Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Several dual PPAR-α/γ agonists have failed for toxicity, and safety issues raise questions about the approvability of the two leading agents – AstraZeneca's Galida, which is associated with elevated creatinine; and Bristol-Myers Squibb/Merck's Pargluva, which causes weight gain, heart failure, and edema. ♦ Doctors are very receptive to Lilly/Amylin's Byetta, predicting 13%-16% of their patients will be on it within a year. The weight loss is expected to trump the injections and nausea – if the nausea is as mild as the companies are portraying it. ♦ There was no real excitement about inhaled insulin, but experts predicted Pfizer/Sanofi-Aventis/Nektar's Exubera will get FDA approval, but other promising inhaled insulins and other delivery systems are close on Exubera's heels. ♦ A one-year pilot study of Lilly's Arxxant, a PKC-β inhibitor for diabetic nephropathy, looked promising. ♦ Sanofi-Aventis racked up another win with its diet drug, Acomplia. It not only helped diabetic patients lose weight, but it improved their glycemic scores as well.

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

AMERICAN DIABETES ASSOCIATION (ADA)

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More than 18 million Americans have diabetes, including 6.3% of adults. Over the next 20 years, the number of diabetics is expected to increase by 57% in North America, 21% in Europe, and 72% world-wide. An estimated 63% of diabetics are not at the ADA HbA_{1c} goal <7%.

ADA HbA_{1c} Goals

HbA_{1c} goal	Adults age 20-74 who reach goal
>10%	12.4%
>9%	7.8%
>8%	17.0%
7%-8%	25.8%
<7%	37.0%

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARS)

The two currently approved PPARs – GlaxoSmithKline's Avandia (rosiglitazone) and Lilly/Takeda's Actos (pioglitazone) – are both PPAR-γ agonists. Large and important trials are ongoing with PPAR-γs including:

- **PROACTIVE.** This 5,238-patient study compares Actos to placebo after a cardiovascular (CV) event. The primary endpoint is occurrence of a new CV event or death. The results are expected at the European Association for the Study of Diabetes (EASD) meeting September 10-15, 2005, in Athens, Greece.
- **RECORD.** This 6,000-patient study looks at the addition of Avandia to existing therapy, with six-year follow-up. The primary endpoint is time to reach combined cardiovascular event.

Weight Change with Various Medications

Measurement	Sulfonylurea n=3,665	Metformin n=4,125	Insulin n=1,587	Actos and Avandia n=169
Drug duration	1.4 years	3 years	5.6 years	6.9 years
Weight change	+2.04 pounds	-5.14 pounds	+8.79 pounds	+11.02 pounds
Sulfonylurea initiations	+3.94 pounds	-5.29 pounds	+7.32 pounds	+10.84 pounds

GLAXOSMITHKLINE'S Avandia (rosiglitazone)

Typically, Avandia and Actos are given to Type 2 diabetics not on insulin, but they are now being explored as add-on therapy in Type 2 diabetics not well-controlled on insulin. Researchers reported on a 24-week trial of 2 mg Avandia+insulin vs. 4 mg Avandia+insulin vs. insulin alone, following a two-week run-in period. The 4 mg Avandia dose appears the most effective.

Avandia in Type 2 Diabetics on Insulin

Measurement	Avandia 2 mg + insulin n=186	Avandia 4 mg + insulin n=193	Insulin only n=189
Change in HbA_{1c}	-0.64	-0.78	-0.44
Treatment difference	-.26	-.38	N/A
FPG	-1.8	-17.7	-5.7
Treatment difference	+.04	-12.4	N/A
HbA_{1c} <7.0	~13%	~15%	~7%
FPG <126	~28%	~35%	N/A
Changes in total daily insulin dose	+1.9	+0.2	+1.5
Treatment difference	+.02	-1.7	---
Changes in C-reactive protein	-21.98	-34.16	+2.37
Treatment difference	-22.19	N/A	---
Change in fibrinogen	-10.5	-12.0	-2.7
Treatment difference	-7.9	-7.6	---
Changes in MMP-9	-10.04	-17.06	+10.52
Treatment differences	-15.28	-23.31	---
Adverse events			
Hypoglycemia adverse events	45.5%	45.0%	41.0%
Edema	5.7%	11.0%	10.8%
CV-related adverse events	2.4%	2.9%	1.9%
Weight gain adverse event	0.5%	2.9%	1.4%
Weight change	Up 4.2 pounds	Up 7 pounds	Up 1.8 pounds

DUAL PPARS

PPAR-α agonists – such as fenofibrate – are the therapy of choice for elevated triglycerides. They have demonstrated a reduced risk of recurrent CV disease if a patient has low HDL, and they also can be safely added to statin therapy.

At least three dual PPAR-α/γ agonists are in development. They would be a new class of agent which, theoretically, would have the advantages of both PPAR-γs and PPAR-αs. The hope is that the dual agents would have fibrate-like effects on dyslipidemia, lower CRP, have a positive effect on thrombotic risk, improve cardiovascular risk, and improve lipids.

The dual PPARs furthest along in development are:

- **ASTRAZENECA'S Galida (tesaglitazar).** Phase II data have been reported.
- **BRISTOL-MYERS SQUIBB/MERCK'S Pargluva (muraglitazar).** Phase III data were reported at ADA, and the drug has been filed with the FDA. The PDUFA date is in October 2005.
- **LILLY'S navaglitazar.** There was no new information on this at ADA.

Why is there a need for a dual PPAR? Why not just prescribe a fibrate with a PPAR-α? A speaker suggested, "That question is not answered. Increasingly, we, as doctors, have become comfortable with combinations – for example, multidrug therapy for hypertension and management of hyperglycemia. It remains to be clearly determined what impact we get from combining a pure PPAR-α and a pure PPAR-γ. There are no large trials with outcomes." Dr. Barry Goldstein of Thomas Jefferson University said, "We are still waiting for long-term outcome studies with (PPAR-γ), but those are likely to be positive…They have cardiovascular and anti-inflammatory benefits as well as glucose lowering, but they don't seriously impact lipids as much as (Lilly and GlaxoSmithKline) would like people to believe. There is some effect. The dual PPAR approach is trying to add an alpha without losing the PPAR-gamma activity…The ideal PPAR-γ would be the same as what we currently have if not better – and that has been difficult…Adding a PPAR-α takes the place of adding another medication."

ASTRAZENECA'S Galida (tesaglitazar)

This dual PPAR is currently in Phase III development, with eight Phase III trials underway, but only Phase II data were available at ADA from the GLAD trial. GLAD was a randomized, double-blind, placebo-controlled dose-finding study in 418 Type 2 diabetics. Galida appeared effective, but the study raised questions about creatinine levels with the drug.

It appears that the problem with Galida is with creatinine elevation, not creatinine clearance, which would be much more serious. Speakers suggested that the drug increases production of creatinine rather than interfering with elimination of creatinine. Dr. Goldstein, a Galida investigator, said, "There is some creatinine elevation. It is not something to be ignored. How much of a problem it will turn out to be is the question. There are other drugs used frequently that can do the same thing, such as fenofibrate – which means it could be tied into the PPAR-α mechanism. Cimetidine also does that. The creatinine elevation doesn't damage the kidneys, but they compete at a kidney level with creatinine for creatinine excretion, so the creatinine goes up in the blood. We know from the GLAD study that there is no evidence of kidney damage (with Galida)." Asked if kidney damage would be

likely to be seen in a 12-week trial, he responded, "You might. It would be much more worrisome if it had been noticed…AstraZeneca has embarked on a large, separate study to look at this very carefully…What reassures me is how carefully they (AstraZeneca) are going about evaluating it."

The weight gain with the Galida dose going forward appeared comparable to weight gain with Actos 45 mg. Dr. Goldstein said, "I think for the class it (weight gain) is unfortunate, but it is seen with all members…The higher dose has a higher effect, but that is where we see safety issues – weight gain and fluid retention. If you look at the 1 mg dose used in Phase II, then the weight gain is 1.1 kg (2.43 pounds) at 12 weeks, which is similar to what is seen with Actos or Avandia."

12-Week SIR Phase II Trial Results with Galida

Measurement	Galida 0.1 mg n=60	Galida 0.25 mg n=70	Galida 0.5 mg n=58	Galida 1.0 mg n=65	Placebo n=137
Primary endpoint: Change in FPG	---	---	---	-8.5 mg/dL (p<.0001)	---
Change in fasting Triglycerides	-37% (p<.0001)				---
Change in post-prandial FPG	---	---	---	-41% (p<.0001)	---
Total cholesterol	---	---	---	---	---
Increase in HDL	---	---	---	+16% (p<.0001)	---
Insulin resistance by HOMA	---	---	---	-41% (p<.0001)	---
Adverse events					
Any adverse event	65%	51%	67%	60%	55%
Serious adverse events	1 patient	0	0	0	1 patient

12-Week GLAD Phase II Trial Results of Galida

Measurement	Galida 0.1 mg n=72	Galida 0.5 mg n=73	Galida 1.0 mg n=70	Galida 2.0 mg n=70	Galida 3.0 mg n=73	Placebo n=70	Actos 45 mg n=68
Primary endpoint: Change in FPG (mg/dL)	-8.9	-30.3 *	-41.1 *	-55.0 *	-60.9 *	---	-38.5
Change in triglycerides	-5.4%	-17.2% (p<.01)	-32.9% *	-41.0% *	-40.9% *	---	-7.6%
Increase in HDL	1.0%	4.6%	15.0% *	13.0% (p<.001)	12.9% *	---	5.8%
Total cholesterol	-2.6%	-5.2%	-6.0% (Nss)	-14.1%	-15.5%	---	-0.5%
LDL	-2.9%	-4.5%	-6.4%	-11.1% (p<.002)	-17.3% *	---	-4.4%
Safety							
Edema rates	4.2%-6.8%					2.9%	4.2%
Edema cases	3-5 cases	3-5 cases	3-5 cases	3-5 cases	3-5 cases	2 cases	---
Any adverse event	58%	65%	66%	90%	84%	69%	65%
Fatal adverse events	0	0	0	0	0	0	0
Non-fatal serious adverse events	1%	1%	1%	4%	4%	1%	4%
Discontinuations	19%	20%	27%	41%	60%	19%	22%
New cases of heart failure	0	0	0	0	0	0	0
Weight gain	N/A	2.2 pounds	2.43 pounds	5.07 pounds	6.39 pounds	N/A	3.31 pounds
Dose-dependent increase in creatinine **	---	6%	15%	25%	25%	---	---

* p<.0001

** No proteinuria, no hematuria, all returned to normal.

In GLAD, patients received Galida (0.1 mg, 0.5 mg, 1.0 mg, 2.0 mg, or 3.0 mg) or open-label Actos 45 mg QD for 12 weeks, after a four-week run-in. Researchers reported that Galida produced significant, dose-dependent improvements in glucose control and lipid abnormalities and compared favorably with Actos. Adverse events were dose-dependent, and there were no cases of heart failure or excess edema.

