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By Lynne Peterson

SUMMARY

Amylin's Symlin and its GLP-1, exenatide, are both likely to gain FDA approval. Usage will depend on how much of the weight loss is due to nausea, which is significant but declines over time. The outlook for a long-acting version, LAR, and an anti-obesity drug, PYY_{3-36} is still questionable. ♦ DPP-4 inhibitors look promising, but there are safety concerns. Novartis's LAF-237 lowers HbA1c but not much, and it did not cause weight loss. ♦ Inhaled insulin can't be used by active smokers and causes antibodies, but the antibodies do not appear to have clinical significance. ♦ Several dual PPARs have failed, and most of the others appear to be me-too drugs, except perhaps GlaxoSmith-Kline's PPARpan. ♦ Early data indicate Johnson & Johnson's Topamax and Avanir's Neurodex may be helpful in diabetic neuropathy and GlaxoSmithKline's Avandia may prevent restenosis.

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A plethora of new products are on the near horizon in diabetes. A few are exciting, but questions remain about many of them. Among the topics covered in this report: GLP-1 Inhibitors, DPP-4s (page 5), an insulin adjunct (page 5), new insulins (page 7), PPARs (page 10), anti-obesity agents (page 12), and diabetic neuropathy (page 13).

GLP-1 Inhibitors

The problems with GLP-1 inhibitors are:

- Half life.
- Injections.
- Side effects. These are gastrointestinal, cardiovascular, and neurologic. A speaker said, "There have been some reports of cardiovascular concerns." Another speaker warned that GLP-1 antagonists are actually potent anxiolytics in rats, "There is a dark side to the GLP-1 story. They could produce visceral illness (nausea) and activate stress, so there is some concern in recruiting the GLP-1 system…Exendin worries me because it really gets into the central nervous system…What happens when a benzodiazepine is combined with exenatide?"

The University of Cincinnati has filed a use patent for GLP-1 as an anxiolytic.

AMYLIN/LILLY'S Exenatide (synthetic exendin-4, AC-2993, Exendin)

Exenatide, a peptide isolated from the salivary secretions of the Gila monster, is administered BID subcutaneously, has shown "a hint that it has some effect in addition to promoting insulin secretion." Sources were not particularly enthusiastic about exenatide. ADA President Dr. Eugene Barrett said, "At least it is a different approach." An Ohio endocrinologist said, "I think it has a shot, but I can't say it is a sure thing." "A New Mexico endocrinologist said, "Exendin is a little more promising than in (Amylin, pramlintide acetate). I've seen some data, and it looks okay, but I'm not sure it will be a big drug."

Sources raised serious questions about whether patients will use this drug if and when it is approved, but they admitted that if the randomized Phase III trial confirms the open label Phase III data, it probably is approvable. Amylin officials said the company did a Special Protocol Assessment with the FDA, which increases the chance of approval if the pivotal Phase III data is positive. Amylin expects to file the NDA for exenatide in 2004. By the time of the filing, Amylin expects to have more than 200 patients who have been on the drug more than a year and "many" more than two years.

An expert said, "Exenatide probably will have an easier time at the FDA than the DPP-4s…but I think the FDA will want at least two-year studies. FDA Commissioner Mark McClellan said he wanted fast throughput for diabetes drugs, but I think the agency will still wait for long-term data for an injectable agent."

AMIGO Phase III Trials of Exenatide

Trial	Size	In combination with
AMIGO-1	400 patients	maximum metformin therapy
AMIGO-2	400 patients	maximum sulfonylurea therapy
AMIGO-3	800 patients	maximum metformin and maximum sulfonylurea therapy

Data from AMIGO-1 will be presented at the International Diabetes Federation (www.idf.org) meeting August 25-26, 2003, in Paris, but a press release may be issued in June 2003. Results of the other two trials are expected by press release in November 2003.

These eight-month AMIGO trials are studying patients with HbA1c of 7.5%-11%, and company officials expect the baseline average to be 8%-9%. The studies have three arms: (1) placebo, (2) 5 µg for 8 months, or (3) 10 µg BID after the titration period. For 5 µg, the trial is powered for an alpha of 0.05 and a beta of 90, for a difference of 0.4 in HbA1c. For 10 µg, the trial is powered for an alpha of 0.05 and a beta of 90, for a difference of 0.6 in HbA1c. There is a 30-day wash-out period before patients begin the active part of this trial, which Amylin officials expect will help eliminate dropouts -- patients who will be non-compliant or who find the injections objectionable. An Amylin official said that the dropout rate in injectable trials is usually about 30% and "we are less than that" in AMIGO.

As part of the toxicity studies, monkeys were followed for nine months, and the company just finished a carcinogenicity study in mice for over two years. An official said the mouse study was the longest study the company has, but he said he didn't know the results.

A randomized, placebo-controlled, 28-day Phase II trial of exenatide was conducted at a dose of 0.08 µg/kg. An official said, "At that time we didn't know enough of the PK or PD to be able to do a fixed dose. We studied patients failing metformin, a sulfonylurea or the combination of both. There was both a BID and a TID regimen. At the end of the trial, HbA1c declined 0.95% with exenatide, compared to 0.26 with placebo. If you affect a change in plasma glucose, it takes three months to see a change on HbA1c, so 28 days was not enough to see the full change." This trial did not shown any weight loss benefit to exenatide.

Based on these results, Amylin began a open-label, six-month, uncontrolled, single arm Phase III study of adding exenatide in 155 patients who were failing on oral agents. Results of that Phase III study were presented at ADA. An Amylin official said the Phase III trial provides "a view of perhaps what is happening in the AMIGO trials."

The first four weeks of the open label trial were an "initiation period," with a 5 µg BID dose (10 µg/day), followed by a "maintenance period" with a dose of 10 µg BID (20 µg/day). So far, there is 20-week data on all these patients, 77 patients (on an intent-to-treat basis) who completed 24 weeks, and 63 of these are evaluable. Of the evaluable patients: 43% were male with an average HbA1c of 8.6. The company reported that HbA1c continued to drop for 12 weeks and then leveled off, with ~50% of subjects achieving the HbA1c target of ≤7.0. Fasting plasma glucose feel from an average of 218 to roughly 174-180 at week 8 and was stable thereafter. There was no change in LDL, total cholesterol or triglycerides from baseline to Week 24. Patients also lost an average of about 5 pounds over five months on exenatide, and Amylin officials insisted this was independent of the nausea. More than half the patients developed antibodies, but these were not associated with neutralization of the glycemic effect. An expert said, "The data looks good, but it needs to be confirmed in the AMIGO trials."

Six-Month Data from Exenatide Open Label Phase III Trial

Measurement	All patients n=677	Exenatide + metformin	Exenatide + sulfonylurea	Exenatide + metformin + sulfonylurea
Nausea	27%	46%	33%	21%
Vomiting	13%	0	22%	13%
Hypoglycemia	12%	0	17%	13%
Subjects achieving HbA1c at week 20	52% (n=105)	N/A	N/A	N/A
Subjects achieving HbA1c at week 24	45% (n=63)	N/A	N/A	N/A
Change in body weight	-2.4 kg at week 20 (n=63)	N/A	N/A	N/A

On the positive side, exenatide:

- Effectively lowers HbA1c to ~7.2.
- Slows gastric emptying.
- Is a fixed dose.
- Appears to cause less hypoglycemia than insulin.
- Lowers weight by about a pound a month (5 pounds over five months). An Amylin official said, "The weight loss is absolutely not related to the GI side effects. The nausea

was transient. More than 70 patients had no nausea, and they lost weight the same way. The nausea was over mostly in the first month or two, and there was weight loss past that point. And this is consistent with the animal models." An Amylin official said, "Jenny Craig and others say that we might be able to double the weight loss if patients were counseled on diet, exercise, etc., but I haven't confirmed that yet." Another official said the weight loss will be a huge factor in helping sales of this agent, but he admitted the company will have to be careful about making claims about weight loss. He emphasized that the company is not positioning exenatide as a weight loss agent. However, Amylin has another agent, PYY-3-36 in development that may be an obesity agent.

