we have no concern about cancer."

Risk of Cancer with Levemir vs. Lantus

Cancer	Event rate per 100 patient years	
	Levemir n=1,219	Lantus n=830
Breast	0.11	0.48
Bladder	0.22	0
Colorectal	0	0.16
Lung	0.11	0.32
Pancreas	0.11	0.16
Skin	0.22	0.16

Asked if there is a need or urge to take further action on preclinical or clinical data on the Levemir/cancer issue, a Novo Nordisk official said, "You always have to have a medical hypothesis underlying a hazard, and from a scientific and medical perspective, we know our analogs have no cause for concern. There is even a reduced mitogenic potential… And, with several million patient-years, we haven't found any (cancer) signal…Nor, did we find one in the meta-analysis where we had small numbers but a robust sign (of no problem)…This makes us feel that, while the lab will continue to investigate the safety of this and other products…we have no cause for concern and no need to do anything further at this time."

Impact on clinical practice

Most experts at EASD were adamant that they are not changing their practice or even informing patients about any potential risk of cancer. Only one said he is going to inform patients about it and note that in the patient's chart, but he does not plan to have patients sign an informed consent form.

- *Dr. Johnson, Canada:* "Guidelines around the world suggest metformin should be the first-line therapy…and epidemiologic evidence to date continue to support that… Metformin has greater benefits than we thought. SUs and TZDs are second-line and should remain second-line therapy. Epidemiologic evidence suggests there might be some benefits of TZDs on cancer, but TZDs have well-known cardiovascular risks. Therefore, the new evidence in these stories don't change treatment recommendations …I think we shouldn't change therapies. I think we might be more cautious before we push early and aggressive insulinization…There is a lot of interest in that, but the full risks are not fully understood yet."
- *Dr. Smith, Sweden:* "I'm not changing clinical practice – yet…My real conclusion is we need to understand much more about this…At least we are raising issues that need to be clarified. With metformin, we are at the stage we can say that it must be first-line therapy."
- *Netherlands:* "It's not really a concern. I'll tell patients only if they ask."
- *Dr. Michael Stumvoll of the University of Leipzig, Germany, honorary EASD secretary:* He compared this issue to the early days of cholesterol and the Framingham Heart Study, saying "Maybe we are some 20-30 years away from those kind of conclusions, but often times in clinical medicine, these things start on an epidemiologic basis."
- *California endocrinologist:* "I'll tell patients about the problem, and I'll note it in their charts, but it doesn't require informed consent."

INSULIN: OTHER (NON-CANCER) NEWS

HALOZYME THERAPEUTICS' recombinant human hyaluronidase (rHuPH20)

The company had a poster on a Phase II PK and a crossover test meal study in 22 Type 1 diabetics for this enzyme that boosts prandial insulin permeation. The results showed that rHuPH20:

- Accelerated the absorption of both lispro and regular insulin.
- Reduced T_{max} for both lispro and regular insulin.
- Could be used effectively with lower doses of lispro and regular insulin than previously tested.
- Significantly reduced hypoglycemia.

A Phase II study in Type 1 diabetics is underway, with glycemic control the primary endpoint.

NOVO NORDISK's Levemir (detemir), a long-acting insulin analog

At a Novo Nordisk sponsored press conference, Dr. Luigi Meneghini, a Florida endocrinologist, presented some new data on patient satisfaction from the previously published TITRATE trial of Levemir, a 244-patient study in insulin-naïve patients already taking oral anti-diabetic medications, which showed Levemir reduced HbA_{1c} with only a small increase in weight. He emphasized that the new data showed high patient satisfaction with Levemir, saying, "Increasing patient satisfaction may increase treatment adherence and subsequent control." He added, "This study had two fasting plasma glucose (FPG) targets – an aggressive one and a less aggressive one – and yet these targets were achieved safely. That gives us less concern about some of the possible risks as we try to get patients to goal with Levemir."

However, there was no statistically significant difference in patient satisfaction with Levemir vs. NPH insulin. Dr. Meneghini called it a "trend to improved satisfaction" with Levemir, but he did not know the p-value.

Oral insulin

There were no new data on this at EASD, but it remains an important – though distant – hope.

Inhaled insulin: MANNKIND's Afresa (Technosphere)

At EASD, Dr. Nikhil Amin of MannKind reported on the long-term sustained safety and efficacy of continued use of Technosphere insulin in MKC-TI-010, an open-label, multi-center, uncontrolled extension study in Type 2 diabetics who had previously completed one of two Phase II placebo-controlled, randomized studies (PDC-INS-0008 and MKC-TI-005). Technosphere was administered 2-4 times a day at the beginning of a meal, with a maximum dose of 90 U. Prandial injectable short-acting insulins were not allowed, but patients could use long-acting insulin QD in the evening. The study found:

- Lung function changes with the continued use of Technosphere for up to 4 years were small and similar to what is expected in Type 2 diabetics.
- Glycemic control was maintained long term.
- Therapy was well tolerated. The most common adverse event was cough, but Dr. Amin said this was usually dry, disappeared over time, and did not interfere with therapy.

Doctors questioned at EASD about Technosphere were generally dubious about any inhaled insulin after the commercial failure of Pfizer's Exubera. An endocrinologist from the Netherlands said, "I think it will crash and burn the same way Exubera did – at least in Holland. Injecting insulin is not a big deal any more, with pens."

Results of Technosphere Extension Study

Measurement	Technosphere n=229
Early discontinuations	30.1%
FEV_1	Steady over 48 months
FVD	Steady over first 42 months, then slight uptick
Lung diffusion capacity	Steady over 48 months
HbA_{1c} control	Steady over 45 months
Any adverse event	83.8%
Serious adverse event	13.1%
Adverse event leading to discontinuation	7.0%
Cough	28.4%
Upper respiratory tract infection	17.5%
Nasopharyngitis	14.0%
Arthralgia	8.3%
Hypoglycemia	Event rate increased from 36-48 months (0.2 at 6-12 months 0.17 at 24-30 months 0.42 at 36-43 months)
Hypoglycemia at any time	41%

FATIGUE WITH NEW ORAL DRUGS IN THE PIPELINE

There was a surprising lack of enthusiasm for any new drugs in the pipeline to treat Type 2 diabetes beyond new GLP-1s or DPP-4s. One speaker noted that at least 183 drugs are in development, but none of the numerous experts questioned were excited about any of these or about any new classes. Instead, the focus was on using the older oral drugs – particularly metformin – and on learning more about the GLP-1s and DPP-4s. One U.S. doctor commented, "There are no new agents that I am wed to or even want to date."