Based on this study, the 0.5 mg and 1.0 mg doses are being used in the Phase III trials. An investigator said, "Even though the pioglitazone was just a benchmark, the data from this relatively short, small study are that the drop in dyslipidemia, improvement in HDL, and decrease in triglycerides is quite good…It (Galida) goes further than what we have now. People are not using TZDs (thiazolidinediones) as lipid drugs, and I don't think they should because the effects are small. We would like a way to manage the lipid profile, the part that goes along with insulin resistance – the metabolic syndrome: triglycerides, HDL, and LDL…The way

the data look now, tesaglitazar is nowhere near as potent as a statin, and the LDL lowering was only significant at the higher dose where there were more side effects, so I don't see Galida replacing a statin. What we are looking for is using this in combination with a statin…People currently can combine a fibrate with a statin, but that combination can potentially cause muscle damage in some small percentage of people, and clinicians are a little wary of that combination."

SIR, another randomized, double-blind, placebo-controlled, 12-week Phase II study in 390 non-diabetics with insulin resistance, found Galida reduced the prevalence of metabolic syndrome.

BRISTOL-MYERS SQUIBB/MERCK'S Pargluva (muraglitazar), a dual PPAR-α/γ

Results from three key Pargluva trials were presented at ADA, and the drug looks effective, though perhaps not as effective as AstraZeneca's Galida. The comparisons were against Actos, but at 15 mg and 30 mg doses of Actos, not the highest dose of 45 mg. Most sources doubted that Pargluva would have an efficacy advantage over the 45 mg Actos dose. Thus, there may not be enough efficacy advantage to outweigh the negative side effects.

Following are trial data on Pargluva presented at ADA.

➢ **A Phase III head-to-head comparison of Pargluva and Actos**.

➢ **Preliminary results from a Phase III 26-week extension study.** Adverse events over the 50 weeks appeared similar between Pargluva and Actos. Four additional deaths were reported for patients on Pargluva (stroke, MI, sudden cardiac death, and a previously-diagnosed pancreatic cancer), but these were not believed to be drug-related. There were two additional cases of heart failure on Pargluva and one on Actos, but there were no deaths due to heart failure.

➢ **Phase II Extension Study.** This was a randomized, double-blind, dose-ranging (0.5 mg, 1.5 mg, 5 mg, 10 mg, or 20 mg) trial of Pargluva vs. Actos 15 mg in 1,477 Type 2 diabetics inadequately controlled with diet and exercise. After the initial 24-week dose-ranging study, patients were continued into an ongoing long-term extension phase on their current dose of study medication – except that 0.5 mg Pargluva patients were increased to 1.5 mg, and 20 mg Pargluva patients were decreased to 10 mg, leaving only the 1.5 mg, 5 mg, and 10 mg doses. Concurrent fibrate therapy was excluded during the initial study but permitted in the extension.

The side effect issues raise serious questions about the approvability of this dual PPAR-α/γ.

1. **Weight gain.** There is some weight gain with all PPARs, but the weight gain with Pargluva appears to far exceed that with Actos or Avandia. The average weight gain with the Pargluva 5 mg dose (the dose for which approval is being sought) at 24 weeks was 1.4 kg (3.1 pounds), and at 104 weeks patients gained a whopping 13 pounds. The 10 mg dose produced an average 20 pound weight gain at 104 weeks. There also were no data presented to suggest patients don't continue to gain weight on Pargluva beyond 104 weeks.

For comparison purposes, the weight gain at 12 weeks with AstraZeneca's Galida (tesaglitazar) was 2.2 pounds at the 0.5 mg dose and 2.43 pounds at the 1 mg dose (the doses of that drug which are going forward). There are no long-term data on weight gain with Galida. The weight gain with Actos, according to the Actos label, is in a chart on page 5.

24-Week Phase III Comparison of Pargluva and Actos

Measurement	Pargluva 5 mg + metformin n=587	Actos 30 mg + metformin n=572
24-Week results		
Drop outs	60-70 patients	60-70 patients
Primary endpoint: Reduction in mean HbA_{1c}	Down 1.14%	Down 0.85%
Patients achieving HbA_{1c} target <7%	60%	45%
Patients achieving target HbA_{1c} <6.5%	34%	23%
Secondary endpoint: Fasting plasma glucose (FPG) change from baseline	Down 44 mg/dL *	Down 33 mg/dL
Fasting plasma insulin (FPI) change	Down 5.0 µU/mL *	Down 3.6 µU/mL
HOMA-IR	6.0 *	3.3
CRP	Down 30% (p=.04)	Down 24%
PAI-1	Down 30% (p=.0002)	Down 22%
Other *secondary endpoints* at 12 weeks		
TGL	Down 28% (p=.0001)	Down 14%
HDL	Up 19% *	Up 14%
LDL	No significant effects	
Safety at 24 weeks		
Any adverse event	64%	62%
Serious adverse event	4%	3%
Death	0.35%	0.25%
Discontinuations due to adverse events	2.7%	1.6%
Discontinuations due to edema	1 patient	1 patient
Edema-related events	9.2%	7.2%
Net weight change	Up 3.1 pounds	Up 1.3 pounds
CHF	3 patients **	1 patient **
Hypoglycemia serious adverse event or withdrawal	0	0
Confirmed hypoglycemia	3 patients	1 patient

* p<.0001

** All had medical histories of cardiac disease, and all recovered with diuretic therapy and/or withdrawal of study drug

Labeled Weight Change with Actos in 16-26 Weeks

Drug	Placebo	Actos 15 mg	Actos 30 mg	Actos 45 mg
Monotherapy: Weight change (median) from baseline				
Actos only	Lose 3.1 pounds n=256	Gain 2 pounds n=79	Gain 2.2 pounds n=188	Gain 5.7 pounds n=79
Combination therapy: Weight change (median) from baseline				
With sulfonylurea	Lose 1.1 pounds n=187	Gain 4.4 pounds n=183	Gain 6.8 pounds n=528	Gain 9 pounds n=333
With metformin	Lose 3.1 pounds n=160	N/A	Gain 2 pounds n=567	Gain 4 pounds n=407
With insulin	Gain 0.4 pounds n=182	Gain 5.1 pounds n=190	Gain 7.3 pounds n=522	Gain 9 pounds n=338

Weight gain alone is unlikely to be enough to kill Pargluva, but for a chronic drug for a chronic condition, this level of weight gain could be a real problem. All of the doctors questioned about the outlook for Pargluva said they probably wouldn't use a drug with that much weight gain – that patients would reject it. A Virginia doctor said, "That amount of weight gain does matter, and it could be significant. That is a high amount of weight gain. It is a very negative aspect. Patients can be better off with a reduction in HbA_{1c} and some weight gain…but there are not enough data to say weight gain doesn't matter."

A speaker at a Bristol-Myers Squibb-sponsored symposium argued that the weight gain with Pargluva is comparable to insulin-related weight gain and clinically insignificant. He called it simply a "cosmetic" problem, insisting the glycemic benefits outweigh any impact of the weight gain. He said, "That (weight gain) is something clearly of concern to our patients…It appears to be characteristic redistribution…The more potent the activation of PPAR-γ, the more propensity to weight gain there is. While weight gain is of cosmetic and social concern to patients, we…need to strike a balance between glycemic control and the perceived negative consequences patients have of weight gain." Another speaker said, "The weight gain is cosmetic only. It is cosmetically unappealing but metabolically beneficial."