On the negative side, exenatide:

- Is dosed BID (once before breakfast and once before dinner).
- Is injected subcutaneously. The drug is aimed at Type 2 patients who have failed oral therapies, but who want to avoid going on insulin, generally because of the need for injections. Thus, most experts said they see no advantage to this drug, but Amylin officials insisted the weight loss and lipid profile would make this appealing to doctors and, thus, to patients.
- Causes nausea and vomiting in a significant number of patients. The nausea declined with time but persisted throughout the trial. Four patients (8%) withdrew due to nausea in the first eight weeks, but none due to vomiting. The package insert for Pfizer's sulfonylurea Glucotrol (glipizide) lists a nausea/vomiting rate of <3%, and package insert for Bristol-Myers Squibb's Glucophage (metformin) reports a 25.5% nausea rate, though sources said the rate generally is lower because doctors now titrate the dose. With both drugs, the nausea diminishes with time, and in the exenatide trial patients were all stable on metformin and/or sulfonylurea for six months before entry into the trial. The addition of exenatide could have reactivated the side effects of metformin or sulfonylurea, but most of the nausea is due to exenatide, not the other drugs, an Amylin official confirmed. An expert said, "The nausea would be a killer if it occurs at these rates in the AMIGO trials."

Incidence of Nausea

Time period	Nausea	Experiencing first-time nausea
First 4 weeks	18%	14 patients
Weeks 5-8	9%	4 patients
Weeks 9-12	6%	1 patient
Weeks 13-16	3%	1 patient
Weeks 17-20	N/A	1 patient

- Generates antibodies in about 52% of patients at week 20, and even higher (>65%) at some points earlier in the trial. However, the antibodies have not been associated with any negative effects on glycemic control. One Amylin official said, "The antibodies are like insulin antibodies – they don't inhibit anything and they are not neutralizing." Another Amylin official said, "How do we report the incidence to the FDA? We will have to talk to the FDA about that…What is the threshold at which you say a person is antibody positive? The FDA doesn't know what to do about that. They don't want to report 1/25 as positive. Maybe we will report it as far less than we said here, but that's because analytic techniques have too many false positives."

	Antibody Titers				
	1/3125	1/125	1/25	1/5	Total positive titers
Treatment emergent	2%	6%	35%	10%	52%

Some unanswered questions about exenatide:

1. ***Will the effect on HbA1c be maintained beyond 24 weeks?*** Experts dismissed a suggestion that there is an uptick in the last month, insisting that the effect appears to be maintained from week 12 through week 24.
2. ***What happens when the drug is stopped?*** Amylin plans to continue this trial until the regulatory submission, so that information is not available.
3. ***Will patients develop tolerance or desensitization to exenatide?*** An Amylin researcher said that the only study indicating that GLP-1 leads to desensitization was a cell line study, not human data. Another researcher said, "I can't see why tolerance would develop. There is no biological hypotheses to suggest that, and we have 50-week data and haven't seen it."
4. ***What percent of patients in the open label trial required a dose reduction of other medications?*** That data has not been available, but it is expected to be available for the AMIGO trials. That means there may be some exenatide monotherapy data from the AMIGO trials.

Asked how exenatide would be used clinically if it is approved, an endocrinologist said, "I don't think we want to compare it to the TZDs (Avandia and Actos)…To me, the competition is insulin or increasing the insulin dose rather than these drugs (and metformin and sulfonylurea)…I think when doctors try it and see the weight loss, this drug will catch on." Another clinician said, "I would be appealing if there is no weight gain or actually is a weight loss. Any weight loss is worth its weight in gold…It is crazy for exenatide to go head-to-head with insulin, so it has to be better than insulin in some way – e.g., weight loss. And the weight loss has to be a spectacular added benefit to be approved and used."

AMYLIN'S LAR

Amylin researchers are very excited about this longer-acting version of exenatide, which is also given subcutaneously, but there was no new data at this ADA meeting.

Researchers said LAR could compete with oral anti-diabetic medications, and they pointed out that in rodents it promotes beta cell differentiation, indicating that it might preserve beta cell function. An expert said, "I doubt it is beta cell protective. You really can't measure that…Just lowering ambient glucose levels helps preserve beta cell function, but we don't know for how long. It is beta cell function failure that transitions patients to insulin."

ADA President Dr. Barrett also is more optimistic about this, saying, "It may be the differentiating factor in promoting beta cells. If that bears out, it would be reasonably exciting. The issue is that it is a peptide. The long acting version could be injected once a week or so, which would be advantageous because initial actions of the drug are to mimic GLP-1, but that has a vanishingly short half-life. The GLP-1 peptide has to be given by injection (which lasts 20 minutes), so it would have to be given 4-5 times a day, giving it no advantage over insulin. But if LAR can be given once a week, allows augmentation of insulin secretion and promotes beta cell growth, it might be taken on top of insulin or before a patient needs to start on insulin. That would be exciting."

Among the questions that have been raised about exenatide and LAR include:

- **LAR trial status**. An Amylin official confirmed a Phase II trial already is underway. He said this is a testing two sub-therapeutic doses and described it as a PK study.
- **Dosing.** BID dosing is a drawback for exenatide, but researchers downplayed the significance. A source also said it is not clear yet how often LAR will need to be given, and that may not be determined until the Phase III trials, which will test different dosing strategies, including weekly and monthly administration.
- **Antibodies.** As with exenatide, researchers expect antibodies to form but do not believe they will be neutralizing.
- **Tolerance**. Researchers said there has been no indication so far (out to 26 or 50 weeks) of any tolerance to either exenatide or LAR. One commented, "There is no biological hypothesis to suggest that, and we haven't seen it."
- **Potential cardiovascular complications.** This problem was seen in early animal studies, but no human signal has been seen yet.
- **Hypoglycemia risk.** There does not appear to be a significant problem with this but it is being carefully monitored.
- **Nausea**. A source suggested that the LAR could have worse nausea than exenatide, but an Amylin official said patients would be started on exenatide firs to tolerize them before LAR administration, which he believes will allow the nausea to be minimized.
- **Drop outs.**
- **Weight loss.** No data is available yet, but company officials are hopeful that it will be at least as much as with exenatide.

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

The company's GLP-1 clinical program was stopped due to "formulation issues," but it resumed in February 2003, and a multi-dose trial was due to start in March 2003. In a Phase I trial of healthy volunteers, a single dose had, on average, a 10-12 day half-life, demonstrated good tolerability, and produced "encouraging insulin and glucose responses with the higher doses." ConjuChem currently has four Phase I/II trials ongoing in the U.S. and Europe: (a) QD injection study, (b) rechallenge immunogenicity study of subcutaneous DAC:GLP-1, (c) single dose IV administration, and (d) multidose subcutaneous administration. All four of these trials will be completed in September 2003, and the results are expected to be available shortly after that. The company will then begin its Phase II program, starting with a dose optimization study.

HUMAN GENOME SCIENCE'S Albugon

Albugon has a human half life of 5-8 days, which means it may be able to be dosed weekly. In rodents, it increased glucose tolerance and beta cell mass and decreased gastric emptying and weight gain. However, an expert said, "I doubt beta cell mass is doubled, as the HGSI poster claims. It's too hard to measure beta cell mass."

NOVO NORDISK'S Liraglutide (NN-2211)

Novo's GLP-1 is in late Phase II development as monotherapy for early Type 2 diabetes and combination therapy for later disease. It compares to Amylin's exenatide in several key ways:

- There is no tachyphylaxis with either this or exenatide.
- The side effects with liraglutide are typical of a GLP-1 and similar to exenatide except:
  - The nausea with liraglutide reportedly resolves in less than one week. An official said, "It is transient, linked to dosage, and looks like an onset thing."
  - Liraglutide is associated with some diarrhea, and Amylin officials claim there was no diarrhea with exenatide.
- It is human-based.
- It is and administered subcutaneously but only once-a-day.