There was a general consensus that:

- Amylin/Lilly's exenatide once-weekly ("Byetta LAR") will be an advance, and it is likely to be adopted if it gets approved, but doctors predicted that many patients will still prefer Novo Nordisk's Victoza (liraglutide) even though it is a daily injection because the injections are easier to give and less painful than Byetta LAR will be. As one doctor put it, "Some patients will prefer easier injections more often than a difficult injection once a week." A U.S. doctor added, "LAR looks kind of better, and maybe there will be fewer side effects, but will patients forget to take it? And the pain and size of needle will be an issue."
- Metformin remains the gold standard, but sulfonylureas (SUs) cause weight gain and are associated with more cancer risk, so SU use is expected to decline. Thus, DPP-4 use is likely to increase as they are increasingly seen as a replacement for SUs. In fact, new American Association of Clinical Endocrinologists (AACE) guidelines are expected to be issued in the next month that move SUs down the treatment algorithm, below DPP-4s.
- TZDs still have a role, and, in fact, may see a little resurgence. One new dual PPAR in development worth watching is InteKrin's INT-131. An expert said, "Animal studies have not been a good predictor in this class in the past…INT-131 is a viable alternative, but I'm not wildly enthusiastic." Dr. Alex DePaoli, InteKrin's chief medical officer, said INT-131 does not appear to have the edema seen with Lilly's Actos (pioglitazone) or GlaxoSmith-Kline's Avandia (rosiglitazone).
- SGLT-2s were generating little interest and no excitement. In fact, one expert described them as "silly" or "weak." However, on a more positive note, there also was not a lot of concern about the urinary side effects.

Other drugs under investigation include:

- Glucagon antagonists
- Glycogen phosphorylase inhibitors
- Protein tyrosine phosphatase inhibitors
- Glut 2 transport (gut) inhibitors
- PPAR A/G agonists

- LA GLP agonists
- UCP-2
- Glucosylceramide synthase inhibitors

INCYTE's INCB-13739, an oral small molecule inhibitor of 11-beta-HSD1

Reid Huber, PhD, of Incyte presented the results of Study 202, a 12-week, multicenter, double-blind, placebo-controlled, randomized Phase II trial of INCB-13739 plus metformin in Type 2 diabetics. He reported:

- The two highest doses (100 mg and 200 mg) met the primary endpoint (reduction in HbA_{1c}). The highest dose (200 mg) also significantly reduced FPG, HOMA-insulin resistance, and total cholesterol.
- Normal cortisol levels and rhythmicity were maintained.
- ACTH plateaued at Week 4 and returned to baseline after cessation of therapy.
- A modest reduction in body weight (~1 kg) that continued out to Week 12 without plateauing.
- In men testosterone was not changed, but there was a modest change in females.
- INCB-13739 has a half-life of 11 hours.

Asked if the suppression of cortisol with INCB-13739 would be dangerous in situations of stress (e.g., pneumonia, anxiety, surgery), Dr. Huber said, "The enzymes are not involved in the synthesis of cortisol…We did stimulation testing on a small number of subjects…and preclinical studies all indicate that adrenal response to stress is completely normal…Given that the enzyme is not involved in biosynthesis, this is something that has to be monitored in long-term trials, but there is no *a priori* (reason to think it will have a negative effect)."

INTERCEPT PHARMACEUTICALS' INT-747, a farnesoid-X receptor agonist

Dr. David Shapiro of Intercept said INT-747 reverses fibrosis and cirrhosis in a rat liver fibrosis model and in a Type 2 diabetes/non-alcoholic fatty liver disease (NAFLD) model. He reported on a small study in which the low dose (25 mg) but not the high dose (50 mg) significantly increased the glucose disposal rate, but significantly decreased body weight only at the high dose. (*See chart on page 10*)

A study in non-alcoholic steatohepatitis (NASH) is expected to start in 2010.

12-week Results of Phase II Trial of INCB-13739

Measurement	Placebo n=50	Metformin + INCB-13739				
		5 mg	15 mg	50 mg	100 mg	200 mg
Primary endpoint: HbA_{1c} change	+ 0.09%	- 0.21% **	- 0.11%	- 0.9%	- 0.38% *	- 0.47% *
Pre-specified subgroup analysis: HbA_{1c} change in patients with baseline ≥8%	- 0.10%	- 0.39%	- 0.24%	- 0.65%	- 0.72% *	- 0.65% *
FPG	+ 12.6	+ 6.0	+ 2.3	- 4.7	- 1.6	- 11.5
Body weight change	- 0.23 kg	---	---	---	- 1.10 kg	- 0.85 kg
Lipids						
Cholesterol (mg/dL)	+ 1.2	- 0.7	- 1.2	- 3.9	- 6.6	- 7.3
LDL	+ 2.3	- 1.2	+ 0.4	- 7.0	- 4.6	- 4.3
Triglycerides	0	- 4.4	- 27.4	- 12.4	- 11.5	- 10.6 **
Endocrine Labs						
ACTH	4.9	8.3	7.1	9.2	9.4	11.2
DHEA-sulfate (male)	4.1	3.7	5.2	5.0	5.4	6.6
Adverse events						
Any adverse event	23	25	22	27	25	20
Treatment-related adverse events	3	8	8	9	4	5
Serious adverse events	0	1	0	0	1	1
Serious treatment-related adverse events	0	0	0	0	0	0
Nasopharyngitis	1	4	3	5	3	1
Diarrhea	3	3	1	3	3	1
Cough	0	1	2	1	3	2
Nausea	1	2	0	1	1	4
Upper respiratory tract infection	3	3	2	2	2	1

*p<0.01 ** p<0.05

INT-747 Results in Type 2 Diabetes/NAFLD

Measurement	Placebo n=23	INT-747 25 mg n=20	INT-747 50 mg n=21
Glucose disposal rate: low dose insulin	- 0.75 *	+ 0.50 * (p=0.04)	+ 0.6 *
Glucose disposal rate: high dose insulin	- 0.7 *	+ 0.7 * (p=0.036)	+ 0.3 *
Body weight change	- 0.1% *	- 1.1% *	- 2% * (p=0.008)
Adverse events			
Any adverse event	61%	45%	76%
Constipation	0	0	24%
Headache	4%	5%	14%
Pruritis	9%	5%	10%
Upper respiratory	9%	0	5%
ALT/AST elevation **	4%	0	5%

*all measurements approximate ** only severe adverse event

VIVUS's Qnexa (VI-0521 – 15 mg phentermine + 92 mg topiramate)

VI-0521 is a low-dose, controlled-release version of two approved drugs being developed as a weight loss agent. The phentermine dose is half the typical U.S. dose, and the topiramate dose is one-fourth the approved dose. At EASD, Dr. W. Timothy Garvey of the University of Alabama at Birmingham presented data which suggested Qnexa may have a role beyond weight loss in Type 2 diabetics.

He presented the results of the 56-week Study DM-230 in Type 2 diabetics, 74% of whom were Hispanic or African American. Qnexa was administered on top of standard-of-care oral diabetes medications. The study found:

- HbA_{1c} was reduced 1.6%.
- Patients lost an average of 9.4% of body weight.
- There were significant improvements in metabolic and cardiovascular risk factors.
- No severe hypoglycemia and no drug-related serious adverse events were seen.
- Diabetic medication use decreased, and fewer Qnexa patients required rescue.

Asked about pulmonary blood pressure results, Dr. Garvey said, "That wasn't measured in this study. I think you may be referring to a fenfluramine side effect. Phentermine does not have that side effect profile. It is not an issue with phentermine. Phentermine has been tested for valvulopathy, and that is not part of the profile of phentermine."