104-Week Phase II Dose-Ranging Study of Pargluva

Measurement	Pargluva 1.5 mg + metformin	Pargluva 5 mg + metformin	Pargluva 10 mg + metformin	Actos 15 mg + metformin
HbA_{1c} change from baseline at Week 24	Down 0.57%	Down 1.18%	Down 1.52%	Down 0.57%
HbA_{1c} change from baseline at Week 104	---	Down 1.52% (n=88)	---	---
HbA_{1c} at Week 104	60%	64%	---	45%
Lipid results				
TGL at Week 11/12	Down 13%	Down 22%	Down 31%	Down 12%
HDL at Week 11/12	Up 17%	Up 29%	Up 25%	Up 18%
LDL at Week 12	Down 10%	Down 6%	Down 5%	Down 8%
Safety				
Discontinuations due to adverse events	8%-11%			5%
Edema-related adverse events at Week 24	9.7%	8.6%	N/A	14.3%
Edema-related events at Week 104	18.7%	25.0%	48.1%	30.8%
Death	0.4% *			0.4% *
CHF	0	3 patients	6 patients	0
Weight effects				
Changes in mean body weight at Week 24	Up 0.22 kg (0.49 pounds)	Up 1.60 kg (3.5 pounds)	Up 3.19 kg (7.0 pounds)	Up 0.19 kg (0.42 pounds)
Changes in mean body weight at Week 104	Up 0.56 kg (1.2 pounds)	Up 5.86 kg (12.9 pounds)	Up 8.94 kg (19.7 pounds)	Up 1.91 kg (4.2 pounds)

* Not considered drug related

2. Carcinogenicity. A source reported that carcinogenicity (bladder cancer) was seen in at least one animal model (mouse), and the glitazar field is littered with other agents that failed for toxicity/carcinogenicity, so this may not be an entirely dead issue. It is unclear whether the Pargluva carcinogenicity was seen prior to commencement of the Phase III trial, but even if it was, a senior FDA source insisted that does not mean the carcinogenicity issue has been resolved and will not either delay approval or lead to non-approval. A Pargluva speaker said, "These (dual PPARs) are somewhat sloppy activators and differ substantially in what they turn on and off…Unquestionably, some of the compounds in development – either due to fluid retention or gene transcription – (are associated with carcinogenicity)…But to lump them together as a single PPAR activator is wrong."

Another speaker attempted to defend Pargluva from the signal seen with other dual PPARs, saying, "To date, animal models have been poorly reflective…So I think I am not as concerned when we see incidental development of carcinoma in animals. It also appears with every PPAR activator and dual agonist – if you find the right animal model – you can generate some form of cancer."

3. Edema. There is a high rate of peripheral edema, but this is also true of the glitazones. At 24 weeks, edema was slightly higher with muraglitazar than 30 mg Actos, but at two years, it was lower than 15 mg Actos. Alone, this might not be a killer issue, but taken in the context of the

other issues with this drug it could be. Another expert said, "I'm not very concerned about the edema, but I want to know why it occurs."

4. Heart failure. There appears to be an excess of heart failure with Pargluva. There are occasional cases of heart failure with all PPARs, but the number appears higher than average with Pargluva, perhaps twice or three times the rate with Actos. In the 104-week trial, there were three cases at 5 mg, and a total of 15 cases at all doses out of ~1,100 patients on Pargluva. This compares to zero cases with Actos in ~350 patients. Even if the 5 mg dose of Pargluva were heart failure-free, the FDA traditionally looks at the side effect profile of the next-higher dose because doctors tend to up-titrate patients. Patients ***can*** recover from drug-induced heart failure but only if that heart failure was caused by sodium retention – not if it is caused by myocardial injury. An expert said there are animal data on muraglitazar that may not have been published which shows the heart failure is due to myocardial injury.

One of the speakers at a company-sponsored symposium on muraglitazar was unaware of the extent of the heart failure, but he said if these figures are correct, muraglitazar could be "a non-starter." He added, "I don't think the heart failure is real, but I'm a little concerned…If Pargluva were available today, I would use it like a glitazone, but first I'd need to be sure in my mind that the edema, heart failure, and weight gain are not worse than the glitazones."

5. Class history. So many drugs in the PPAR class have failed for toxicity that the FDA may take a harder look at the toxicity of any drug submitted.

The good news for Pargluva is that it doesn't appear to have the creatinine issues that Galida has. The onset of action is 10-12 weeks, which is similar to Actos and Avandia.

INCRETINS: GLP-1S AND DPP-IVS

Incretins are hormones released during nutrient absorption. They are released in proportion to meal size, are active in normal physiology, and are necessary for normal glucose tolerance. Three incretins are known:

- GLP-1 (glucagon-like peptide-1), made by L-cells in the GL distal gut (ileum).
- GIP (glucose-dependent insulinotropic peptide), made by K cells in the upper gut (jejunum). It exists on beta cells, alpha cells, adipocytes, the brain, adermal, and pituitary.
- DPP-IVs (dipeptidyl peptidase-IVs).

Comparison of GIPs and GLP-1s

Measurement	GIP	GLP-1
Metabolized by DPP-IV	Yes	Yes
Effects on food intake	None significant	Reduces
Immunotropic in non-diabetic humans	Yes	Yes
Immunotropic in diabetics	No	Yes
Cells that make it	K-cells in the upper gut (jejunum)	L-cells in the distal gut (ileum)
Response to stimuli	Direct	Indirect/neuronal
Major target tissues	β-cells, alpha cells, adipocytes	β-cells, alpha cells, heart, brain, GI
Receptor KO mice	Yes, with IGT	Yes, with IGT
Effect on gastric emptying	May accelerate	Slows
Stimulation of islet cell growth/mass	Yes	Yes
Impact on β-cells	Stimulates β-cells growth and survival	Promotes restoration of normal β-cell function
Effects on insulin secretion	Stimulates	Stimulates
Effects on insulin sensitivity	Unknown	May improve
Secretion in Type 2 diabetes	Preserved	Impaired
Insulinotropic response to exogenous administration in Type 2 diabetes	Impaired	Preserved
Effects on glucagon secretion	None significant	Suppresses

Other interesting comments about incretins included:

- **Nausea and weight gain.** GLP-1s and DPP-IVs are weight neutral and not associated with nausea.
- **Hypoglycemia.** These agents are expected to be associated with less hypoglycemia.
- **Use in gastric bypass patients.** A speaker speculated that it may be possible to give DPP-IVs to gastric bypass patients, though he noted that this has not yet been studied formally.
- **Side effects.** Asked if there are any unexpected or untoward side effects with incretins, a speaker said, "To date the data are that they are safe. We've seen Phase II data that the side effect profile is favorable to date…but that is no substitute for large Phase III trials. With any new inhibitor, one always has to keep an open mind. My guess is that these drugs will prove to be safer than one might have predicted several years ago, based on what we now know about their mechanism of action.
- **Responders.** Asked if there are differences in which patients are likely to respond to incretins, a speaker said, "From the studies we've done, most Type 2 diabetics respond in some way when given GLP-1…People who have done studies with 50 patients will have 47 of 50 respond, with their blood sugar coming down…So far, it has been difficult to find patients who respond and those who don't…We've seen no decrement in response as

people get older. There is some thought that older people may secrete less GLP-1, but I tend to think older patients would be good candidates because they (incretins) tend not to cause hypoglycemia, which we are always very concerned about with older patients."

- **Patients with gastropathy.** It is not yet clear whether GLP-1 receptor agonist will make patients worse who have bad gastric paresis. A speaker said, "That is an open question in my mind. So far, those patients are excluded from trials, but it seems to me that it is something that needs to be watched carefully in larger trials and post-marketing trials. What happens to these patients? It is a real possibility that there is an untoward effect."
- **Insulin sensitivity.** These agents clearly improve insulin sensitivity, a speaker said, adding, "We don't entirely understand the mechanism, but there is no question these drugs improve insulin sensitivity."

CONJUCHEM'S CJC-1131 (DAC:GLP-1)

The data are still early on this GLP-1, but it has the potential to be dosed less frequently than other agents in development, perhaps weekly. Researchers reported the half-life of CJC-1131 is ~9-14 days with a single dose and ~10 days with multi-dose administration. An investigator said, "Dosing less frequently is clearly practical after steady state, but those studies have not been done. In Phase II we are limited to short duration of exposure."

One advantage of CJC-1131 is a lack of antibody formation, but the problem appears to be nausea – a third or more of patients get nausea. An investigator said, "Slow titration and working with patients to get through this period is critical."

A randomized, double-blind, placebo-controlled Phase II trial tested CJC-1131 at several QD doses – from 1 µg/kg to 12 µg/kg – in Type 2 diabetics, following a four-week wash-out period. Doses were titrated up based on tolerance, not glycemic control. The treatment period was 12 weeks, followed by an eight week maintenance phase.

Results of 24-Week Phase II Trial of CJC-1131 vs. Metformin

Measurement	CJC-1131 low dose (4 µg/kg) n=28	CJC-1131 high dose (12 µg/kg) n=30	Metformin n=28
Completers	16 patients	22 patients	19 patients
Average dose	2.2	2.4	---
HbA_{1c} change	-0.06%	-1.01%	N/A
% of patients achieving $HbA_{1c} \leq 7\%$	---	57%	---
Change in body weight at 12 weeks	Down 6.5 pounds	Down 4.9 pounds	Down 3.6 pounds
Nausea	35.7%	33.3%	3.6%
Vomiting	0	10%	0
Dizziness	24.3%	10%	N/A
Discontinuations for nausea	0	10%	0

ConjuChem has two other DAC:GLP-1s in preclinical development – CJC-1525 and CJC-1575. An official said these are "more for Type 2 diabetics." They were described as "very long lasting – much longer than Lantus."

LILLY/AMYLIN'S Byetta (exenatide), an injectable GLP-1 analog

Byetta, a first-in-class incretin mimetic, was approved by the FDA on April 28, 2005, as adjunctive therapy to improve glycemic control in Type 2 diabetics who have not achieved adequate control on metformin and/or a sulfonylurea, but Byetta wasn't launched until June 2005. Doctors at ADA were excited about Byetta – because of the weight loss as well as the glycemic control – and Byetta events were mobbed.

Amylin CEO Ginger Graham said both the Amylin and Lilly sales forces were fully trained two weeks after approval, and they began field promoting it in May 2005. She claimed reimbursement activities are "exceeding expectations," with all payors so far placing it on Tier 3. First Data Bank gave it a unique code *(Anti-hyperglycemic, Incretin Mimetic – GLP-1 Receptor Agonist)*. She also said Byetta is not being evaluated as a weight loss medication, "It is not our best choice in the short-term to position it as an obesity agent. But we are studying pramlintide (Amylin's Symlin) as an obesity agent."