- No antibodies have been seen so far with liraglutide, but Novo official admitted this is still a long-term issue that needs to be monitored.

ZEALAND PHARMACEUTICALS'S ZP-10

No details were available on this GLP-1 except that to confirm that it is in development.

DPP-4 INHIBITORS

DPP-4 is a peptidase that is expressed in many tissues and acts on a number of substrates, so the question is whether it will cause any unexpected adverse events. A speaker wondered, "Are we going too fast too quickly with DPP-4 or GLP-1…DPP-4 could have an impact on the immune system."

DPP-4s are supposed to:

- Function as incretins
- Stimulate insulin secretion
- Preserve beta-cell function
- Inhibit glucagon secretion
- Delay gastric emptying
- Induce satiety

NOVARTIS'S LAF-237

This oral agent appears to be the DPP-4 furthest along in development. Interestingly, a source said a double-knock-out mouse – with DPP-4 and GLP-1 knocked out – still showed beneficial effects with LAF-237, suggesting that LAF-237 works on another enzyme besides DPP-4.

A small, double-blind, placebo-controlled, fixed-dose trial found LAF-237 reduces fasting, prandial and 24-hour glucose in dietary-controlled Type 2 diabetics. Patients were given 100 mg (or placebo) 30 minutes before breakfast daily for four weeks. A researcher said:

- There was no statistically significant change in body weight.
- LAF-237 reduces DPP-4 activity by approximately 70% after 12 hours.
- HbA1c was reduced by approximately 0.4 after four weeks, but he said this was not reliable due to the small size and short length of the trial.

Four-Week Results with LAF-237 *

Measurement	LAF-237 n=20	Placebo n=20	p-value
30-minute increase in GLP-1	+ 5.0	+ 1.0	p<.001
AUC glucose at 240 minutes	- 5.0	- 1.0	p<.01
Insulin secretions at 240 minutes	- 0.01	+0.01	Nss
30-minute increase in glucagon (pg/ml)	-12	+1	p<.05
All adverse events	12.9	N/A	N/A
Nasopharyngitis	4	1	Nss
Dizziness	2	3	Nss
Pruritis	2	2	Nss
Headache	3	0	N/A
Myalgia	1	1	Nss
Hypoglycemia	0	0	Nss

* all values estimated from bar chart

Other DPP-4s in development include:

- **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.
- **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-4s, but a researcher expressed concern with the safety of these agents because of their lack of specificity.
- **NOVARTIS'S DPP-728**, a second DPP-4.

AN ADJUNCT TO INSULIN

The problem: At end of three years on metformin, 44% of diabetics have an HbA1c ≤7.0, but by nine years, only 13% had an HbA1c ≤7.0. For patients on sulfonylureas, 50% have an HbA1c ≤7.0 after three years, but only 24% have an HbA1c ≤7.0 after nine years. Among Type 2 diabetics, 40% are on oral monotherapy, 29% on oral combination therapy, and 19% on insulin only. In 1998, 20% of Type 2 diabetics on insulin took one shot a day, 70% took two shots a day, and almost 10% took three or more shots a day.

With intensive insulin treatment, the incidence of hypoglycemia increases and patients tend to gain weight. In the DCCT study, 25% of diabetics on insulin gained a mean of 40 pounds and another 25% gained 22 pounds. This weight gain also worsens lipid profiles in Type 1 patients – triglycerides go up, LDL increases, and HDL decreases – and both diastolic and systolic blood pressure tend to go up. Metformin, sulfonylureas and TZDs [GlaxoSmithKline's Avandia (rosiglitazone) and Lilly's Actos (pioglitazone)] lower HbA1c but also cause weight gain (about six pounds over six months).

AMYLIN'S SYMLIN (pramlintide)

Amylin is seeking approval to market Symlin as an adjunctive therapy to insulin for the treatment of people with Type 1 or Type 2 diabetes who use insulin. Symlin is a soluble analog of human amylin and is administered subcutaneously at mealtimes (preprandial) in addition to insulin, not in lieu of it, though the insulin dosing may need to be adjusted. A researcher said, "Patients probably will require reductions in short-acting insulin doses, especially if the pre-meal plasma glucose is near normal….A reduction in the pre-meal insulin dose should be considered or recommended when pramlintide is added. This data -- and other data -- clearly indicate that reductions in pre-meal insulin dose will be indicated in many cases."

Amylin received an approvable letter for Symlin from the FDA in October 2001, but the agency had several questions. On June 16, 2003, Amylin submitted an NDA amendment answering those questions, and company officials said they believe all the of the agency's concerns are adequately addressed with the additional data from a dose-titration study in Type 1 diabetes plus four smaller pharmacology studies. They said the nausea and severe hypoglycemia that occur frequently during the initial four weeks of therapy are reduced with up titration of the Symlin dose and down titration of other agents.

The company also believes the new data answers these questions posed by the FDA:

1. Will the effects of Symlin still be evident in patients under better glycemic control at the time they start Symlin?
2. Can Symlin be safely initiated in subjects pursuing recommended glycemic targets?
3. Do the effects of Symlin on postprandial glucose control that is observed acutely persist during chronic therapy?

A randomized, single-blind, placebo-controlled, five-way cross-over study of diabetics using Lispro found that Symlin, given at mealtimes and the time of Lispro administration, appears to produce a robust reduction in postprandial glucose. A researcher said, "The addition of pramlintide to the rapid-acting insulin Lispro reduced post-prandial glucose excursions in both Type 1 and Type 2 diabetics. Optimal administration appeared to be at or just prior to a meal."

The drug was generally well-tolerated, with nausea the most common side effect. The nausea rate with Symlin was 25% in Type 2 patients, 30% in Type 1 patients and 5% with placebo. An Amylin official said this rate of nausea was similar to that seen in larger studies, and he described it as "transient," saying it dissipated in two to four weeks and the vast majority (80%-85%) are mild-to-moderate, which means it did not interrupt their daily activities."

There were no severe hypoglycemic episodes, though some mild to moderate hypoglycemic events occurred when fasting plasma glucose concentrations were <126 mg/dL. There also was minimal weight loss -- about 2 kg/year (4.4 pounds/year) -- which caused a researcher to quip, "This is not a weight loss drug." Another researcher said, "Symlin has an effect on food intake, independent of the nausea. We are dong a study to try to find the mechanism for the weight loss."

Symlin Study Single-Blind Study

Measurement	AUC 0-2 hours	AUC 0-4 hours	Insulin dose
Type 1 Diabetics (n=21)			
Placebo	---	---	6.3
Symlin 15 minutes before meal	>100%	36%	6.2
Symlin at time of meal	>100%	75%	6.1
Symlin 15 minutes after meal	89%	54%	6.1
Symlin 30 minutes after meal	57%	39%	6.0
Type 2 Diabetics (n=19)			
Placebo	---	---	17.9
Symlin 15 minutes before meal	77%	42%	17.7
Symlin at time of meal	>100%	81%	18.1
Symlin 15 minutes after meal	89%	73%	17.5
Symlin 30 minutes after meal	55%	59%	17.9
Safety			
Nausea in Type 1 diabetics	33%	5%	N/A
Nausea in Type 2 diabetics	25%	5%	N/A

Another trial – a randomized, triple-blind, 29-week safety trial at 29 U.S. centers – compared mealtime Symlin or placebo given three to four times a day in patients on an intensive insulin regimen (pump or multiple daily injections). After a four week initiation period, the Symlin dose was titrated weekly from 15 µg to 30 µg, and if they tolerated that, the dose was titrated up to 45 µg and then 60 µg. More than 75% of patients achieved the 60 µg dose level, and nausea rate in these patients was twice the level of placebo. In the patients who remained at the 30 µg dose, 95% had nausea, but an official said this was because they were held at that dose because they experienced nausea, adding, "Of those who later had hypotension, more than 65% had nausea first, and about 15% of hypotension events occurred on days when the subject experienced nausea, so nausea is a flag that identifies patients who are at great risk for severe hypotension. That is a useful tool for writing label language. If a subjects experiences nausea during dose titration, that person deserves more attention, more glucose monitoring and perhaps further reductions in insulin – and maybe counseling about eating."