Asked what the mechanism of action for topiramate is, Dr. Garvey said, "Unknown. It probably has central action to reduce appetite…but that remains to be (investigated)."

56-Week Results of Study DM-230 of Qnexa in Type 2 Diabetics

Measurement	Placebo n=55	Qnexa n=75	p-value
Primary endpoint: HbA_{1c} change	- 1.13%	-1.61%	0.038
Patients achieving HbA_{1c} <6.5%	16%	32%	<0.05
Change in concurrent diabetes medications	+ 30%	- 16%	---
FPG (mmol/L)	- 1.42	- 2.41	0.02
Treatment-related hypoglycemia	1.8%	2.7%	---
Weight	- 2.7%	- 9.4%	<0.001
≥5% weight loss	24%	65%	<0.0001
≥10% weight loss	9%	37%	0.0004
Patients with ≥3 CV risk factors	71%	57%	---
Treatment-related adverse events			
Tingling/Paresthesia	0	13.3%	---
Nausea	0	8.0%	---
Dry mouth	0	6.7%	---
Dizziness	0	6.7%	---
Insomnia	1.8%	8.0%	---
Constipation	0	5.3%	---

Asked about previous studies with higher doses of topiramate that were stopped for side effects such as depression, Dr. Garvey said, "This drug (topiramate) is currently approved for the treatment of epilepsy in children and adults at much higher doses. It can have effects on cognitive function and cognition. That is much less marked at these lower doses. In this trial, the quality of life indicators and psychometric testing show better scores on VI-0521, probably because they were losing weight. We did not see a signal for depression or psychological issues that would be a concern. The strategy for this combination is: Phentermine is established as a drug that can enhance cognition and alertness, and this may counteract any decrease in cognition that topiramate may induce…But both doses are much lower than the approved drugs."

Asked about heart rate and blood pressure, Dr. Garvey said, "In Europe phentermine is a controlled drug because of abuse potential. There was no increase in blood pressure…In fact, there was a 2-3 mmHg decline in blood pressure. I'm not sure about heart rate."

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

DPP-4s currently have only a very small share of the market in Europe (<10%) experts estimated. That is, 10% of patients on any oral diabetic medication. However, they expect them to continue to gain share, particularly at the expense of sulfonylureas, which are increasingly getting painted as poor actors – linked to weight gain and cancer. The problem with broader use of DPP-4s, at least in Europe, is cost.

Comments included:

- *Germany #1:* "It makes sense to use DPP-4s in lieu of SUs. What is holding back use is education and cost. As long as the GLP-1s and DPP-4s are relatively costly, they will not be used too frequently."
- *Netherlands:* "DPP-4s are a difficult issue in the Netherlands because they are not well reimbursed."
- *U.S. #1:* "DPP-4s don't have any advantage except being oral and a lack of nausea. The efficacy on HbA_{1c} is 0.7% on their best day. Added to metformin, Byetta lowers HbA_{1c} 1%-1.2%, but sitagliptin and vildagliptin only lower it 0.5%-0.7%. DPP-4s don't produce any weight loss, and they are very expensive."
- *U.S. #2:* "The skin problems are still a concern with vildagliptin. Each DPP-4 is different. Sitagliptin is the most specific; the others have wider specificity. I'm being careful because I don't want another troglitazone or rosiglitazone."
- *Germany #2:* "I don't see any difference with Onglyza (Bristol-Myers Squibb/Astra Zeneca, saxagliptin) from Januvia. I look at them as a group."

BOEHRINGER INGELHEIM's linagliptin

There was no news at EASD about this DPP-4, but shortly before the meeting, the company announced the conclusion of a pivotal Phase III trial of its oral, once-daily linagliptin in >4,000 patients in 40 countries. The results of that trial are expected to be presented at a medical conference in 2010.

Bristol-Myers Squibb/AstraZeneca's Onglyza (saxagliptin)

Onglyza was approved by the FDA in late July 2009, and just after EASD it was approved for sale in 27 European countries. The companies were promoting it at EASD, but it wasn't a big push – yet. Doctors questioned about Onglyza insisted that it is likely to expand the market more than simply take market share from Januvia.

There haven't been any reports – again, yet – of pancreatitis with Onglyza.

The interim results of a long-term, placebo-controlled extension of a randomized trial (CV181-014) presented at EASD showed that the benefits of Onglyza held up out to two years (102 weeks), but the results certainly were not impressive enough to generate excitement for this drug. The dropout rate was very high – more than 80% of patients discontinued or required a third drug because they failed to meet the HbA_{1c} target, and the HbA_{1c} reduction was very modest at 2 years. However, Dr. Shoba Ravichandran of Bristol-Myers Squibb said that patients in the extension study were required to meet increasingly lower HbA_{1c} targets, starting at 8%, then 7.5%, and finally 7%. If patients did not meet goal, they were encouraged to take Actos as a rescue medication or discontinue the trial.

Two-Year Onglyza Extension Study

Measurement	Onglyza 2.5 mg + metformin n=192	Onglyza 5 mg + metformin n=191	Onglyza 10 mg + metformin n=181	Placebo + metformin n=179
Primary endpoint: HbA_{1c} change	- 0.4%	- 0.45%	- 0.3%	+ 0.3%
Patients achieving HbA_{1c} <7%	24%	30%	33%	12%
Change in FPG	- 8	- 11	- 8	+ 7
Change in PPG	- 40	- 35	- 23	- 4
Adverse events				
Any adverse event	89.6%	78.0%	86.7%	78.8%
Treatment-related adverse events	26.0%	29.3%	33.7%	27.9%
Deaths	0	0	0.6%	1.1%
Any serious adverse event	0	0.5%	0.6%	0
Discontinuations due to adverse events	4.7%	7.3%	5.5%	4.5%
Influenza	10.4%	11.5%	12.7%	12.8%
Nasopharyngitis	13.0%	11.0%	13.8%	10.6%
Upper respiratory tract infection	12.0%	8.9%	10.5%	7.8%
Discontinuations				
Discontinued for lack of glycemic control at any point	89%	87%	82%	91%

GLUCAGON-LIKE PEPTIDE 1 (GLP-1) ANALOGS

Dr. Urd Kielgast of Denmark called for long-term trials to study the combination of a GLP-1 and insulin in Type 1 diabetics to determine if that combination would:

- Reduce the need for exogenous insulin.
- Improve 24-hour glucose profiles.
- Be associated with changes in the risk of hypoglycemia.
- Improve beta cell function in a subgroup of patients with residual beta cell function.

ADDEX PHARMACEUTICALS

There were no data on this company's GLP-1 at EASD, but an expert said it is a ***small molecule*** worth watching.