Lilly/Amylin also have a strong effort underway to educate doctors and patients about Byetta. More than 500 physician speakers are expected to be trained by the end of August 2005. One of the doctors who has been trained already said he expects about 20% of his Type 2 diabetics will be on Byetta within a year, "It is possible I will put some Type 1s on it as well. I'll probably try it on them. I'll put my dad and maybe my wife on it – she needs to lose some weight…I just got coupons for the drug and kits with free drug, so I don't have a real feel for Byetta yet. I'm worried about the nausea, but the company told us it may not be real nausea, just a 'feeling of fullness.' If I tell a patient the nausea is not a sign of anything going wrong or a danger, they may get through it. I've been dealing with nausea with Cymbalta (Lilly, duloxetine), but many of those patients quit because of the nausea. It is clear we have to figure out how to titrate Cymbalta. In the Byetta trials, I heard patients took anti-nausea medications…Patients will be accepting of an injection because of the weight loss. The weight loss gets their attention. It's important to tell them about the weight loss before you tell them it is an injection with a pen. And we were told to give patients a saline shot with the pen to demonstrate how painless it is right then –

before they go home and think about it…I'm a pen connoisseur, and I think this is a great pen."

Another 20 doctors were questioned about the outlook for Byetta. Only five had already tried it, but 10 of the other 15 plan to try it. Two doctors said they offered Byetta to patients, and the patients all turned it down. Only three do not expect to prescribe Byetta over the next year. Overall, these doctors predicted 13% of their diabetic patients would be on Byetta within a year, and among the doctors who definitely plan to prescribe Byetta, the estimate rises to 16%. Among the comments they made were:

- *Alabama:* "Byetta is pretty exciting for obese Type 2 diabetics. The weight loss is appealing to patients."
- *California:* "It is very promising, especially for overweight Type 2s. I'm pre-diabetic, and I'll try it myself."
- *Georgia:* "Injections are not an issue…Patients may be willing to tolerate the nausea for the weight loss."
- *Kansas:* "I'll offer it to 20%, and I expect half will accept."
- *Louisiana:* "My fear is whether patients will stay on it."
- *Maryland:* "Byetta is not on my formulary yet, but the injections and nausea are really not issues."
- *Nevada:* "The injections are not an issue, but I need to see how the nausea is."
- *New Hampshire:* "Byetta is exciting. The weight loss may overcome the injections. The nausea is manageable – patients tolerate it with metformin. The company portrays the nausea as 'satiety.'"
- *New York:* "I'll try it in very motivated patients who are at the end of the line. I'll use it for very isolated patients who are maxed on all else – even patients on insulin."
- *Utah:* "Injections are more of an issue than the nausea."
- *Virginia #1:* "Injections will be a hard sell."
- *Virginia #2:* "I told the company they would have difficulty selling a new class like this to primary care physicians, who are comfortable with other medications – especially with a new medication that is injected. Primary care doctors will be very hesitant (to use Byetta), and 90%-95% of Type 2 diabetics are cared for by primary care doctors."
- *Wisconsin:* "The injections are a major barrier, but the weight loss may overcome that."

At a Lilly/Amylin-sponsored breakfast, speakers emphasized these aspects of Byetta:

- Reduction in $HbA_{1c.}$
- Weight loss is not a function of nausea.
- Little hypoglycemia.
- An injection that is not insulin.
- Available in pre-filled pens, making it simpler than insulin.
- The nausea side effect decreases over time.
- Byetta must be refrigerated, and a cool pack should be used for traveling. However, a speaker said, "It is not a deal breaker if it is left out of the refrigerator. It (the pen) can be left out for up to 144 hours. It is not ruined if it is left out during the day."

Among the issues with Byetta that speakers addressed were:

➢ **First-time patients.** A Byetta speaker said, "Metformin still has the best outcomes. We have four decades of European experience with metformin. It is still first-line, but once we address some of the insulin resistance issues with metformin, then this (Byetta) is a good add-on." Another speaker suggested that patients may begin to ask for Byetta as they learn more about it.

➢ **Market size.** Sources estimated that 8%-17% of Type 2 diabetics are candidates for Byetta**.**

- One speaker estimated that 8% of her practice would qualify for Byetta. She said about 50% of diabetics are Type 2, with half of those on insulin. Of the insulin-dependent Type 2 diabetics, ~40% have an HbA_{1c} >7%.
- Another Byetta expert estimated 17% of his patients would be eligible for Byetta. Of his 1,180 patients, half are Type 2 diabetics. Of these, ~60%-67% are not on insulin, and ~45%-50% have HbA_{1c} >7%.

➢ **Physician starter kits.** Doctors are being given starter kits that include a 30-day sample supply for patients, a demonstration injection pen for the doctor's office, a DVD, and educational information.

➢ **Nausea and vomiting.** Throughout ADA, Byetta speakers attempted to minimize this side effect by dismissing it rather than offering doctors concrete tips on dealing with it. In the past a Byetta researcher had described the nausea with Byetta as comparable to the nausea of pregnancy, but at ADA speakers described it variously as "a feeling of fullness" or "satiety." One speaker said, "What is astonishing is that 20% of placebo patients got nausea…If I badgered you each time by asking about nausea, you would report it…That is not to minimize the nausea, but it isn't something we have to deal with. There is 5%-8% nausea in metformin trials, and 25%-33% of patients have GI problems with metformin in clinical practice…With Byetta, there is little nausea after the first four weeks. Patients in extension trials chose to be there, and if they have another episode, it is clearly tolerable. Even in clinical trials, I found it a very minimal limitation to my use of the compound. The first patient we randomized had fairly substantial nausea…but he was really describing a desire not to eat." There may be less nausea if Byetta is titrated slowly,

and a speaker suggested, "We need to learn from the metformin experience…I would certainly suggest the company consider more and smaller steps."

➢ **Primary care physicians.** Endocrinologists may jump on the Byetta wagon much faster than primary care doctors. It may take some time for Byetta to filter down to primary care doctors. A speaker suggested the company may be counting on patient demand to help spur use by primary care doctors: "To me this is a new class, and it takes even specialists some time to understand it. But this is a relatively simple and a novel approach, and it works quickly, so there is feedback to patients and primary care providers. Also, patients will hear about this, and they will drive some of the questions. And once you use it, and if it works well and the experience is good with patients, (then use will grow)…But a period of a few months would be required to see patients back. We won't need to see a hundred patients to make this change. Lantus – which was picked up quickly – could be substituted for other insulins. Here, we are not converting; it is a new use of this compound. But I see it as relatively short uptake."

Among the data on Byetta presented at ADA were:

➢ A 551-patient, 26-week, randomized, multicenter, open-label, two-arm, parallel Phase III study compared Byetta 5 µg BID for four weeks followed by Byetta 10 µg BID for the remainder of the study to QD Sanofi-Aventis's Lantus (insulin glargine) in patients inadequately responding to metformin+ sulfonylurea. The trial found glycemic control with Byetta was non-inferior to Lantus. All patients received metformin and a sulfonylurea during the study.

ITT Results of 26-Week Phase III Comparison of Byetta and Lantus

Measurement	Byetta BID n=282	Lantus QD n=267
Discontinuations		
Withdrawals	19.4%	9.7%
Due to adverse events	9.5%	N/A
Due to patient decision	2.8%	1.5%
Lost to follow-up	1.8%	2.6%
Protocol violation	3.5%	4.1%
Results		
Primary endpoint: Mean change in HbA_{1c}	-1.0%	-1.1%
Weight change	Lost 5.1 pounds	Gained 4.0 pounds
Weight loss in patients with no nausea	4.3 pounds	---
Weight loss in patients with nausea	5.2 pounds	---
Nocturnal hypoglycemia	0.9%	2.4%
Daytime hypoglycemia	N/A	Lower
Discontinuations due to GI effects	6%	1%
Patients reaching target HbA_{1c} <7%	46%	48%
Patients reaching HbA_{1c} <6.5%	32%	25%
Hypoglycemia	7.3 events per patient year	6.3 events per patient year
Severe hypoglycemia	4 episodes *	4 episodes *
Nausea	57%	9%
Vomiting	17%	4%
Weight change based on nausea		
In patients with no nausea	-4.3 pounds	---
In patients with any nausea	-5.2 pounds	---

* none required medical assistance

Response to Byetta by Weight Quartile

Measurement	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Reduction in mean HbA_{1c}	1.8%	1.2%	0.9%	1.0%
Average weight reduction	4 pounds	2.6 pounds	0.2 pounds	2.2 pounds
TGL	-92	-58	+7	-3
HDL-C	+7.0%	+3.5%	+3.0%	+3.8%

An 82-week open label extension cohort (n=265) from the 3 AMIGO trials was reviewed. The trial found sustained improvement in glycemic control (–1.2%) and continued weight loss (-10.1 pounds).

82-Week Byetta Extension Cohort of 3 AMIGO Trials

Measurement	26 weeks	82 weeks
Reduction in mean HbA_{1c}	~ -1.0%	-1.2%
Average weight change	Down 4.4 pounds	Down 10.1 pounds
Nausea	---	46%
Withdrawals due to nausea	---	3.6%
HDL change	---	+4.46 mg/dL
LDL change	---	-1.41 mg/dL
Triglyceride change	---	-36.94

NOVO NORDISK'S liraglutide, a QD injectable GLP-1 analog

There were no significant new data on this agent at ADA. A speaker said it is efficacious, with mild, transient nausea in ~25% of patients, leading to discontinuations in ~4%.

DPP-IVs

A speaker estimated that there are 29 DPP-IVs currently in development.