During the initiation phase, hypoglycemic events were slightly higher than the expected 2.8 per year but an official said they were still "in the realm of what is expected in insulin patients…We achieved the safety goals…We mitigated the nausea and hypoglycemia. So, in terms of regulatory requirements, we can stop here, and go home and file the NDA." And that is exactly what Amylin did.

Symlin Safety Study

Side Effect	Placebo	Symlin
Nausea	36.1%	62.8% *
Sinusitis	8.8%	14.9%
Increased sweating	12.2%	14.2%
Vomiting	6.1%	13.5%
Withdrawal due to nausea	0.7%	1.4%
Weight change	Up ~3 pounds	Down ~3 pounds

*70% of these had mild nausea, and 20% of these had moderate nausea.

Patient diaries in this trial also provided some additional information: With Symlin:

- Patients used 13% less total daily insulin.
- Patients lost weight instead of gaining wait. An official said, "The total is a difference of 6-7 pounds in body weight, which is clearly significant. This is the difference of one dress size in a female." An endocrinologist said, "If presented with a drug which is going to improve glycemic control and allow them to lose weight or not gain weight, a number of patients will be willing to do this…Without weight loss, I don't think Symlin would do anything, but with weight loss, that will be a powerful message."

Doctors and nurses were questioned about how they – and patients – will use Symlin if it is approved, and the responses were mixed.

Pro: A Texas doctor said, "I used it in a trial. It works very well – if someone will take the injection. I think about 40% of my Type 1 diabetics would use it – if insurance covered it -- but none of the Type 2s would use it." An Ohio doctor said, "I used to be a total skeptic, but I am starting to believe some of the data now. I don't think this will be for all diabetics, but I think there will be a niche of people without good control who will use it."

Con: A New England doctor said, "I'm not enthusiastic about Symlin." A Massachusetts doctor said, "The data is okay, and there is weight loss, but I'm not sure if it does anything clinically meaningful." A nurse said, "I don't know if patients will be standing in line for another injection! The nausea also looks like it will be an issue." Another source said, "This is a drug with a great lose/lose potential." A Maryland doctor said, "I'm fairly enthusiastic about this because there is weight loss, rather than the weight gain you see with insulin."

INSULIN

Long acting insulin is not causing a slowdown in use of short-acting insulin, doctors insisted. One commented, "There is definitely not a decrease in SA insulin because of LA insulin." A California doctor said, "Mechanistically and clinically, long-acting and short-acting insulin are very different. There is an increase in use of short-acting insulin, not a decrease." A Novo Nordisk official said, "Short-acting insulin sales are fast growing. They haven't been hurt by long-acting insulin, but long-acting insulin has hurt sales of NPH insulin."

NOVO NORDISK'S detimir, a long-acting insulin, is BID, while Lantus is supposed to be once-a-day, but a source said many times patients need Lantus BID. Lantus changes two amino acids in human insulin to form crystals and create long-acting insulin. Detimir adds a fatty acid chain to the insulin molecule so it binds to albumin in the body. An official said, "The albumin is a nice buffer reservoir, and the insulin leaks out in a controlled manner."

Critics accused detemir of being "very variable" and "similar to Ultralente" in terms of variability. One said, "It binds to albumin, so there is a large reservoir of insulin floating in the blood. The concern is the potential for a large bolus of insulin to be released at some point. A source wondered, "What unbinds it?" However, Novo officials insisted that this will not occur. They said they have done a lot of detimir testing, looking for any drug-drug interactions (among the usual suspects) and haven't found anything that could unbind it.

Common Types of Insulin

Generic	Brand	Company	Type
Insulin lispro	Humalog	Lilly	Short-acting (rapid)
Insulin aspart	NovoLog	Novo Nordisk	Short-acting (rapid)
Soluble insulin	Humulin-R	Lilly	Short-acting
Soluble insulin	Novolin	Novo Nordisk	Short-acting
Isophane insulin	NPH	Lilly	Intermediate
Insulin Zinc	Lente	Novo Nordisk	Intermediate
Human insulin zinc extended	Ultralente	Lilly	Long-acting
Insulin glargine	Lantus	Aventis	Very long-acting
Detimir	**Not yet FDA approved**	Novo Nordisk	Very long-acting
Insulin lispro protamine +lispro injection	Humalog mix (75/25)	Lilly	Combination short-acting and long-acting

A variety of new delivery methods for insulin are under investigation, including inhalation, oral, buccal, and even an insulin patch. Doctors also are investigating the value of using subcutaneous insulin earlier in the development of diabetes. The 10,000-patient ACCORD (Action to Control Cardiovascular Risk in Diabetes) study will test three approaches to lowering the risk of heart disease and stroke in adults with Type 2 diabetes: controlling blood glucose, blood pressure, and lipid levels. The trial began in February 2003

and runs until June 2009. The principal investigators for ACCORD are Dr. Hertzel Gerstein and Dr. Salim Yusuf, who headed the HOPE trial of ramipril (King's Altace), both of McMasters University in Hamilton, Canada. Experts hope this study will provide new information on when to initiate insulin therapy.

INHALED INSULIN

Safety is really the key issue with this approach, and doctors are waiting for longer-term safety data from Phase III trials. Asked if we will ever see inhaled insulin on the market, an expert said, "There is no major impediment to inhaled insulin…I don't believe pulmonary function is a problem, and antibodies are not a problem…If it formed neutralizing antibodies, that could be an issue, but most of the time non-neutralizing antibodies don't make much clinical difference. The exception is Eprex (Johnson & Johnson, epogen sold in Europe)." However, there was some news on inhaled insulin at ADA, including:

- Antibodies do form, but they do not appear to have any clinical significance.
- Patients cannot smoke ***at all*** when using inhaled insulin, but second-hand smoke does not appear to be a problem.
- Pfizer's Exubera was shown to be superior to GlaxoSmithKline's Avandia (rosiglitazone) in a six-month trial.

Antibodies

A whole session was devoted to this topic, and the basic conclusion was that inhaled insulin does generate antibodies, but there are no negative clinical effects from this. A speaker said, "The insulin antibody response is greater with inhaled insulin than with subcutaneous insulin, it is greater in Type 1 diabetes than Type 2, and the differences are maintained over two years of exposure."

With **Novo Nordisk's AERx** iDMA inhaled insulin (using NPH insulin), the median percent of antibody binding increased to 34% over 12 weeks of therapy in Type 2 patients vs. no change in antibody formation with subcutaneous insulin delivery. A speaker explained, "These were IGG antibodies, non-neutralizing, with no impact on dosage requirements or metabolic control." With **Pfizer/Aventis's Exubera** dry powder inhaled insulin, antibody binding in patients with Type 1 and Type 2 diabetes was 29% compared to 5%-6% with subcutaneous insulin.

Issues regarding inhaled insulin.

- *Is insulin delivery by inhalation more or less immunogenic than subcutaneous delivery?* **More.**
- *How quickly do antibodies form?* **Within six to 12 months.**
- *Do patterns of immunologic responses with inhaled insulin differ from patterns with subcutaneous insulin?* **No.** The patterns of antibody responses are consistent with the subcutaneous insulin experience.
- *Does the presentation of antibodies with inhaled insulin correlate with adverse outcomes?* **No.** Inhaled insulin is not associated with adverse immunology outcomes.
- *Does antibody development affect glycemic control, dose requirements, etc?* **No.**
- *Is there pre-sensitization?* **Probably, in Type 2 patients.** Pre-sensitization can prime a patient for immunogenicity and would greatly diminish patient response to inhaled insulin, at least in naïve Type 2 patients. A speaker said, "Pre-sensitization does, in fact, affect pulmonary response to inhaled insulin…I think the presensitization phenomenon is very real…but that doesn't mean chronic exposure over a very long time might not produce some immune responses…There was a creep up in antibodies in naive patients who only got inhaled (not subcutaneous) insulin."
- *Do antibodies affect lung function (FEV_1)?* **No.** A study found no significant correlation between antibody formation and lung function.
- *Does inhalation of insulin result in more allergic events than subcutaneous insulin?* **No.** Inhaled insulin is not associated with increased adverse events of an allergic nature. Inhaled insulin antibodies are predominantly of the IGG class.
- *Do antibodies increase the risk/incidence of a hypoglycemic event?* **No.** An expert said, "Hypoglycemic events are ***not*** influenced by antibody status in intensively-treated Type 1 patients. There is no relationship between hypoglycemic events or severe hypoglycemia in these patients."