GLAXOSMITHKLINE's Syncria (albiglutide)

This long-acting GLP-1 analog has a half-life of ~5 days, reaches steady stage in 4-5 weeks of first dose, and has a narrow peak/trough with QW dosing that widens with less frequent dosing. Dr. Julio Rosenstock of Dallas TX reported on a 361-patient, dose-finding study of albiglutide given weekly, biweekly, or monthly in Type 2 diabetics. Among the findings were:

- Similar reductions in HbA_{1c} were achieved with the highest dose in each dosing schedule.
- There is an apparent direct relationship between circulating albiglutide levels and glycemic response.
- Nausea was less than with Byetta except for the monthly dosing which spiked higher at the time of dosing. Asked if the fluctuations in nausea and vomiting with once-monthly dosing were clinically relevant, Dr. Rosenstock said, "Oh, yeah. Nausea and vomiting are always clinically relevant to patients. The peak/trough really tells you the side effect profile of these drugs (GLP-1s) are related to the dosing."
- The dropout rate was fairly high.
- Once-weekly dosing gives the most steady FPG.
- The lowest frequency of GI side effects was with 30 mg once-weekly, and it declined over the course of the study, with no reports after 8 weeks.
- There was no effect on heart rate or blood pressure.
- Hypoglycemia was not increased.
- Skin reactions following injections were small, localized, and infrequent.
- Antibodies were infrequent, non-neutralizing, low-titer, and generally transient.

LILLY's LY-2189265

The data on this once-weekly potential competitor for Byetta LAR were confusing. In **two Phase I posters** – one in 20 healthy volunteers and another in 43 Type 2 diabetics – LY-2189265 looked efficacious, with a good response at both the 3 mg and 5 mg doses. Its large molecular size reduces renal clearance. Other features of this drug of note are: The half-life is ~4 days, C_{max} is 48-70 hours, and it is fused to immunoglobulin G with an Fc moiety, which reduces its immunoreactivity.

The problems were:

- The highest dose tested, 12 mg, caused vomiting in ***all*** patients, making it mandatory that a lower dose be used. However, vomiting was still seen at lower doses, but the rates were not given.
- Weight loss was only achieved at 5 weeks at doses of ≥5 mg. Below that, patients actually ***gained*** a little weight, which would be a serious competitive disadvantage vs. Byetta, since one of the big attractions of Byetta is the associated weight loss.
- Safety issues appear to demand the dose be <5 mg, and there are several safety issues. Though QTc is not prolonged, in fact, just the opposite, there is an increase in:
  - Heart rate
  - Systolic blood pressure
  - Diastolic blood pressure

16-Week Results of Albiglutide in Type 2 Diabetics

Measurement	Placebo n=51	Byetta BID n=35	Albiglutide weekly (4-15-30 mg) n=99	Albiglutide biweekly (15-30-50 mg) n=90	Albiglutide monthly (50-100 mg) n=69
Completers	77%	83%	58%	71%	71%
Primary endpoint: HbA_{1c} (%)	- 0.2	- 0.5	- 0.1 at 4 mg - 0.5 at 15 mg **- 0.9 at 30 mg ***	- 0.6 at 15 mg - 0.8 at 30 mg **- 0.8 at 50 mg ***	- 0.6 at 50 mg **- 0.9 at 100 mg ***
Weight change (approximate)	- 1 kg	- 2.5 kg	- 1.9 kg at 30 mg	- 1.6 kg at 50 mg	- 1.9 kg at 100 mg
FPG change	0	- 1.5	- 1.2 at 30 mg *	- 1.3 at 50 mg *	- 1.5 at 100 mg *

* p<0.05 vs. placebo

Thus, it appeared from the posters that efficacy and safety would best be balanced with the 3 mg dose, but the 3 mg dose caused a little weight gain, not weight loss.

However, an **oral, Phase II presentation** made LY-2189265 look more viable, with weight loss instead of weight gain with low doses, even in the first 4 weeks. The Phase II study was larger, but the Phase I data still raise questions about the weight loss in Phase II. Why did patients gain weight with 1 mg in one trial and lose in another? The second trial where they lost weight was larger, but the patient groups were still relatively small (~30 patients per dose).

The Phase II study was a 16-week trial in 262 Type 2 diabetics on a stable regimen of 2 oral anti-diabetic drugs (OADs). The results with the highest dose tested (1 mg titrated up to 2 mg) were:

- Significant reduction in HbA_{1c}, FPG, post-prandial glucose AUC and excursion, and body weight.
- Significant increase in a marker of beta cell function (HOMA2-%B)
- Few adverse events or discontinuations. The most common adverse events were constipation, vomiting, nausea, diarrhea, and abdominal distention and pain.
- Increased hypoglycemia at the beginning of the study, but by 16 weeks no statistically significant difference from placebo.
- A low rate of antibody formation.

No data were provided on heart rate and blood pressure. Dr. Guillermo Umpierrez of Emory University in Atlanta GA said only, "There was a minor increase in heart rate – a couple millimeters of mercury…We really need long-term studies with more patients, and those studies are being conducted. We are paying attention to this, among other things, but so far it is not a big noise but should be followed up in further studies…The blood pressure increase was only 2-3 mmHg, and we are following it."

Lilly is taking LY-2189265 into Phase III.

16-Week Results of LY-2189265 in Type 2 Diabetics

Measurement	Placebo n=66	LY 0.5/1.0 mg n=66	LY 1.0/1.0 mg n=65	LY 1.0/2.0 mg n=65
Primary endpoint: **HbA_{1c} change from baseline** ***(p<0.001 vs. placebo for all LY measurements at all time points)***				
Last visit	- 0.1	- 1.1	- 1.2	- 1.4
Week 4	- 0.3	- 0.6	- 0.8	- 0.7
Week 8	- 0.4	- 1.1	- 1.2	- 1.2
Week 16	- 0.2	- 1.4	- 1.3	- 1.6
LOCF	- 0.3	- 1.3	- 1.3	- 1.5
Other results ***(All LY doses significantly better than placebo)***				
Change in fasting serum glucose	- 0.5	- 2.1	- 2.0	- 2.6
Blood glucose (AUC) in response to test meal at endpoint	Nss change	Down significantly	Down significantly	Down significantly vs. placebo and other doses
HOMA2-%B change	+ 1.0	+ 39.2	+ 44.3	+ 45.6
Weight change ***(** only LY dose/time point not significantly better than placebo)***				
Week 4	- 0.1	- 0.5 **	- 1.1	- 1.3
Week 8	- 0.1	- 1.4	- 1.7	- 2.1
Week 16	- 0.1	- 1.4	- 1.3	- 2.6
LOCF	- 0.1	- 1.6	- 1.4	- 2.5
Adverse events ***(only constipation significantly higher with LY than placebo)***				
Any treatment-related adverse event	54.5%	60.6%	53.8%	63.1%
Nausea	7.6%	13.6%	16.9%	13.8%
Vomiting	3.0%	4.5%	1.5%	10.8%
Abdominal distension	6.1%	4.5%	7.7%	13.8%
Abdominal pain	4.5%	7.6%	3.1%	6.2%
Diarrhea	7.6%	7.6%	6.2%	13.8%
Constipation	0	9.1% *	4.6% *	9.2% *
Treatment-related adverse events possibly drug-related	22.7%	33.3%	30.8%	41.5%
Discontinuations of study drug due to adverse events	1.5%	6.1%	6.2%	6.2%
Serious adverse events	1.5%	4.5%	3.1%	1.5%
Deaths	0	0	0	0
Hypoglycemia				
Week 4	0.3%	1.1% *	1.4% *	0.9% *
Week 8	0.3%	0.9% *	0.9%	0.8%
Week 16	0.3%	0.3%	0.6%	0.4%
LOCF	0.2%	0.7%	0.8% *	0.7% *