MERCK'S sitagliptin (MK-0431)

The data on sitagliptin, an oral twice-daily DPP-IV, are very early, but it looks promising. The half life is 8-12 hours, but the duration of action is not clear.

A small (28-patient) two-period cross-over study was presented at ADA. After a five-week lead-in (stabilization period), patients were randomized to four weeks of metformin plus either sitagliptin or placebo, and then reversed for another four weeks. The primary endpoint was 24-hour weight mean glucose (WMG) calculated as an integrated assessment of

12-Week Efficacy Study of Sitagliptin

Measurement	Glipizide (5-20 mg)	5 mg sitagliptin	12.5 mg sitagliptin	25 mg sitagliptin	50 mg sitagliptin
Change in HbA_{1c}	-1.00	-0.38	-.64	-.66	-.77
FPG change	-32.7	-817	-20.9	-20.9	-26.1
2-hour PPG	-72.1	-35.0	-38.6	-45.2	-54.2
Any adverse events	28%	---	---	---	12%
Hypoglycemia	17%	0-4%			
GI-related adverse events	4%	80%-17%			

glycemic exposure over the 24 hour period. Secondary end-points included FPG, mean daily glucose, 24-hour C-peptide, etc. Researchers reported a "significant" carryover effect in the sitagliptin group following Period 1, with blood glucose levels not returning to baseline. They said the mechanism of carryover is not known. As a result, they presented only the data on Period 1, which, in effect, was a parallel group study.

Researchers concluded adding sitagliptin to metformin results in:

- No clinically meaningful differences in adverse events.
- Hypoglycemic events.
- No differences in GI-related adverse events.
- No body weight change.
- No clinically meaningful change in hepatic or muscle enzymes (no rhabdomyolysis).

4-Week Results of Sitagliptin vs. Placebo

Measurement	Sitagliptin 50 mg BID n=15	Placebo n=13	p-value
Primary endpoint: 24-hour mean glucose	Significantly lower throughout entire 24 hour period -32.8 mg/dL		<.001
Mean daily glucose at 4 weeks	157 mg/dL	184 mg/dL	<.001
24-hour C-peptide concentrations	N/A	N/A	Nss

NOVARTIS'S vildagliptin (LAF-237)

There were little data on this oral DPP-IV at ADA this year. Phase III data are expected later this year, and speakers predicted it would be available in early 2007. Hundreds of doctors who wanted to attend a Novartis-sponsored dinner symposium on incretins couldn't get in, so interest in this agent and the class is high.

A speaker emphasized that vildagliptin is an oral agent, while Novo Nordisk's liraglutide and Lilly/Amylin's Byetta (exenatide) require injections. He cited these characteristics of DPP-IV inhibition with vildagliptin:

- Increases the GLP-1 response in Type 2 diabetes.
- Improves glucose control in Type 2 diabetes.
- Improves glucose tolerance in Type 2 diabetes.
- Maintains the insulin response in Type 2 diabetes.
- Decreases the glucagon response in Type 2 diabetes.
- Synergizes with metformin to improve glucose control.
- Synergizes with metformin to improve β-cell function.

Asked if vildagliptin could be used in diabetes prevention, a speaker said, "That is the way we are all moving – prevention and to slow development. It has been clearly demonstrated that lifestyle intervention can act to slow progression...I think the use of a DPP-IV to do the same thing is exciting…And an oral agent like this (vildagliptin) that doesn't cause hypoglycemia, makes it safe to use."

Other DPP-IVs in development include:

- **BRISTOL-MYERS SQUIBB'S saxagliptin.**
- **LILLY'S LY-307161-SR.** A poster at ADA did not show any dose response effect, and there were significant injection site reactions, which may explain why Lilly partnered with Amylin on exenatide and LAR.
- **MERCK'S ILT** is in preclinical development. Merck researchers declined to discuss this agent.
- **NOVARTIS'S DPP-728**, a second DPP-IV, separate from vildagliptin.
- **PFIZER'S CP-867534-01**, also is in preclinical development, but it has shown unacceptable intestinal side effects (necrosis and intestinal bleeding). Pfizer is working on other DPP-IVs, but a researcher expressed concern with the safety of these agents because of their lack of specificity.

OTHER ANTIHYPERGLYCEMIC AGENTS

AMYLIN'S Symlin (pramlintide)

This is also a first-in-class, an amylinomimetic approved for insulin-using Type 1 and Type 2 diabetics who are not well-controlled on insulin alone. Nausea is the most common adverse event, generally mild-to-moderate and dissipates over time. It has a boxed warning that highlights the potency and ensures that healthcare professionals understand they must reduce mealtime insulin if they prescribe Symlin.

Sales of Symlin have not been remarkable, but the company remains upbeat about this drug. An Amylin official said reimbursement activities are ahead of plan. The drug has been given a unique code by First Data Bank *(Anti-hyperglycemic,*

Amylin Analogue type). Payors are asking to review both Symlin and Byetta at the same time.

METABOLEX'S metaglidasen (MBX-102), a selective PPAR modulator (SPPARM)

SPPARMs are different from the thiazolidinedione PPARs, which are full agonists of the PPAR nuclear receptor. The PPAR receptor controls the expression of genes involved in glucose metabolism, lipid metabolism, and inflammation. In theory, SPPARMs modulate the genes needed for insulin sensitization without activating those responsible for weight gain and edema. The first SPPARM is likely to be Metabolex's metaglidasen.

A randomized, double-blind, placebo-controlled, 12-week, Phase II trial in 217 insulin-using Type 2 diabetics found metaglidasen, an oral insulin-sensitizer, significantly reduced HbA_{1c} but, unlike PPARs, did not appear to cause weight gain or edema. The company is ***not*** testing a 600 mg dose in a second Phase II trial, with a Phase III trial expected to start in 2006. Metabolex is looking for a partner to develop this drug.

12-Week Phase II Trial of Metaglidasen

Measurement	Metaglidasen 200 mg QD + insulin	Metaglidasen 400 mg QD + insulin	Placebo + insulin
Change in HbA_{1c}	-0.9%	-1.0%	-0.3%
FPG	N/A	-41 mg/dL vs. placebo	---
Change in triglycerides	N/A	-21% vs. placebo	---
Uric acid	-7.5%	-20%	---
Edema	11%	5.8%	16.2%
Weight gain	1.1 pounds		1.8 pounds
Heart failure	0	0	0
Triglycerides	No change	Down 15%	N/A

PULMONARY INSULIN

Experts generally believe that inhaled insulin is now on-track for FDA approval, and patient demand is expected to be high enough to overcome the higher cost. There are numerous inhaled insulin products in development, but a speaker suggested the leading four companies/consortiums are Lilly/Alkermes, Pfizer/Sanofi-Aventis/Nektar, Novo Nordisk/ Aradigm, and Generex.

Pfizer's Exubera is likely to be the first inhaled insulin to get FDA approval, but first-to-market may not be a big advantage, especially since the market needs to be developed – and the Pfizer device does not appear optimal. An expert said, "I expect the FDA will examine it (Exubera) carefully because it is a first-in-class…but I think it will meet the regulatory hurdles…There are no safety issues, and it is clearly efficacious."

However, there wasn't a huge buzz at ADA about inhaled insulin. Another expert said, "I don't think inhaled insulin will change insulin usage drastically. Patients say, 'If you want to help me, eliminate finger sticks.' Inhaled insulin won't have the precisions we now have with insulin. One class of patients who will demand inhaled insulin are those with a serious fear of needles, but with the new pens, the injection issue is much less today."

The lung offers an absorption area of 100-140 m^2, which is equivalent to the size of a tennis court. The efficiency of inhalation varies by the device, but is usually in the range of 8%-15%. From 60%-80% of the insulin molecules do not even reach the lung.

Third party payors may be reluctant to cover the higher cost of inhaled insulin. An expert predicted that patient demand may overcome that, "I think they will be influenced by patient demand. If there is patient demand for this and doctors are prescribing it, they will buy in to some degree or another, and patients may reach into their pockets for this."

Among the pulmonary insulin products in development are:

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

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

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

COREMED'S Alveair – This appears to still be in preclinical development.

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

GENEREX – a dry powder formulation, using a mechanical delivery device, but it is delivered by a buccal, not pulmonary, route.

KOS PHARMACEUTICALS – a liquid formulation with a multi-dose, breath-activated inhaler. Dr. Jay Skyler of the University of Miami said, "This is very interesting. This has a canister with up to 128 inhalations, while all the others are single dose devices."

LILLY/ALKERMES – a dry powder formulation with AIR technology and a small, light, simple, breath-activated inhaler (that looks somewhat like an asthma inhaler). This inhaled

insulin, which is a little behind Pfizer's Exubera in development, has more rapid onset of action than regular insulin but is longer acting than Lispro – again, sort of in-between.

Studies presented at ADA found that human insulin inhalation powder (HIIP), delivered with the AIR system, lowers blood sugar as effectively as traditional injected insulin. Lilly and Alkermes plan to begin enrolling Type 1 and Type 2 diabetics in additional clinical trials in July 2005. These 24-month studies will include ~1,000 patients in the U.S., Canada, Mexico, South America, Europe, India, Taiwan, Thailand, Singapore, and the Philippines. A subset of COPD patients and asthmatics will also be studied.

In a small (22-patient), early-stage study researchers reported that HIIP delivers a dose similar to an injection of quick-acting insulin Lispro. Smokers and patients with hay fever, rhinitis, or sinusitus were excluded from the trial. There were no pulmonary safety concerns, and the only adverse event was a case of non-serious flu. Researchers concluded that HIIP offers consistent equivalency to Lispro across a range of doses, "Patients should be able to transition between HIIP and Lispro with predictable results. HIIP provided dosing reproducibility comparable to Lispro with a suitable time-action profile, and HIIP was equally well-tolerated." (NOTE: 2.6 mg HIIP=6 U Lispro.)