Smoking

An Aventis study found that insulin absorption is increased in smokers, and the time to peak concentration occurs earlier in smokers. An Aventis researcher said, "One week of smoking cessation decreases total pulmonary absorption to almost that of healthy non-smokers, but C_{max} and T_{max} indicate that absorption remains altered. Resumption of smoking reverses the changes immediately. Smokers must refrain from smoking before and during treatment with inhaled insulin…Acute passive smoke doesn't change absorption (rates)."

The trial was a randomized, crossover study of 30 healthy male volunteers – smokers and non-smokers – given 1 mg inhaled insulin or 3 IU of regular subcutaneous insulin. Participants were told to smoke for a week, stop smoking for seven days and then resume smoking for another two or three days. In this trial, smoking cessation reduced the effect, returning insulin absorption closer to normal, but resumption

of smoking completely reverses the beneficial effect of smoking cessation. A speaker said, "Short-term cessation of smoking increases insulin absorption and biovailability to 15%…but the reasons are unclear. Longer cessation of smoking progressively reduces bioavailability to 11% after 3 days and to 9% after one week."

Effect of Smoking on Inhaled Insulin

Measurement	Smoker	Non-Smoker
AUC ratio	0.12	0.8
C_{max}	0.21	0.09
AUC ratio %	122	64
C_{max} ratio	36	61
Relative bioavailability over 6 hours	12%	8%

Exubera vs. Avandia

Measurement	Inhaled insulin (n=75)	Avandia 4 mg BID (n=68)
Baseline HbA1c	9.5	9.4
HbA1c at 6 weeks	-1.5%	<-1.5%
HbA1c at 12 weeks	-2%	<-2%
Primary endpoint: % of patients with HbA1c <8%	82.7% *	58.2%
Secondary endpoint: % of patients with HbA1c <7%	44.0% *	17.9%
FPG	-64 mg/dL †	-56 mg/dL
2-hour PPG at Week 12	-92 †	-92
Hypoglycemic events	0.7%	0.048%
FVC	0.016	0.007
TLC	0.045	0.075
Weight gain	1.8 pounds	0.9 pounds
Total cholesterol	-2.0	+10.5
HDL	+4.0	+3.0
LDL	+4.5	+15.0
Triglycerides	-35.0	No change
Mean antibody binding	6.2%	<3.0%
Antibody binding	>20%	7%
Safety		
Adverse events	131 events	41 events
Total events	68%	32%
Severe events	0	3%
Serious events	0	0
Hypoglycemia	48%	7%
Peripheral edema	1%	9%
Respiratory	13%	2%
Cough	4%	2%
Pharyngitis	4%	0

* p<.05 † nss

Inhaled insulin vs. Avandia

A three-month trial compared Exubera and Avandia (rosiglitazone) in Type 2 diabetics not optimally-controlled on diet and exercise alone. It found that Exubera, given pre-meal, lowers HbA1c faster and further than Avandia. The presenter said the findings held up on both intent-to-treat (ITT) and last-observation-carried-forward (LOCF) analysis. He also noted, "The cough was generally mild, and patients didn't make a big issue of it. Patients felt this was good therapy. Pharyngitis has not shown up in previous studies, but there were only three patients, and my interpretation is that it was a chance association…The hypoglycemia was small, mild and similar to what is seen in other studies with oral agents."

GENEREX'S Oralin (buccal delivery of insulin)

Generex is working on a system that delivers a fine spray of insulin to the oral cavity through the inner mouth mucosa (buccal delivery). The RapidMist device is somewhat similar in size and design to an asthma inhaler. Lilly had a commercialization and development agreement with Generex but ended that in May 2003, but Lilly is still providing the insulin to Generex, which is now talking to other possible partners.

This is a mealtime insulin, not a basal insulin. It is designed for Type 1 and Type 2 insulin patients.

Like inhaled insulin, bioavailability is about 7%-11%. But instead of the rest of the insulin going into the lungs, it is swallowed. "The particle size is too big to pass into the lungs," a Generex official said, adding, "This means we will need seven to 10 times more insulin that subcutaneous delivery, but the cost will only be about 1.5 times subcutaneous insulin when we commercialize it."

Three studies were presented in posters at ADA showing Oralin has a faster onset of action and a comparable T_{max} compared to subcutaneous insulin.

1. A randomized, crossover proof-of-concept study of the efficacy and reproducibility Oralin absorption (10 puffs, no NPH) in 11 Type-1 diabetic patients after a standard meal challenge at breakfast-time on Day 0 and then Day 3 or Day 7. This was compared to subcutaneous insulin. The onset action of Oralin was much faster (T_{max} at 20 minutes vs. 60 minutes for subcutaneous insulin). There was no statically significant difference on any day in absorption, and there was no inter- and intra-subject variability in the Oralin-treated patients.

2. A randomized, crossover, open label, dose-ranging study looked at three different Oralin strengths (75 u, 150 u, 225 u) on three occasions three to seven days apart, in comparison to subcutaneous insulin 0.11 u/kg (7-9 units) under fasting conditions. The onset action of Oralin was much faster and reached T_{max} at 30 minutes vs. 60 minutes with subcutaneous insulin. The absorption of Oralin was found to be linear. As the Oralin dose increased, there was an increase in hypoglycemia and a decrease in C-peptide and glucose levels.
3. A single-center, randomized, two-way crossover study in 10 adults. Oralin showed faster onset of action compared to subcutaneous insulin, with time to T_{max} comparable to that of Lispro.

A 90-day, Phase IIb trial in the U.S., Canada, Europe and Israel is ongoing. So far, about 85 patients have been enrolled, with a goal of 250 patients. This trial is expected to end in late 2003 or early 2004. A Phase III trial of 2,000-4,000 patients is due to start in 2004. It will run a minimum of six months.

Generex expects to have its Phase II meeting with the FDA in February 2004 and will seek a Special Protocol Assessment. An official said, "The FDA is most concerned with reproducibility." So far, 450 patients have been treated.

ALTEA THERAPEUTICS' Insulin Patch

Altea's insulin patch is in Phase I development of an insulin patch for Type 2 diabetes. The patch infuses insulin through the skin via micropores.

EMISPHERE'S Oral Insulin

A 20-patient study of oral insulin found that bedtime administration suppressed overnight fasting insulin secretion, may increase liver sensitivity, and had physiological effects that last more than 8 hours. It was well-tolerated and did not cause hypoglycemia.

PEROXISOME PROLIFERATOR-ACTIVATOR RECEPTORS (PPARS)

Targeting insulin resistance, which is a core abnormality in Type 2 diabetes, led to the introduction of the thiazolidinedione (TZD) class of drugs which act by binding to the peroxisome proliferator-activator receptor (PPAR). The first of these agents, Warner Lambert's Rezulin (troglitazone) was withdrawn because of rare but fatal hepatotoxicity after Avandia and Actos became available. Overall efficacy remains less than ideal and side effects, including fluid retention and anemia limit their use.

Use of PPAR-alpha agonists – fibrates – became more problematic after Bayer's Baycol (cerivastatin) was found to increase the risk of rhabdomyolysis, especially when taken in combination with a fibrate. Fibrates now are contraindicated with all statins. However, fibrates are very good at improving lipid profiles, and Abbott sponsored a symposium at the ADA at which experts claimed the statin interaction does not occur with Abbott's TriCor (fenofibrate), just with Pfizer's Lopid (gemfibrozil).