*** <0.05 vs. placebo**

5-Week Results of LY-2189265 QW in Type 2 Diabetics *

Measurement	Placebo	LY 0.05 mg	LY 0.3 mg	LY 1 mg	LY 3 mg	LY 5 mg	LY 6 mg
HbA_{1c} change	+ 0.3%	- 0.7%	- 0.2%	- 0.6%	- 1.2%	- 0.9%	- 0.95%
Body weight change	+ 0.75 kg	+ 0.7 kg	+ 0.3 kg	- 0.5 kg	+ 0.4 kg	- 2.5 kg	- 2 kg

*** All numbers approximate**

5-Week Results of LY-2189265 QW in Healthy Volunteers **

Measurement	Placebo	LY-2189265					
		0.01 mg	0.3 mg	1 mg	3 mg	6 mg	12 mg
Heart rate change, supine	---	+ 1 bpm	+ 3.5 bpm	+ 3.5 bpm	+ 6 bpm	+ 9 bpm	+ 14 bpm
SBP change, supine (mmHg)	---	+ 2.2	- 1.0	+ 0.7	+ 0.1	+ 1.2	+ 0.75
DBP change, supine (mmHg)	---	+ 0.75	- 0.2	+ 1.6	+ 2.0	+ 3.25	+ 4
QTc interval	---	- 6	- 9	- 13	- 11.5	- 10	- 9
Vomiting	0	2 patients					6 of 6 patients
Serious adverse events	0	0	0	0	0	0	4 events in one patient *
Dyspepsia	0	16 events					
Nausea	1 patient	11 patients					
Anorexia	0	11 patients					
Lower abdominal pain	3 patients	6 patients					
Upper abdominal pain	0	4 patients					
Headache	3 patients	12 patients					
Injection site irritation	3 patients	10 patients					
Dizziness	4 patients	4 patients					
Fatigue	2 patients	5 patients					

*** hematemesis, increased blood bilirubin, oesophagitis, and gastritis**
**** all heart rate, blood pressure, and QTc numbers approximate**

MANNKIND

MannKind reportedly has an inhaled GLP-1 in development. There was no news at EASD about it, but an industry source said it has similar issues to the Lilly long-acting GLP-1.

NOVO NORDISK's Victoza (liraglutide)

European regulators approved Victoza on June 30, 2009. European doctors at EASD generally described it as superior to Byetta, and they expressed virtually no concern about thyroid cancer or cardiovascular safety. One doctor said, "The thyroid cancer concern is ridiculous. There is no sign of that in humans." A U.S. doctor commented, "The C-cell hyperplasia is a rat/mouse issue. There is no evidence it is a human issue."

Thus, it isn't surprising that Victoza has begun to capture market share in the countries where it has been launched – Germany, the U.K., and Denmark. It will be rolled out throughout Europe over 2009 and 2010 as reimbursement is obtained. Technically, it is available everywhere because of EMEA approval, but the company is not really launching it until reimbursement is available. France, for example, will take many months because the reimbursement process there tends to be lengthy. A Novo Nordisk official cautioned that sales in 2009 will not be major because use "all hangs on reimbursement" and that takes time.

In the U.S., Victoza was filed in May 2008, and the original FDA PDUFA (action) date was March 23, 2009, but the FDA still hasn't made a decision on the drug. In April 2009, an FDA advisory committee expressed concern about the safety of Victoza.

The panel concerns were:

- Not convinced of the CV safety of liraglutide, voting 8 to 5 that it was safe.
- Concerned over a potential increase in thyroid cancer, thyroid surgeries, and a need for screening or monitoring patients for thyroid cancer. Panel members were skeptical about the company's mechanistic explanation for the animal findings.
- Concerned that calcitonin levels might continue to rise over time.
- Not convinced that liraglutide offers sufficient benefit to warrant the risk.

Novo Nordisk officials said they have been in "daily contact with the FDA even since Onglyza was approved, and they said "formal feedback" is expected in 4Q09. They remain optimistic about final FDA approval. When it is approved, the plan is to roll it out first to key national leaders, followed by local key

Victoza European Roll-Out

Measurement	Germany	U.K.
Specialists reached	95%	~ 80%
Specialists reached 3x or more	80%	45%
Brand message recall	70%	~ 60%
Reimbursement	Yes	Good formulary access but takes time
Sales force	Doubled	Roughly doubled
Market share vs. Byetta	0.9% vs. 1.7%	N/A
Share of GLP-1 market	34.3%	N/A
Patients on 1 OAD	45%	~ 45%
Patients on insulin	35%	25%

opinion leaders, and then others. An official insisted that the FDA is not waiting for data on other GLP-1s to make a decision on Victoza, "(Roche's) taspoglutide is a different NME (new molecular entity)…The key issue for the FDA is not political but perhaps a management decision."

Asked if it would make sense to launch Victoza in the U.S. if the FDA requires calcitonin monitoring, a company official said, "All the experts I've spoken with say having a standard baseline monitoring would be a killer commercially, but, on the other hand, it is an irrational thing to do. Probably 30%-40% of patients have elevated calcitonin, and that would mean too many thyroidectomies. So, I'm sure there won't be a requirement for routine baseline calcitonin monitoring."

Victoza was filed with Japanese regulators in July 2008, and the company is having "regular interactions" with the Pharmaceuticals and Medical Devices Agency (PMDA) and are "progressing according to plans," with a decision expected in 1H10. Once it is approved, it should take another three months to resolve reimbursement, and then it will be launched there.

In China, a Phase III trial has been completed, and Victoza was filed with regulators in August 2009. Launch appears on target for 2H10.

Asked why the Byetta uptake/launch has not fared very well, and how the Victoza launch is different from Byetta, a Novo Nordisk official said, "My subjective assessment is that I think you have two things: convenience and better efficacy…It is quite clear that having one daily injection instead of two injections timed to meals, no refrigeration, etc., means that Victoza is significantly more convenient for patients to use. Add to that, efficacy is clearly better. We have a trial that shows that when you move from Byetta to Victoza, you see improvement in control…that should indicate you can do better than the competitive product. And on top of that, we try to execute better, encouraging doctors to use it early, when metformin fails. Maybe we have a simpler message…This is a launching game, launching successfully and staying with it five, 10, 15 years. You will see a steady penetration curve. We don't expect it to run out of speed, but we don't know about reimbursement. We think early indications are positive."

Asked what dose is being used by doctors where Victoza has been launched, a Novo Nordisk official said, "Most people are using 1.2 mg, as the main dose. That is what is being recommended by authorities. That is what they are focusing on, and that is what we are recommending. 1.8 mg is for up titration where you can't get adequacy with 1.2 mg…We do know that it is being used early on but also in many combinations."