Another study, a 137-patient, three-month crossover Phase II trial, looked at the safety and efficacy of post-prandial HIIP vs. injected insulin in non-smoking Type 1 diabetics. Patients were given a six-week run-in, then for Period 1 they were randomized to HIIP+glargine vs. Lispro vs. regular insulin+glargine. For Period 2, they were to crossover for another three months. Researchers concluded:

- HIIP has significantly lower FPG values.
- Using glargine as basal insulin, meal-time HIIP and subcutaneous insulin treatments were equivalent in efficacy for HbA_{1c}.
- Dlco was significantly reduced for HIIP. The difference was small, reversible, and not clinically meaningful.
- Any hypoglycemia and severe hypoglycemia were similar for HIIP and subcutaneous insulin.
- Nocturnal hypoglycemia was significantly greater for HIIP, suggesting a need for insulin regimen adjustments.
- Patient acceptance of HIIP may result in better glycemic control.

12-Week Study of HIIP

Measurement	HIIP 2.6 mg	HIIP 5.2 mg	HIIP 7.8 mg	Lispro 6 U	Lispro 12 U	Lispro 18 U
AUC	28.5	59.0	105	37.1	65.8	78.7
NGD	12	31	13	12	32	14
$G_{tot(0-600)}$	87.2 g	137 g	175 g	82.5 g	132 g	161 g
G	48.5	37.1	40.6	42.4	35.3	N/A
Onset of action	2-41 minutes					---

12-Week Study of HIIP

Measurement	HIIP +glargine	Regular insulin+ glargine	p-value
Primary endpoint: HbA_{1c} non-inferiority (margin of 0.3%)	7.9%	8.0%	Nss
Hypoglycemia at 2 weeks	13%	9%	---
Severe hypoglycemia	Similar		---
Nocturnal hypoglycemia	More	---	p<.001
FEV_1	3.13	3.15	.08
FVC	3.93	3.94	.77
Dlco	25.3	26.6	<.05
Cough	~3-fold increase	---	---
Antibodies	~3-fold increase	---	---

MANNKIND'S Technosphere – a dry powder formulation of "technospheres" using a mechanical inhaler. This has much more rapid onset of action than subcutaneous insulin. It also has higher bioavailability (~30%). Dr. Skyler said, "It has a lower or equal variability on PK and longer duration than subcutaneous insulin...which is intriguing because many people were concerned that lower bioavailability in pulmonary delivery might lead to more variability…but, actually, the coefficient of variability is similar or better. Perhaps a surprising observation to some degree."

Patients are currently being enrolled in a Phase III trial of Technosphere inhaled insulin in Europe (Russia) and South Africa. A U.S. Phase III trial is expected to start in July 2005. These are one-year trials which will have a subgroup of asthmatics included. Data are expected in August or September 2006.

Dr. Julio Rosenstock of the Dallas Diabetes Center, presented the results of a 12-week, 123-patient, randomized, double-blind, placebo-controlled, Phase II trial of inhaled Technosphere insulin in Type 2 diabetics. He said bioavailability was 28% of subcutaneous insulin. Patients were started on 6 units before each meal and then titrated up to 48 units before each meal. Dr. Rosenstock indicated the optimal dose has not yet been tested, "The Technosphere cartridges have 6, 12, and 24 concentrations, so patients were taking two cartridges per meal. They were going up to a maximum of 48 units before meals. I think in the future we will need to go a little higher because it is conceivable if we go higher, we will get better results."

There was a significant number of patients who dropped out for adherence issues.

Dr. Anders Boss presented another small (12 patient), randomized, crossover study of Technosphere. This

study found 48 units of Technosphere insulin had ***less*** variability in absorption than subcutaneous insulin, but out to nine hours there was more variability in AUC-GIR with Technosphere insulin.

NOVO NORDISK/ARADIGM'S AERx iDMS – a liquid formulation using an electronically-guided inhaler. A Novo Nordisk employee discussed this product, saying the onset of action is faster than subcutaneous human regular insulin and similar to that of subcutaneous insulin aspart. She presented the results of a single-center, open-label, three period crossover trial in 15 non-smoking Type 1 diabetics. The study also found duration of action was not different from subcutaneous regular insulin but longer than insulin aspart. She concluded, "These characteristics make AERx suitable as a meal-time insulin."

Single-Center AERx Study

Measurement	AERx	Human insulin (HI)	Insulin aspart (IA)
Dose	0.3 U/kg	0.3 U/kg	0.3 U/kg
Onset of action – time to 10% of $ACU_{GIR\ (0\text{-}10h)}$	88	72	N/A
AUC-GIR	1971	1949	2126
GIR max	142 (p=.01 vs. HI)	202	136

PFIZER/SANOFI-AVENTIS/NEKTAR'S Exubera – a dry powder formulation with a mechanical inhaler. It has more rapid onset of action than regular insulin but longer action than Lispro (sort of in-between those). One unit of Exubera equals three units of subcutaneous insulin.

Phase II/III studies demonstrated comparable efficacy between Exubera and subcutaneous insulin in both Type 1 and Type 2 diabetics. The problem was safety. Early trials had one case of pulmonary fibrosis, and there was a small but consistent treatment group difference between inhaled and subcutaneous insulin patients on pulmonary function (FEV_1) tests.

A speaker explained that the FEV_1 tests used in earlier trials were not standardized and that was believed to be the problem. Data presented at ADA appeared to confirm that. A one-year, 226-patient (age 25-65) study with a three-week run-in period showed that Exubera TID does not impair lung function in diabetic patients after two years of use by Type 2 diabetics – when a standardized FEV_1 test was used. The speaker said, "What we did was perform highly standardized PFTs. Every site got the same equipment and software. Every technician/coordinator was trained on healthy volunteers, and we used centralized data collection. Patients were retreated if standards were not met…So, any difference in the two groups could not be explained by the quality of the tests."

Researchers reported an early decline in FEV_1, which was fully manifested by Week 2. After a few weeks any difference between the two groups disappeared, indicating there is a plateau in FEV_1 with inhaled insulin, and the difference is not progressive. When inhaled insulin is discontinued, there is a kind of catch-up, and the curves become the same (overlapping). The cause of the decline in FEV_1 is not known. A researcher said, "I think we can conclude that we are not facing the development of a nasty infiltrative disease. If we had faced fibrosis, the decline would not have been that fast. It would have been progressive, and you wouldn't have seen a full, rapid recovery after discontinuation of inhaled insulin…There was no asthma-like acute reaction."

A review of Exubera long-term use in Type 2 diabetics examined three studies, concluding there were no new safety concerns with Exubera, no significant difference in FEV_1 over two years, and glycemic control was maintained for the duration of treatment. Antibodies did increase with Exubera, plateauing between six and 12 months, but did not correlate with HbA_{1c} changes or changes in lung function.

- **Study 1:** in patients poorly controlled on a sulfonylurea given adjunctive Exubera vs. metformin. This was a four week run-in, then 24 weeks of therapy, 104-week safety study, and then a 12-week wash-out period.
- **Study 2:** in patients poorly controlled on metformin randomized to Exubera vs. adjunctive glibenclamide. This was a four week run-in, then 24 weeks of therapy, a 104-week safety study, and then a 12-week wash-out period.
- **Study 3:** an uncontrolled extension of a Phase III trial.

Phase II Exubera Trial

Measurement	Exubera in Studies 1 and 2 n=478	Comparator in Studies 1 and 2 n=441	Exubera in Study 3 n=626
HbA_{1c} at end	7.7%	8.1%	7.2%
HbA_{1c} change from baseline	-1.8%	-1.5%	-1.5%
Hypoglycemia	0.2	0.148	.793 *
Severe hypoglycemia	1 patient	1 patient	6 patients **
Change in FEV_1	-0.077	-0.067	-0.074

* One-third of these were on insulin from the outset.
** No discontinuations.

At a Pfizer/Sanofi-Aventis-sponsored breakfast, a speaker urged using insulin very early in Type 2 diabetes, suggesting that this strategy could not only sustain glucose control but may also reverse impaired insulin secretion from β-cells, "It is conceivable that insulin administration at the outset of diabetes may have a unique β-cell preserving effect." Another speaker said, "I think we use insulin way too late…It is highly conceivable that if we intervene much earlier, the requirements for supplemental insulin may be much lower…My view is that by acting more dynamically right from the onset, there is a good chance we can succeed. That doesn't necessarily mean we won't use oral agents. I think

insulin sensitizers will play a role…The combination of insulin and sensitizer will probably be a very important combination."

Among the issues that were discussed relating to inhaled insulin were:

- **Smoking.** One of the concerns with the pulmonary delivery of insulin is smoking. Smoking increases lung permeability, so there is more variability in absorption. In the clinical trials of Exubera, smokers were excluded. Respiratory infections can, in some cases, cause patients to stop taking inhaled insulin, and asthma decreases variability compared to healthy subjects. No data on inhaled insulin in COPD patients have been published yet – but a speaker noted that it is hard to find patients with COPD able to use inhaled insulin.

- **Efficacy.** The efficacy of inhaled insulin appears good. A paper to be published in July 2005 on a Phase III trial of Exubera will show an efficacy curve superimposable over subcutaneous insulin in Type 1 diabetics.

- **Type 2 diabetics.** Studies with Exubera, AERx, and the Kos product have all shown efficacy in Type 2 diabetics when inhaled insulin either replaces subcutaneous insulin or is added to metformin or a sulfonylurea.