A variety of other PPAR agonists also are in development. In fact, practically every company has one under investigation. The hope is that the newer dual PPARs will have a role not just in *treating* diabetes but also potentially in *preventing* the disease – and possibly in treating heart disease at the same time. In judging the PPARs, a source said to watch:

- Lipid lowering.
- Effect on glucose.
- Weight changes.
- Peripheral edema, which has called some PPARs.

Among the various PPARs in development are:

- PPAR-gamma agonists.
- Dual PPAR-gamma/alpha agonists with a "balance" between the alpha and gamma aspects.
- Dual PPAR-alpha/gamma agonists with gamma dominant.
- PPAR-delta agonists.
- PPAR-beta agonists.
- PPARpan agonist (PPAR-alpha/gamma/delta agonist).

Measurement	PPAR-α	PPAR-γ
Target disease	Dyslipidemia, atherosclerosis	Type 2 diabetes
Correction of…	Lipid abnormalities	Insulin resistance
Clinical proof-of-concept	Fibrates	Glitazones
Physiological outcome	Lower triglycerides, Raise HDL, Increase fatty acid oxidation	Glycemic control

While there is a lot of work going on with PPARs and dual PPARs, many companies are being very secretive about these projects. The ADA's Dr. Barrett, said, "This is an area where many things would like to distinguish themselves as not me-too, but there is a lot of me-too-ism out there. Even the Avandia and Actos folks are trying to outdo each other, with cardiovascular endpoints, etc. So, far, there have been just little bits of data, nothing huge or compelling and no clinical endpoint data – some intimal media thickness on carotid ultrasounds. And they are being looked at in some cancers. No one is letting on because each is looking for an edge…It is hard to distinguish among them. Each is good, but none is

great. Each has its own issues. People want to play it close to the vest until the 'big announcement'…Lilly, Takeda and Glaxo are doing serious long-term endpoint trials now with their drugs (Avandia, Actos), mostly in Europe. It is hard for a newcomer to really look at clinical endpoints. It takes a long time, and they need a wide spectrum of users…There is no break-through science here (with the new agents in development)…Diabetologists will be more excited when a truly new agent comes along." A cardiologist said, "Are they diabetes drugs or lipid lowering agents? That marketing has to be figured out. Some will be better at one thing, and others better at another. I doubt any will be fabulous at both. And none stand out."

A PPAR researcher disagreed, insisting there really are some potentially valuable new PPARs in development. He said, "Some of these are not me-toos. There are a lot that are me-toos, but that is because someone made a decision they are worth the effort. If there are 10 PPARs under investigation, seven might be me-toos, with a little a different twist. But there are a number that are pretty unique, including a new PPAR-delta activator."

This researcher predicted that most of the me-toos would fail to make it to market, and those that do won't capture much market share. He said, "Most will fall by the wayside because of side effects. They have to be more than me-too to succeed. They won't make it if they are me-too. This isn't a me-too area. The existing PPARs haven't taken the market as some people predicted. They are excellent compounds, but for a variety of reasons I think they've been held at <20% of the oral agent market. They need to make a move, and they will, but it will be a slow uptake…I'm not even sure the FDA will be keen on a me-too; the agency may not stop them, but there will be no hoopla…A new agent must have either fewer side effects or more efficacy, but the company has to prove it. It is harder to market in diabetes than against Viagra (Pfizer, sildenafil, for erectile dysfunction). TZDs have hit a peak, and a new TZD is unlikely to take away Actos' or Avandia's market share unless it is better or a helluva lot cheaper – and that's unlikely because these are expensive drugs to get approved…There is a lot of new stuff, but I'm not sure how potent some of these are. Some me-toos were more potent, but had side effects. If a more potent drug with less or equal side effects were developed, it would be great."

Several dual PPARs have failed due to toxicity problems such as edema, liver enzyme elevations, bladder tumors, anemia, neutropenia, and weight increase. These include:

- **Novo Nordisk/Dr. Reddy's ragaglitazar**. Development was halted due to bladder tumors in rodents. Ragaglitazar was in Phase III trials before the toxicity was discovered.
- **Novo Nordisk** also reportedly returned the rights for the dual PPAR DRF-4158 to Dr. Reddy. This had only been in preclinical development.
- **Pharmacia/Japan Tobacco's reglitazar**, a dual PPAR. This was dropped in October 2002 following completion of Phase II trials, again due to safety concerns.
- **Wyeth's PTP-112**. Development was stopped in June 2002 due to dose-limited side effects and lack of clinical efficacy in Phase II trials.

Among the PPARs currently in development are:

- **Abbott/Sankyo's CS-011/CI-1037**. This has been shown to be 141-fold more potent than rosiglitazone in lowering blood glucose in rats. This agent appears to be highly active at the PPAR-γ but not the PPAR-α, receptor, with an EC_{50} value of 160 nM, compared with 490 nM with rosiglitazone. CS-011 was in Phase I trials in the US, and Phase I trials were planned in Japan. It was reported that CS-011 does not penetrate hepatocytes.
- **AstraZeneca's Galida** (tesaglitazar, AZ-242, a dual PPAR). Sources did not think this was anything more than a me-too drug. Three studies were presented in posters at ADA:
  1. CYP450 interaction. A study found no inhibition of any of the seven CYP450 enzymes.
  2. PK. A study in eight healthy adult males found rapid and complete absorption, complete bioavailability, no safety concerns, and a low potential for clinically significant drug-drug interactions by inhibition of CYP450. The PK profile indicated once-daily dosing is possible.
  3. Food/PK. A study in 28 healthy males found the drug was well-tolerated and food did not significantly affect its absorption.
- **Bristol-Myers Squibb's BMS-298585**, a dual PPAR-alpha/gamma agonist, which recently started a Phase III trial. There was no new data on this agent at the ADA meeting.
- **Calyx Therapeutics**.
  1. CLX-0901. This is a water-soluble, orally-active, small molecule. It is the synthetic analog of CLX-0900, which was originally isolated from a plant source. CLX-0901 was shown to lower blood glucose levels in several animal models of type 2 diabetes. Preclinical studies also demonstrated that it strongly lowers the concentrations of serum triglycerides, free fatty acids and cholesterol (up to 70-90% reduction). It has not caused animals to gain weight, and it has not induced hypoglycemia in normal rats or dogs. Studies suggest that CLX-0901 may be a competitive inhibitor of the binding of insulin to its receptor. In a manner similar to insulin, CLX-0901 acts through the PI-3 kinase pathway to increase glucose uptake in primary adipocytes. Confocal microscopy studies have shown that CLX-0901 stimulates the translocation of the insulin-

responsive glucose transporter GLUT-4 to the cell surface, where it mediates glucose uptake. In addition, CLX-0901 is not an agonist of the PPAR nuclear hormone receptors. Thus, CLX-0901 acts by a mechanism different from that of the TZDs.

2. CLX-0921. This is an orally active, small-molecule PPAR-gamma agonist in Phase II development. CLX-0921 lowers blood glucose concentrations in animal models of Type II diabetes, but reportedly does not cause hypoglycemia in normal, non-diabetic animals. It acts as an insulin sensitizer and is supposed to be effective at very low microvascular concentration in reducing blood glucose. CLX-0921 also exhibits potent anti-inflammatory activity via inhibition of TNF-α. Although CLX-0921 is as potent as rosiglitazone at lowering glucose, it is significantly less adipogenic than rosiglitazone. In various animal models, CLX-0921 has been shown to reduce significantly serum insulin and lipid levels, including the concentrations of triglycerides and free fatty acids. In addition, CLX-0921 offers potential cardiovascular benefits via inhibition of restenosis.

- **GlaxoSmithKline.** The company has at least one PPAR-delta, and that reportedly is the most promising.
  1. Glaxo/Ligand's GW-51516, a PPAR-gamma/RXR in Phase I development.
  2. Glaxo's GW-590735. This may be a dual PPAR-alpha/gamma.
  3. Glaxo's GW-677954. This is probably Glaxo's PPAR-delta.
  4. Compound 1. This is a PPARpan. A study in six obese pre-diabetic rhesus monkeys found Compound 1 (a) improved insulin resistance and symptoms associated with metabolic syndrome and (b) did not induce weight gain.