Asked if Byetta patients are switching to Victoza where Victoza has been launched, a Novo Nordisk official said, "Anecdotally, we are seeing switching from Byetta. The data indicate that is a limited element of the market share."

Asked whether the company will wait for a label or start obesity studies now, an official said, "The prevention of weight regain trial has been recruited and is ongoing, with results due late next year. Two other trials have not been initiated. It is quite clear we need to know the package insert, the label…so we can say the label justifies the program."

Doctors at EASD who were questioned about the outlook for Victoza vs. Byetta predicted Victoza would gain market share, generally by expanding the market but also by taking some share from Byetta. Among their comments were:

- *Germany:* "With liraglutide, the plasma concentration builds up to a steady state. This gives more activity in fasting over night than Byetta…Liraglutide works less well (vs. Byetta) after breakfast and lunch, but overall liraglutide is better. So, some patients will fare better with Byetta – those with low fasting glucose and a quick rise in glucose after meals – but most patients will do better with liraglutide."
- *Netherlands:* "I'm not impressed with what I've seen of liraglutide, but I can't use it yet because there is no reimbursement."
- *U.S.:* "Mostly it is marketing differences, but the clinical data suggest that liraglutide is better."

ROCHE's taspoglutide (RG-1583)

Although eight clinical trials are underway (the T-EMERGE program), the only data on this subcutaneous injectable drug at EASD were two preclinical posters. In both, taspoglutide performed as would be expected. There were no hints of problems, but the posters really didn't offer much new or useful data. However, expectations are high for this drug; experts suggested it could be the category killer, with the efficacy and safety of liraglutide and once-weekly dosing.

T-EMERGE Program for Taspoglutide

Measurement	Phase III T-EMERGE trials							
	1	2	3	4	5	6	7	8
Number of patients	300	990	330	630	990	650	260	2,000
Type of patients	Diet and exercise failures	Metformin + TZD failures	Actos and metformin failures	Metformin failures	Metformin + SU failures	SU ± metformin failures	Metformin failures (high BMI)	CV study vs. placebo
Comparator	Placebo	Byetta	Placebo	Januvia and placebo	Lantus	Actos	Placebo	Standard of care
Status	Fully enrolled	Fully enrolled	Enrolling	Enrolled	Enrolled	Enrolling	Enrolled	Starting December 2009

T-EMERGE-2 – a study vs. Byetta in metformin/TZD failures will be the first trial in the program to report data, and that is expected in 4Q09.

SANOFI-AVENTIS's lixisenatide (AVE-0010)

Lixisenatide, a once-daily GLP-1 receptor agonist, is in Phase III trials at the 20 µg QD dose. The only data on it at EASD were from an oral presentation by Dr. Rosenstock on a Phase II substudy of the post-meal pharmacodynamic (PD) profile. He said the profile supports use in patients with only mildly elevated HbA_{1c} (~7.5%) at baseline.

- Nausea occurred in ~25% of patients and diarrhea in ~9%.
- Either QD or BID dosing resulted in dose-dependent improvements in post-meal glucose levels.
- Post-meal glucagon levels were reduced at all doses but without dose-dependency.

Asked what value this GLP-1 might have over what is already on the market, Dr. Rosenstock said, "I think we will see a plethora of new GLPs, and what is now incumbent on development of these drugs is to do head-to-head comparisons …We can no longer just look at HbA_{1c} reduction…We need to lower hemoglobin with fewer GI side effects, more weight loss, etc."

SGLT-2 INHIBITORS

One SGLT-2 has already failed, GlaxoSmithKline's remogliflozin etabonate, but at least four other SGLT-2 inhibitors remain in development:

1. **Bristol-Myers Squibb/AstraZeneca's dapagliflozin**, which has completed one Phase III trial.
2. **Roche's R-7201**, which is in Phase II development.
3. **Johnson & Johnson's canagliflozin**, which is in Phase III development.
4. **Boehringer Ingelheim's BI-10773**, which is in Phase II development. It is a once-daily drug. There was a pre-clinical poster on it at EASD, but it provided little information except that:
   - It is more selective than some other SGLT-2s.
   - It is superior to GSK's remogliflozin.

Advantages and Disadvantages of SGLT-2 Inhibition

Advantages	Disadvantages
Weight loss	Polyuria
Low risk of hypoglycemia	Electrolyte disturbances
Blood pressure lowering	Bacterial urinary tract infections
Effect independent of insulin	Fungal genital infections
	Unexpected effects

An expert said all of these SGLT-2s are fairly similar, but they do differ in their selectivity for the four SGLT transporters (1, 2, 3, and 4). Other comments about SGLT-2s included:

- *U.S. #1:* "I don't think the urinary issue is important. I wonder if, over time, women's genitourinary tract won't adapt. I don't expect that to be a show stopper."
- *U.S. #2:* "I'm sure all the companies think their drug has substantial promise, but it will take a long time to demonstrate their true effect."

Phase II Substudy Results of Lixisenatide Post-Meal in Type 2 Diabetics

Measurement	Placebo	Lixisenatide QD				Lixisenatide BID			
	n=66	5 mg n=55	10 mg n=52	20 mg n=55	30 mg n=54	5 mg n=53	10 mg n=56	20 mg n=54	30 mg n=54
HbA_{1c} **	- 0.3	- 0.5	- 0.5	- 0.7	- 0.8	- 0.7	- 0.8	- 0.8	- 0.9
FPG	- 4	- 11	- 10	- 14	- 18 *	- 3	- 18 *	- 30 *	- 36 *
Weight change (kg)	- 1.9	- 2.0	- 2.4	- 3.0	- 3.5	- 2.1	- 2.2	- 3.6	- 3.9
Change in 2-hour postprandial glucose (mg/dL) at Week 13 **	- 7.4	- 38	- 64	- 66	- 78	- 36	- 63	- 74	- 83
Change in post-meal glucose AUC (h·mg/dL) at Week 13 **	- 44	- 137	- 199	- 208	- 254	- 119	- 211	- 254	- 285
Change in 2-hour post-meal insulin levels	+ 5.2	-3.1	- 11.6	- 14.7 *	- 19.3 *	- 11.9	+ 3.0	- 11.9 *	- 21.3 *
Adverse events									
Nausea	4.6%	7.3%	11.9%	25.5%	35.2%	7.5%	14.3%	22.2%	33.3%
Diarrhea	7.3%	5.5%	7.7%	9.1%	7.4%	3.7%	7.1%	11.1%	35.9%
Vomiting	0.9%	3.6%	5.6%	5.5%	18.5%	5.7%	7.1%	9.3%	3.7%

* <0.05 vs. placebo ** all lixisenatide doses statistically better than placebo

- *U.S. #3:* "They are silly. It's just using the bladder as a spigot. They will be fairly weak drugs, and they work by increasing glycosuria (secretion of glucose into the urine). To make people spill enough into the urine will make them polyuric, and that will cause yeast infections and urinary tract infections, and perhaps a slight increase in pyelonephropathy. I've yet to see data that indicate they will be useful.