- **Weight changes.** There is some increased weight with inhaled insulin but not as much as with subcutaneous insulin.

- **Safety.** An AERx study found no change in pulmonary function over 360 minutes in healthy diabetics or in asthmatics, though people with asthma do have an expected decrease in function from the start. FEV_1 changes in Type 1 and Type 2 diabetics showed no difference from subcutaneous insulin out to 48 months. However, longer-term studies are needed.

- **Antibodies.** Two years ago researchers reported on an increase in antibodies with Exubera vs. subcutaneous insulin, but the amounts are still low. Longer-term studies are needed.

- **Cough.** One-third of Exubera patients have cough related to inhalation – usually within 15-60 seconds of inhalation – but an expert said there is no evidence of any patient having a glycemic control problem because of the cough.

- **Hypoglycemia.**

- **Quality of life vs. cost.**

- **Non-bioavailable insulin.** What happens to ~80% of inhaled insulin is still not known. Experts believe it probably doesn't reach the lungs and is somehow degraded or lost, but they don't know how.

- **Limitations on use.** Inhaled insulin is not expected to be used, at least initially, in smokers, people with pulmonary infections, and children. The interaction of exercise on inhaled insulin also isn't known.

Other Insulin Delivery Options

Other approaches to insulin delivery include:

- Iontophoresis
- Ultrasound
- Thermal ablation
- Laser ablation
- Microneedles
- Transdermal

TransPharma Medical's ViaDerm

This company is working on transdermal delivery of insulin using an RF approach to generate hundreds of microchannels that penetrate only the skin's outermost layer (independent of skin type and thickness). The device is used on the skin, and then the insulin-filled patch is placed on the body over the treated area. No other substances are added – no absorption enhancers, etc. The dry insulin in the patch is dissolved in the liquid that comes out of the skin and then diffuses into the body.

A non-randomized, non-blinded, crossover study was conducted in five healthy volunteers. A researcher reported the study proved the concept, demonstrating that therapeutic amounts of insulin can be delivered without loss of metabolic activity, but the time action profile was not optimal.

Oral insulin

U.K. researchers reported on DTY-001, an oral insulin in capsule form (150 IU and 300 IU). In small studies in dogs and healthy humans, it appeared effective. There were statistically significant increases in plasma insulin with both doses, with a greater effect at the higher dose. Insulin concentrations reached a peak at ~90 minutes after administration. AUC did not differ significantly between the two doses. However, there was considerable between-patient variability, and one patient at 150 IU got symptomatic hypoglycemia. The results indicate this is definitely something to watch.

The Diabetic Microvasculature

Diabetic retinopathy. Each year 12-24,000 people lose sight as result of diabetic retinopathy. It is frequently present at the time of diagnosis of Type 2 diabetes, and, once present, tends to progress, resulting in microaneurysms, retinal hemorrhages, and severe retinal hemorrhages. Diabetic retinopathy may lead to diabetic macular edema.

New Therapies in Development

Drug	Results	Status/comments
Aldose reductase inhibitors (ARIs)		**Too late, too short, too toxic, and too weak**
Alrestatin	Minor benefits	Withdrawn for toxicity
Sorbinil	Benefits	Withdrawn for toxicity
Tolrestat	Minor benefits	Withdrawn for toxicity
Ponalrestat	No efficacy	Withdrawn for toxicity
Zenarestat	Minor benefits	Withdrawn for toxicity
Epalrestat	Clinical benefits	Marketed in Japan
Fidarestat	Minor benefits	Under investigation
Advanced glycation end product (AGE) receptor blockers		**Benefits but toxic**
Pimagedine	Benefits but toxicity includes anemia, flu-like symptoms, glomuleronephritis, and increased ANA	N/A
Other agents		**Investigational**
Poly (ADP-ribose) polymerase (PARP) inhibitors	Several	Various stages
Benfotiamine	May prevent diabetic retinopathy and nephropathy and may be beneficial in diabetic neuropathy	Approved in Germany
Lilly's Arxxant (ruboxistaurin, a protein kinase C-β inhibitor)	Phase II data suggest benefit in diabetic retinopathy and diabetic nephropathy. 31% risk reduction in progression of DME and trend toward reduced vision loss.	Phase III for diabetic neuropathy and retinopathy

Diabetic nephropathy. This occurred in 20%-40% of all diabetics. It is the most common complication of diabetes, and the leading cause of morbidity and mortality in diabetic patients. It also is the singe leading cause of end-stage renal disease (ESRD). About 25% of Type 1 diabetics and 5%-10% of Type 2 diabetics develop kidney failure.

Diabetic peripheral neuropathy (DPN). This accounts for 50%-70% of the non-traumatic amputations in the U.S., and 87% of the 85,000 amputations in the U.S. each year are due to neuropathy. However, diabetic neuropathy is under-diagnosed.

A 1% decrease in HbA_{1c} results in a risk reduction of:

- 19%-38% in retinopathy
- 22%-50% in nephropathy
- 18%-35% in neuropathy

Four mechanisms of hyperglycemia-induced tissue damage have been the focus for many years, but clinical trials to date have been disappointing. Then, about five or six years ago the idea that a common upstream event – in the mitochondria – activates all four mechanisms that mediate hyperglycemia:

- Increased heosamine pathway flux.
- Activation of protein kinase C (PKC) isoforms. Hyperglycemia does induce PKC activation. Mitochondrial superoxide dismutase (MnSOD) over expression prevents PKC activation, and hyperglycemia induces MnSOD over-expression.
- Increased polyol pathway flux.
- Increased advanced glycation end product (AGE) formation.

However, hyperglycemia is not the major determinant of diabetic macrovascular disease. What is? The conventional explanation is that it is insulin resistance syndrome or the metabolic syndrome, but a speaker argued that it is mitochondrial ROS (reactive oxygen species) overproduction that activates all four. Experiments have found that treating diabetic animals with small catalytic antioxidants (SOD mimetics) restores prostacyclin synthase activity. Thus, small molecular weight compounds which target the M-ROS pathway – superoxides – have become a new therapeutic goal.

LILLY'S Arxxant (ruboxistaurin mesylate)

A one-year pilot study of Arxxant had "encouraging" results. Arxxant, a PKC-β inhibitor, is the first in a new class of compounds being developed to treat complications associated with diabetes. The pilot study was a one-year, multicenter, randomized, double-blind, parallel placebo-controlled Phase II trial of Arxxant in diabetic nephropathy. The 123-patient trial looked at markers of the Arxxant's ability to delay the onset of kidney failure in patients already on an ACE inhibitor or ARB (or both). The study found that the reduction in albuminuria was apparent as early as one month and was sustained for the rest of the trial. Blood pressure was well-controlled and glycemic control was good in both arms. The principal investigator,

1-Year Phase II Arxxant Trial

Measurement	Arxxant 32 mg/day + ACE/ARB n=61	Placebo + ACE/ARB n=62
Albuminuria change from baseline	Down 24% (p=0.02)	Down 9% (p=0.33)
Glomerular filtration rate (GFR) change from baseline	Down 2.5% (p=0.185)	Down 4.8% (p=0.009)
Safety		
Any adverse event	15 reports	9 reports
Deaths	2 (one fell off a ladder and one metastatic cancer)	0
Hypertension requiring interventions	0	8%
Blood pressure	135/75	135/75
Discontinuations due to adverse events	3 patients (decreased libido, subdural hematoma after fall, and metastatic cancer)	0

Management of Symptomatic DPN

Drug category	FDA-approved examples	Off-label drugs used	Comments
Diabetic neuropathy			
NSAIDs	Bayer's Aleve	Sulindac	Some occasionally helpful, but sulindac rarely helpful
Antidepressants	Lilly's Cymbalta (duloxetine)	Imipramine (off-label) Amitriptyline (off-label)	Often first-line agents, amitriptyline has shown proven efficacy in controlled studies, with early symptomatic relief and efficacy related to plasma drug levels.
Anticonvulsants	Pfizer's Neurontin (gabapentin) Pfizer's Lyrica (pregabalin)	Carbamazepine Johnson & Johnson's Topamax (topiramate) GlaxoSmithKline's Lamictal (lamotrigine)	Mechanism of action of gabapentin and pregabalin not understood. Studies of all these agents have shown benefit. Adverse events common with carbamazepine.
Antiarrythmics	Mexilitine	N/A	Short-term use only
Pain medications	Opioids	Tramadol	Tramadol's efficacy has been shown in a randomized clinical trial, but side effects include nausea, somnolence, and constipation.
Diabetic retinopathy			
Anti-hyperglycemics	Various	---	Glycemic control prevents progression as well as incident retinopathy but does not induce regression and may cause rapid progression of existing retinopathy if initiated suddenly
Blood pressure control	ACE inhibitors: captopril ARB inhibitors: losartan, irbesartan	Lisonopril, perindopril Various others	Tightening blood pressure control reduces risk of : • worsening diabetic retinopathy by 34% • worsening of visual acuity by 47%
Photocoagulation	---	---	Vitrectomy should be reserved for the end-stage eye
Diabetic nephropathy			
Anti-hyperglycemics	Various	---	Glycemic control can prevent diabetic nephropathy
Blood pressure control	ACE inhibitors ARB inhibitors Beta blockers	Various	ACE: 50% reduction in risk of death, dialysis, and transplantation ARB: Reduction in risk of ESRD, in doubling of serum creatinine concentration

Dr. Katherine Tuttle of the Providence Medical Center and the Heart Institute of Spokane WA, called the results "very encouraging…The significant improvement of albuminuria with ruboxistaurin suggests the drug may be helpful in further slowing the progression of kidney disease."