- **Lilly/Ligand Pharmaceuticals**:
  1. LY-519818, a gamma dominant dual PPAR-alpha/gamma. This oral, once-daily drug started a Phase II trial in March 2003. It is comparable to Avandia in lowering both glucose and triglycerides.
  2. LY-510929, a balanced dual PPAR-alpha/gamma. It appears to work in rats and mice and entered Phase I human clinical trials in June 2002.
  3. LY-674. This is probably a dual PPAR-alpha/gamma. It began Phase I at the end of 2002.
  4. LSN-862, a gamma-dominant dual PPAR-alph/gamma agonist. In rats it is more potent than Avandia in lowering plasma glucose.

- **Merck's MK-0767** (KRP-297, L-410,198), a once-a-day dual PPAR-α/γ that was licensed from Kyorin. A Merck researcher said this is not really a balanced PPAR and is not gamma dominant, making it unclear how to correctly characterize this. Potency reportedly is comparable to Actos, and the lipid effects are additive to simvastatin. Phase III trials started in late 2002, but only animal data was presented at ADA. Merck reportedly is aiming for a 40% decrease in triglyceride levels and a 20% increase in HDL cholesterol. Merck has said that early trials found this agent "generally safe and well-tolerated." There is no weight loss with this agent.

  A 5-year, multicenter, double-blind, randomized, placebo and active-controlled parallel study of MK-0767 began in September 2001. The trial was evaluating the glucose and lipid altering efficacy and safety of MK-0767 in 450 patients with type 2 diabetes. One site was in Christ Church, New Zealand.

- **Merck KgA's EML-257**, a dual PPAR-alpha/gamma. A study in 197 Type-2 diabetics found that EML-257 reduced HbA1c and fasting plasma glucose levels. The minimum effective dose was 100 mg BID. **(NOTE: Merck KgA later advised that this is not a PPAR.)**

- **Novo Nordisk/Dr. Reddy's balaglitazone** (NN2344). Novo also had a commercialization agreement with Novartis on NN622, which it licensed from Dr. Reddy, and Novo reportedly returned the rights to Dr. Reddy for the dual PPAR DRF-4158 which was in preclinical development. A study found that, compared to Avandia, balaglitazone had a better cardiovascular safety profile in rats, and better glycemic control in mice.

- **Roche's R-483/BM-131258.**

- **Takeda's TAK 559.** A researcher said, "This has the potential to be a whole lot different."

- **Tularik's T-131.** This PPAR-gamma is in Phase I studies. Preclinical studies showed that animals treated with T-131 did not demonstrate heart enlargement, anemia or weight gain side.

- **Wyeth's WY-14643.**

OBESITY

There are numerous obesity agents in development, but an expert said there are "none that look very promising."

APO-A-4 reduces food intake, but APO-A-1 doesn't. APO-A-4 works on the brain to inhibit gastric motility, hunger and gastric acid section. It is expressed by the hypothalamus and regulated by fasting/feeding. Thus, APO-A-4 is a satiety signal. However, researchers said they can't rule out peripheral action of APO-A-4. One speaker said, "Is there an APO-A-4 receptor in the brain? We don't know."

When administered to the gut, both NPY and PYY stimulate APO-A-4. An expert said, "In 1984 we showed that PYY infusions in man at physiological concentrations delayed gastric emptying…In chronic malabsorption, PYY is very elevated…When PYY_{3-36} is administered peripherally, it

decreases food intake…The $64,000 question is: Is this a rodent phenomenon or does it happen in man?…And we found that PYY_{3-36} causes a 33%-36% decrease in food intake over 24 hours – a decrease in total calorie consumption – so humans are exactly like the rats."

Another study found that obese people respond in a similar way to PYY_{3-36} to lean people. The effect appears to last out to 24 hours (long past the 30-60 minute infusion of the drug).

There is some reason to believe that there may be nausea associated with PYY_{3-36}. The researcher said, "We didn't measure gastric emptying, but PYY_{3-36} does have an effect on gastric emptying…I think it will cause nausea at high doses."

Obesity Drugs In Development

Drug	Company	Phase	Type
Axokine	Regeneron	Phase III	N/A
Rimonabant	Sanofi	Phase III	Cannabinoid
Aodl-9604	Metabolic Pharm	Phase II	GH agonist
ATL-962	Alizume	Phase II	Lipase inhibitor
BVT-933	Biovitrum	Phase II	5HT2c agonist
Ecopipam	Schering-Plough	Phase II	Dopamine D2 agonist
GW-320659	GlaxoSmithKline	Phase II	Adrenergic uptake inhibitor
HMR-1426	Aventis	Phase II	N/A
Leptin analog	Amgen	Phase II	N/A
ORG-12962	Akso Nobel	Phase II	5HT2c agonist
P57	Phytopharm (Pfizer)	Phase II	N/A
AZ-40140	Ashai/GlaxoSmith Kline	Phase I	Beta 3 agonist
GI-181771	GlaxoSmithKline	Phase I	CCKA agonist
MLN-4760	Millennium/Abbott	Phase I	N/A

Amylin's PYY_{3-36}

Amylin is developing this agent as an anti-obesity agent, and the company has applied for patent protection. However, an expert in the field warned that Amylin may not be granted a patent because of research that was published several years ago, before Amylin started working with PYY_{3-36}.

Ghrelin

A speaker reviewed some current thinking about ghrelin:

- Plasma ghrelin comes mainly from the stomach. It is a potent stimulator of food intake, not satiety. Anti-ghrelin suppresses appetite.
- Ghrelin causes weight gain even if the food intake is not increased.
- Ghrelin is thought to be responsible for meal initiation, but plasma ghrelin levels do not predict the spontaneous request for a meal in a human.
- Ingesting food lowers ghrelin levels, but insulin does not.
- Ghrelin levels are high in anorexic or lean women and low in obese women.
- When someone is on a low-fat diet, ghrelin fails to increase with weight loss, so maybe ultra low fat diets work because they don't increase ghrelin production.
- A Danish study found that women have higher ghrelin levels than men.

Ghrelin has been identified as a possible key weight regulator. A speaker said, "We need ghrelin antagonists from the drug companies…(but) it could be that ghrelin-antagonists will be like leptin and have no effect on weight loss." Another expert said, "Normally, obese people have low ghrelin levels, so ghrelin is not contributing to weight gain…But when obese people diet, ghrelin goes up, so it is hypothesized that an increase in ghrelin when dieting may cause people to eat and gain weight, defeating the diet…Gastric bypass does not raise ghrelin, which may be why gastric bypass leads to less hunger and longer and more profound loss of weight than other types of weight loss…We found that people who consumed glucose-sweetened beverages got marked and quite significant suppression of ghrelin that attenuated when they consumed sucrose….So, not all carbohydrates are the same, suggesting that sweeteners high in fructose have less impact and could, over time, lead to weight gain."

Diabetic Neuropathy

Avanir's Neurodex (AVP-923, dextromethorphan and quinidine)

The results of a four week , open label, dose escalation trial showed that Neurodex decreased pain intensity significantly from baseline. By Day 8, 91% of the patients reported pain relief compared to baseline; and by Day 15, 97% reported pain relief. The degree of pain relief increased with the amount of time on drug.

Johnson & Johnson's Topamax (topiramate)

Based on a small, uncontrolled study of 11 thin (not obese) patients, topiramate appears to stimulate nerve regeneration. Patients were started on 25 mg/day of topiramate and titrated up to 100 mg. A researcher concluded that topiramate:

- Increased intraepidermal nerve fiber density.
- Increased dendrite length.
- Improved amplitudes.
- Improved symptoms compatible with improved C-fiber function.
- Improved blood pressure, HbA1c and total cholesterol.