BRISTOL-MYERS SQUIBB/ASTRAZENECA's dapagliflozin

Two oral presentations shed a little more light on this SGLT-2, which is the furthest along in development. Dapagliflozin was described by investigators as having "modest" efficacy and by non-investigators as "weak." However, given the number of Type 2 diabetics even modest efficacy would give it a place. The issue, then, is not efficacy but safety, particularly genitor-urinary infections.

Dapagliflozin has a half-life of ~16 hours. The metabolites are inactive and excreted in the urine. It works by blocking the SGLT-2 "gate" in the proximal tubules, which blocks glucose reabsorption into the bloodstream, instead promoting urinary glucose secretion and, thus, lowering blood glucose. The glucose reaches the SGLT-2 receptors before the SGLT-1, -4, or -5 receptors, and there are more SGLT-2 receptors, which explains why SGLT-2 specificity is important.

Dapagliflozin vs. placebo. Dr. Clifford Bailey of Aston University in the U.K. presented the results of a randomized, double-blind, placebo-controlled trial of placebo vs. three doses of dapagliflozin in 546 Type 2 diabetics. All patients were on metformin. Dapagliflozin was given daily before the morning meal. He reported dapagliflozin:

- Dose-dependently reduced HbA_{1c} 7%-8%.
- Reduced blood pressure without orthostatic hypotension. Dr. Bailey called the blood pressure reduction an "interesting feature" of dapagliflozin. 30%-37% of patients hypertensive at baseline achieved goal (130/80) on dapagliflozin.
- Was associated with these side effects: headache, back pain, diarrhea, urinary tract infection, influence, nasopharyngitis, hypertension, upper respiratory tract infection, and cough. Urinary tract infections were described as "similar across the groups," but there was a "small increase" in genital infections.
- Reduced weight 2-3 kg. About 25% of patients lost weight.
- Caused no clinically-relevant changes in laboratory parameters.

Asked about the urinary tract infections and genital infections, Dr. Bailey – who is the diabetes representative to the European Medicines Agency (EMEA) – described it as a "matter of personal hygiene," indicating women are reluctant to discuss it, making correct identification difficult. He said none of the women were examined by either a urologist or a gynecologist during a reaction/infection, and none were cultured, but he indicated that this needs to be done – and it seems obvious that the FDA will want that information. Other points he made included:

- "These were symptoms of genital thrush basically…It cannot be confirmed exactly what everyone had…You can't say, 'Can I have a look?'"
- "It is difficult to say exactly how many (women) had them. Everyone was asked, and some said, 'Yes, I may have had some itch,' so a box was ticked, but generally speaking, this did not seem to be a major issue."

24-Week Results of Phase III Trial of Dapagliflozin

Measurement	Placebo n=137	Dapagliflozin 2.5 mg n=137	Dapagliflozin 5 mg n=137	Dapagliflozin 10 mg n=135
Baseline HbA_{1c}	8.1	8.0	8.2	8.0
Primary endpoint: HbA_{1c} change	- 0.30	- 0.67 (p<0.001)	- 0.70 (p<0.0001)	- 0.84 (p<0.0001)
Secondary endpoint #1: Patients achieving HbA_{1c} <7%	29.5%	33.0% (Nss)	37.5% (p<0.05)	40.6% (p<0.05)
Secondary endpoint #2: FPG change	- 6 mg/dL	- 17.8 mg/dL (p<0.005)	- 21.5 mg/dL (p<0.005)	- 23.5 mg/dL (p<0.005)
Weight change	- 8.89 kg	- 2.21 kg (p<0.0001)	- 3.04 kg (p<0.0001)	- 2.86 kg (p<0.0001)
Patients losing ≥5% weight	5.9%	24.1%	25.4%	28.0%
Patients losing ≥10% weight	0	1.5%	3.6%	3.0%
Adverse events				
Any adverse event	88%	89%	95%	98%
Any related adverse event	16.1%	16.1%	18.2%	23.0%
Any serious adverse event	3.6%	2.9%	2.9%	3.0%
Deaths	0	0	0	0
Hypoglycemia	2.9%	2.2%	3.6%	3.7%
Urinary tract infection	8.0%	4.4%	7.3%	8.1%
Genital infection	5.1%	8.0%	13.1%	8.9%
Hypotension or syncope	0.7%	0	1.5%	0
Hematocrit	Down 1.14%	Up 0.98% to 1.65%		
Serum uric acid	Down 0.04 mg/dL	Down 0.53 to 0.82 mg/dL		
Blood pressure				
Systolic	- 0.2 mmHg	- 2.1 mmHg	- 4.3 mmHg	- 5.1 mmHg
Diastolic	- 0.1 mmHg	- 1.8 mmHg	- 2.5 mmHg	- 1.8 mmHg
Hypertensive patients not at goal at baseline achieving goal at Week 24	8.8%	29.5%	30.5%	37.6%

* statistically significant

- "This is something that has to be considered, but with appropriate words of caution on how to deal with personal hygiene…Right now, we don't say to patients, before they get the drug, that they should wipe carefully, but after approval, I think we can add in helpful instructions like that…The issue is mainly in women…Hygiene, underwear, and activities can be involved."
- "It appears to be a condition that can be effectively dealt with…Most who had the effect say, 'I had it, but it is gone now.' Most of these infections are mild, but one or two are more serious, which is why we know it is candidiasis."
- "When a patient has an infection, and you advise them (about hygiene), it seems to go away, but glucose also goes down over time."
- "There has been no pyelonephritis. The type of diuresis you might expect would be fairly modest, and this is only a 26-week study, and you need to think years down the line…If you are waiting for a patient to complain of symptoms, expect to wait a long time. If you look for markers of infection or inflammation, you might find something, but in these studies patients didn't complain of anything that would be related to this…We didn't look at any markers, but you could look at pain, palpate the kidney and note a change in pain, or look for an increased frequency of urination. But the amount of glucose is no different than many poorly controlled diabetics would have. There is no evidence of pyelonephritis. It is only a theoretical issue. Nothing has shown up…There is no change in frequency of urination and no evidence of any cystitis."
- "Dapagliflozin causes less change in blood volume than a diuretic."

Asked if the genitourinary infections are yeast infections or something more, Dr. Bailey said, "What patients report are symptoms consistent with a yeast irritation at the periphery in most cases. We need to get some women in early and culture them."

Asked if there was any significant dehydration, Dr. Bailey said, "Actually measuring dehydration is different from looking at fluid loss that you might equate to using a diuretic. If you look at the rate at which weight was lost, you see initially a sharper loss then subsequent more gentle weight loss…There are studies going on to study precisely the body changes going on…Preclinical studies say there are some changes with weight loss…but these things correct themselves as people feel thirsty and drink fluids."

Asked if there is a loss of sodium as well as glucose which could explain the reduction in blood pressure, Dr. Bailey said, "We don't have an answer to that. There are preclinical studies which might show marginal changes in the first day or so that correct themselves, but clinically it has not been possible to show there are sufficiently large changes that you could equate to the change in blood pressure. Very detailed studies are underway to try to resolve this. Watch this space."