As part of the study protocol, investigators conducted a comprehensive battery of lab tests and ECG tests, and they found no difference by group. Dr. Tuttle said no indication of any QT prolongation problem has been seen with Arxxant, "We are continuing to monitor the people very carefully, but not because of any (QT) signal in Phase I…We didn't see any signal of any particular concern, but we always have to be cautious. At least at the present time, it appears to be safe."

The hope is that Arxxant will prove to be a useful add-on drug that could be given to patients already on best medical therapy, not a substitute for current therapies. At least initially, use would likely be in patients with clearly established kidney disease, not as a preventive and not in advance disease.

Diabetic nephropathy is only one of three indications that Lilly is pursuing for this product. Lilly is expected to file Arxxant for diabetic neuropathy in the second half of 2005, and Phase III trials in diabetic retinopathy are ongoing. What's next for Arxxant in diabetic nephropathy? Dr. Tuttle hopes that Lilly will fund further studies, "We would like to do a large outcomes study based on this, but whether or not we do it will depend on whether Lilly goes forward with support. At this point, the investigators would like to do a trial, and we are waiting to hear if that is going to be approved (by Lilly)."

Weight Loss Drugs

Sanofi-Aventis's Acomplia (rimonabant) in the RIO-Diabetes trial

Sanofi racked up another win with Acomplia, this time in diabetics in the RIO-Diabetes trial. Sanofi submitted Acomplia to the FDA for both smoking cessation and weight loss in April, and that started the PDUFA clock ticking. The FDA has not yet accepted the filing, so the company does not yet know if it has fast-track status.

RIO-Diabetes tested two doses of Acomplia in 1,045 Type 2 diabetics who had been on metformin or a sulfonylurea for ≥6 months. All patients were on a hypocaloric diet and got exercise advice. Patients who planned to quit smoking were excluded from this trial. On an intent-to-treat basis at one year, there was little difference between 5 mg and placebo,

making it clear that the dose in this patient population is likely to be 20 mg. The average age of onset of diabetes in the U.S. is age 54-55, and the average age of patients in RIO-Diabetes was 56. There are no data on Acomplia in older patients (>age 70) or in adolescents.

The principal investigator said Acomplia is being proposed for chronic use – because diabetes is a chronic disease. He called it a life-time drug.

The key findings in RIO-Diabetes were:

1. **Weight loss.** Patients lost significantly more weight with Acomplia (11.7 pounds) than with placebo (3.1 pounds), meeting the primary endpoint.
2. **Glycemic control.** Acomplia lowered HbA_{1c} 0.6%, with less than half of this due to weight loss, and more than half the Acomplia patients reached the HbA_{1c} target <7%.
3. **Lipids.** Acomplia raised HDL, lowered triglycerides, and reduced the incidence of metabolic syndrome.
4. **Side effects.** The most common side effects were nausea and vomiting, but the incidence was low. Anxiety and depressed mood disorders are rare but continue to attract attention.

1-Year RIO-Diabetes Safety Results

Measurement	Placebo n=231	Acomplia 5 mg QD n=229	Acomplia 20 mg QD n=232
Any adverse event	79.3%	81.8%	85.9%
Any serious adverse event	4.3%	7.5%	8.0%
Discontinuations for adverse events	5.5%	7.8%	15.0%
Discontinuations due to nausea/vomiting	0.3%	N/A	1.5%
Discontinuations due to anxiety and depressed mood disorders	0.9%	N/A	3.3%
Systolic blood pressure change	Up 1.6 mmHg	Down 0.4 mmHg	Down 0.8 mmHg
Diastolic blood pressure change	N/A	N/A	N/A
Nausea	5.7%	6.1%	12.1%
Dizziness	4.9%	3.1%	9.1%
Diarrhea	6.6%	6.1%	7.4%
Arthalgia	8.0%	9.8%	8.8%
Vomiting	2.3%	3.9%	5.9%
Fatigue	3.7%	5.3%	5.3%
Hypoglycemia	1.7%	1.4%	5.3%
Anxiety	2.6%	1.1%	5.0%
Hospital anxiety and depression (HAD) score	N/A	N/A	3

1-Year RIO-Diabetes Efficacy Results

Measurement	Placebo n=231	Acomplia 5 mg QD n=229	Acomplia 20 mg QD n=232
Primary endpoint #1: Weight loss by ITT with LOCF	3.1 pounds (1.4 kg)	5.1 pounds (2.3 kg)	11.7 pounds (5.3 kg)
Absolute weight loss in completers (per protocol)	N/A	N/A	N/A
Patients losing ≥5% body weight by ITT	14.5%	21.7%	49.4%
Completers losing ≥5% of body weight	19.5%	27.2%	55.9%
Patients losing ≥10% body weight by ITT	2.0%	6.2%	16.4%
Completers losing ≥10% of body weight	3.0%	8.2%	N/A
Secondary endpoint #1: Change in waist circumference by ITT with LOCF	Down 0.72 inches	Down 1.1 inches	Down 2.05 inches
Completers change in waist circumference	N/A	N/A	N/A
Secondary endpoint #2: Patients with metabolic syndrome at one year	73%	N/A	64%
Decrease in metabolic syndrome at one year	Down 7.6%	N/A	Down 18.9%
Secondary endpoint #3: Change in HDL by ITT with LOCF	Up 2.7 mg/dL	Up 4 mg/dL	Up 6.6 mg/dL
Completers change in HDL	N/A	N/A	N/A
Secondary endpoint #4: Change in triglycerides (TGL) by ITT with LOCF	Up 3 mg/dL	N/A	Down 31.6 mg/dL
Completers change in TGL	N/A	N/A	N/A
Secondary endpoint #5: Change in HbA_{1c}	Up 0.1%	Down 0.1%	Down 0.6%
Patients reaching HbA_{1c} target <7%	26.8%	N/A	52.7%
Patients reaching HbA_{1c} target <6.5%	20.8%	N/A	42.9%

PYY

Amylin, Amgen, and NasTech each have PYY agents in development to treat obesity, but the outlook for all is murky – and not just for patent reasons. Two years ago, PYY, especially PYY-3-36 looked promising in animal studies, decreasing food (caloric) intake in rates by 33%-36% over 24 hours. However, humans may not respond the same way, and nausea is a concern.

An initial animal study and a later small human study by Dr. Steven Bloom of the Royal College/Hammersmith Hospital in the U.K. found a weight loss benefit to PYY, and then another study couldn't replicate the results. Since then, experts have lined up on both sides, with some claiming the weight loss

benefit can be replicated and others insisting no weight loss benefit can be proven. Published papers support both views.

At ADA 2005, experts debated this issue.

Protagonist: Dr. Bloom. Among the points he made were:

1. **PYY inhibits food intake.** "Increasing doses in rodents did, and it was quite lasting. We've looked at different models and demonstrated repetitively that it does that."
2. **Repeatability.** Other researchers have duplicated Dr. Bloom's work, but this is not yet in print. "At higher doses, it definitely does inhibit food intake, and it does so for quite a time. So, I don't think there is any doubt that other groups can demonstrate it, so I think it is probably true, but it might depend on the circumstance."
3. **PYY inhibits food intake in humans.** A study in 12 humans (6 obese and 6 lean) found at 24 hours that food intake was reduced the same in both groups and the hunger score decreased in both groups. "The problem with the data is that obese people are on a chronically different diet from lean people…and depending on the advice given to obese people, you may or may not see the difference on a saline-only day…The take-home message is that obese people don't necessarily have a lower PYY but that they don't have raised levels of PYY…Plasma PYY levels are lower in obese humans following fixed calorie meals."

Antagonist: Dr. Matthias Tschoep of the University of Cincinnati. Among the points he made were:

- **New data.** Very recent data on PYY knock-out mice from Regeneron found no effect on feeding or on body weight.
- **Mechanism of action.** There is no clarity on the mechanism of action.
- **Lack of sustained effect.**

The moderator's conclusions

This is still an unsettled issue. He said, "There are several prominent names on both sides. If this molecule is so finicky that you can see an effect only in re-fed animals and not fed animals or stress affects it, then there is a question whether this will be effective." He called for more human studies.

STATINS

The results of the TNT (Treating to New Targets) trial were presented at the American College of Cardiology meeting in March 2005. The diabetes substudy from that trial was presented at ADA. This was a post-hoc analysis of 1,500 patients with heart disease, diabetes, and LDL <130 mg/dL.

TNT was a five-year, 10,001-patient, double-blind, parallel group study comparing 10 mg and 80 mg Lipitor. Once patients with a starting LDL <130 mg/dL reached an LDL of ~100 mg/dL on 10 mg Lipitor, they were randomized to either 10 mg or 80 mg Lipitor. Patients were followed an average of 4.9 years. The 10 mg Lipitor patients maintained their cholesterol at an average of 101 mg/dL, and the 80 mg Lipitor patients achieved and maintained an average LDL of 77 mg/dL. Compared to low dose Lipitor, high dose Lipitor reduced total major cardiovascular events (the primary endpoint) by 22%, strokes by 25%, and MIs by 22%.

MTOR

Researchers are exploring the effect of mTOR inhibitors (e.g., Wyeth's rapamycin) in diabetes.

- The mTOR pathway regulates growth-related processes.
- mTOR is part of a multiprotein complex, which is referred to as the raptor complex (TOR-1).
- Many of the proteins regulating the mTOR pathway seem to be involved in diseases such as the cell size diseases.
- mTOR has an important role in the AKT/PTEN pathway. The PTEN pathway has a connection to the TOR pathway, but it has resisted the downstream/upstream pathway, instead being sort of inter-digitated with TOR.

A speaker noted that mTOR is involved in both the control of cell growth and proliferation, which has implication for organismal growth. A new rapamycin analog might be able to be developed that would have utility in combating insulin resistance in diabetes. ♦