Asked about any changes in lipids/cholesterol, Dr. Bailey said, "At the current time, there is no evidence of any significant changes in lipid profiles. Separate studies are looking at this. Preclinical studies looked at this in detail. It doesn't appear there are any significant lipid changes beyond what you would expect with glycemic control."

Asked about the "modest" HbA_{1c} reduction, Dr. Bailey said, "It is possible the effect is modest when a patient is close to target, and if you give it to someone in poorer glycemic control, you get a bigger effect."

Asked about plans for a cardiovascular safety trial of dapagliflozin, Dr. Bailey said, "What happens in terms of CV events is often reflective of the state of the patient before the diabetes. So far, the event rate with dapagliflozin is low, and there is no signal in any individual trial. So, our fingers are crossed." However, he would not confirm that any specific CV trial is underway.

Asked what dose is likely to go forward, Dr. Bailey said he believes the 5 mg dose is "where the agent is effective." He added, "I think 5 mg looked good, and weight was still going down…What you see with most weight loss drugs is that they plateau because the body adjusts its metabolic efficiency…The weight effect is similar to orlistat (Roche's Xenical)…The 5 mg dose looked to have the majority of the effect, but if you could increase the dose and advise patients to be careful with hygiene, you might be able to titrate up…20 mg was used in insulin-treated patients, but we didn't want to use a dose (in these patients) that would disturb electrolytes, create hypoglycemia, or cause unanticipated infections. Now, we have the opportunity to scale the dose up, but I don't know if the company will do that."

Asked how dapagliflozin is likely to be used if it is approved, Dr. Bailey said, "It is an ideal agent as a second-line add-on in patients near but not at goal, especially if they had treatment in the past for insulin resistance or are on insulin and can't reach goal because this agent is independent of insulin…You could combine it with anything, providing there are no contra-indications – metformin, insulin…We have to see the clinical results with a DPP-4 or GLP-1 first, but in preclinical studies, it is effective in combination with these."

Dapagliflozin and insulin. Patients on insulin often gain weight, and a reduction in glycosuria is considered the main reason for this. Weight gain is a well-known side effect of insulin therapy. Dr. John Wilding of the U.K. presented the results of a 12-week trial of dapagliflozin plus reduced-dose insulin in Type 2 diabetics. Dapagliflozin was dosed higher than in Dr. Bailey's study. All the patients were on a stable dose of metformin and/or a TZD.

The study showed dapagliflozin:

- Improved HbA_{1c} about 0.6%-0.7%.
- Reduced weight ~4 kg.
- Was associated with a higher rate of symptoms of genital infections.

Asked if the decrease in glucose with dapagliflozin actually improves insulin secretion, Dr. Wilding said, "In humans we don't yet have enough data. Whether this mode of therapy results in long-term improvements in insulin sensitivity and insulin secretion – we just don't have that data yet."

Week 12 Results of Study of Dapagliflozin + Reduced-Dose Insulin in Type 2 Diabetics

Measurement	Placebo n=23	Dapagliflozin 10 mg n=24	Dapagliflozin 20 mg n=24
Primary endpoint: HbA_{1c} change	+ 0.09%	- 0.61% (p<0.001)	- 0.69% (p<0.0001)
PPG	+ 18.7 mg/dL	- 34.3 mg/dL	- 41.9 mg/dL
Weight change	- ~1.5 kg	- ~4 kg	- ~4.3 kg
Urine glucose (g/24 hours)	- 1.5	83.5	85.2
Change in uric acid	+ 0.15	- 0.3	- 0.3
Change in hematocrit	- 0.40	+ 2.5	+ 3.05
Adverse events			
Any adverse event	65.2%	75.0%	66.7%
Treatment-related adverse event	43.5%	41.7%	29.2%
Deaths	0	0	0
Serious adverse event	4.3%	0	4.2%
Treatment-related serious adverse event	4.3%	0	4.2%
Urinary tract infections	0	0	4.2%
Vulvovaginal mycotic infection	0	0	12.5%
Balanitis candida	0	0	4.2%
Vaginal candidiasis	0	0	4.2%
Fungal genital infection	4.3%	0	0
Hypoglycemia			
Hypoglycemia	8.7%	8.3%	16.7%
Major episode of hypoglycemia	4.3%	0	0
Minor episode of hypoglycemia	4.3%	4.2%	8.3%
Event suggestive of hypoglycemia	0	4.2%	8.3%
Approximate blood pressure changes (mmHg)			
SBP supine	+ 2.0	- 0.75	- 5.5
DBP supine	- 4.0	+ 1.2	- 5.75
SBP standing	+ 2.8	- 7.0	- 6.0
DBP standing	+ 0.5	- 1.0	- 4.0

MISCELLANEOUS

Continuous glucose monitoring systems (CGMS)

There are currently three major players in this space: DexCom, Medtronic, and Abbott. Industry sources said Bayer is expected to enter the market, but nothing appears imminent, and there are no other competitors on the near horizon.

Integrated systems combining CGMS and insulin pumps are the holy grail, but that has been a very difficult goal. Austrian endocrinologist Dr. Pieber said, "It is clear that new devices are evolving technology. It is still not as reliable as we want it. That is still the major obstacle…There is a European randomized trial where a sensor signal was used to augment the use of pumps, and they are achieving sustainable improvement…With the next generation of glucose sensors – smaller, less invasive – the attention will start." An American endocrinologist said, "There remains one substantial technical hurdle, and that is the issue of lag. Glucose in tissues lags behind the bloodstream, and the absorption of insulin under the skin takes time…so that combination means you are always behind the curve with the current designs. We are getting better, but we still have a ways to go. And the question is how good you have to be to be better than a human who is incredibly fallible."

Obesity surgery

The idea of obesity surgery for diabetes was a hot topic at the American Society for Metabolic and Bariatric Surgery meeting in June 2009, and the focus was not just on the morbidly obese. Rather, bariatric surgeons were promoting the idea of doing the surgery on normal weight people (with a BMI as low as 25) who had diabetes.

The topic also came up several times at EASD. Most sources thought this approach is too extreme for non-obese diabetics. An American endocrinologist said, "There are some very intriguing data, and some people have become zealots in the field of 'metabolic surgery,' as they call it...but surgical approaches to medical problems have been fraught with fits and starts. Lobotomy was widely viewed as reasonable therapy for psychological disorders, and now it is an abomination…This surgery is sort of a mutilating procedure. If it is associated with improved quality of life and longevity, it might be interesting…but we don't really have the trials yet that demonstrate that." A U.K. endocrinologist said, "If bariatric surgery were a new drug, it would be associated with much more surveillance and oversight…No one is arguing against surgery for the really obese, but it is something that affects patient safety." A German doctor said, "One reason surgeons are targeting diabetes is that the treatments are paid for. Surgery does have lots of advantages for the morbidly obese, but it is a mutilating procedure, and it does concern me. I'm afraid in 2025, they will be asking what were we thinking." ♦