The speaker added, "We suggest topiramate may be the first drug to change the biology of diabetic neuropathy as well as address the components of the dysmetabolic syndrome…This was a hypothesis-seeking study. We extended it and have done another 10 patients…If that holds, we will do a double-blind, placebo-controlled study to be sure this holds."

He said most patients lost weight in the trial, but the changes did not reach statistical significance, primarily because of one outlier patient, and he does not believe the positive benefits seen with topiramate are due to the weight loss, "We think we see an effect that goes beyond weight change."

Topiramate Proof-of-Concept Trial in Neuropathy

Measurement	Baseline	Post-treatment	Change	p-value
Peroneal nerve amplitude	2.8	3.2	+14%	p=.04
Intraepidermal nerve fiber density	3.7	7.2	+98%	p=.04
Dendrite length	1.4	2.3	+65%	p<.05
Pressure	0.8	0.5	-38%	p=.04
Prickling pain	2.3	0.9	-61%	p=.002
Lancinating pain	1.4	0.6	-57%	p=.04
Diastolic blood pressure	83	72	-13%	p=.006
HbA1c	8.0	7.1	-11%	p=.03
Triglycerides	225	178	-21%	Nss
Total cholesterol	191	176	-8%	p=.002

A Belgian trial of topiramate to treat obesity was stopped due to adverse events -- parathesia, tiredness, lassitude, disorientation, confusion, and sleepiness. A speaker said this was due to higher dosing – up to 400 mg/day, "It is very difficult to use topiramate at that level. We experienced (the same problem) at the start, so we dosed down, and we started small and went up only to 100 mg/day, far below the obesity study dose."

LILLY'S ruboxistaurin (LY333531, PKC-β)

PKC-β isoforms are believed to be involved in early hyperglycemia-induced microvascular damage as well as later vascular EGFR-driven neovascularization and vascular leakages that are characteristic of diabetic retinopathy. Ruboxistaurin is currently in Phase III development, but no sources were optimistic about the outcome. Safety does not appear to be an issue, but efficacy has been underwhelming, at least so far. A speaker at a Lilly-sponsored symposium said there is only "a suggestion of an improvement in microvascular complications" with ruboxistaurin, and other sources described the Phase II results as "weak." One doctor commented, "PKC is an idea that has had its time."

GLUCOSE METERS AND PUMPS

Diabetics are being encouraged to test their glucose level frequently, but doctors said patients generally are not testing more frequently today than they did a year ago. A Texas diabetes educator said, "A lot of patients are in denial. Most don't test much."

Doctors and patients like small, quick glucose meters that require only a tiny amount of blood, but the most important factor in the choice of a device is reimbursement. A military nurse said, "We carry only Accu-Chek, which is covered by DOD." A California nurse said, "Unfortunately, patients really don't get to choose the meter because the insurance companies will only pay for certain meters." Another nurse said, "Quite often the patient has no real say in the choice of meter due to (meter company) contracts with the insurance companies."

HMOs often dictate the choice of a device, or provide a limited number of choices. When a choice is permitted, doctors (or the nurse or diabetes educator) generally show the patient several devices, and let them choose. A Texas diabetes educator said, "I'm a diabetic myself, and my meter takes 30 seconds. It's nice if it's faster, but that's not important." A Georgia doctor said, "Up to 30 seconds is okay." A nurse practitioner said, "The amount of blood needed is more important than the time." (NOTE: Kaiser has a contract to use only J&J One-Touch meters.)

Alternative site testing got mixed reviews. Some doctors said their patients rarely do it, but others have found a role for it. A New York doctor said, "I usually recommend alternate site testing for patients with a fear of needle sticks who already know about it. About 20% of my patients do alternate site testing." A nurse practitioner said, "Patients like alternate site testing. For some, it's either that, or they won't do it." A Virginia doctor said, "It's too hard for our patient population (VA). We tried alternate site testing in four patients, and all of them hated it. Patients ask about it, but when they try it, they don't like it."

Doctors insisted that overall pump usage is increasing, though slowly. However, it is primarily Type 1 diabetics who are interested in pumps, not Type 2 diabetics. Insurance reimbursement for pumps does not appear to be an issue. A doctor said, "Pediatrics is the fastest growing area for pumps." Another doctor commented, "The pump market is expanding but modestly. I think it will top out at 35% of Type 1 diabetics, compared to about 25% now." A nurse practitioner said, "More people are aware of pumps, and more people are coming in and asking about them."

Meters

There are a variety of meters available. The most popular, sources said are:

- **Johnson & Johnson's One-Touch Ultra**. A New York doctor said, "It's small, and it uses a small amount of blood."

- **TheraSense's FreeStyle**. Several doctors said their patients are using Freestyle only for finger-sticks, not alternate site testing. A California nurse said, "This is my personal favorite because it requires the smallest amount of glucose. I've tested several meters against lab results, and the FreeStyle is most consistently the most accurate. The strip gets caught often on the One-Touch, and its HCT range isn't as wide as FreeStyle, but both are the same in terms of the cost of the meter and strips."
- **Roche's Accu-Chek Advantage and Complete**. A doctor said, "More and more HMOs have contracted with Roche and are forcing us to use Roche products like Accu-Chek." A nurse said, "The Accu-Chek Complete is good for patients who are very rigid in their care or who are on an insulin pump."
- **Bayer's Glucometer Elite**.
- **Abbott/Medisense's Precision**.

Other meters about which sources had comments include:

- **Bayer's Breeze**. The device had good visibility on the exhibit floor, but that still didn't generate much interest.
- **Becton Dickinson:**
  - **Logic**. This did not show up on any doctor's short list of most popular meters, but doctors who tried it at the BD booth said they really liked it. They liked the small needle (31 gauge, 8 mm long), the pen device, and the amount of blood needed (0.3 µ). An Ohio doctor said, "There is less pain with this device and that will change how much patients use it because pain is a huge variable in getting people to check their glucose." A New England nurse said, "I think Logic will be popular in the pump group, although that isn't the biggest part of the diabetes population." A nurse educator said, "Logic may catch on with Type 1 clients or those Type 2 clients using a pump."
  - **Paradigm**. This will link with the MiniMed insulin pump, automatically capturing and transmitting glucose levels.
- **Deltec's Cosmo.** A Virginia doctor said, "It has cool features."
- **Pelikan**, a private company, is working on a new monitor that they hope to launch in 2004. The company was founded by former Agilent and HP executives. An official said pricing would be competitive and claimed the advantages of this device will be:
  - Less initial and residual pain because of its lancing technology.
  - Convenience. This is a one-step device with one button.
  - Reliability. It is all electronically controlled.
- **Cygnus's GlucoWatch.** Sources said the device has improved, but they generally believe it is too expensive and still has too many "kinks."

Pumps

During the meeting, Roche/Disetronics announced it would stop selling insulin pumps in the U.S. until FDA issues are resolved – which probably means for at least a year. Doctors were caught off-guard by the announcement because officials of both Roche and Disetronics had been saying at their booths that the Disetronics pump problem would quickly be resolved. A Disetronics sales rep had said, "I heard Roche was expanding the Disetronics sales force to match the size of MiniMed's sales force, but that hasn't happened yet."

Disetronics also does not have an integrated pump/monitor, but Disetronics sales reps had thought Roche would develop an Accu-Chek monitor for their pump. However, a Roche business development official said there are no immediate plans for an integrated monitor/pump system, though that is a longer-range goal.

Asked what they will do now that Disetronics pumps will not be available, sources said MiniMed, the 400 pound guerilla of insulin pumps, would pick up some of the business. However, they also said most of those sales would go to other vendors. One doctor explained, "People who are using Disetronics pumps are using them as an alternative to MiniMed, so most of them won't go to MiniMed now. And they want to ensure there continues to be competition in the field, so they will probably give their Disetronics business to someone other than MiniMed. Deltec may be the winner because its Cosmo is a very nice pump." Another doctor said, "My MiniMed business might increase a little, but I'll mostly try other pumps, including Deltec's Cosmo."

Deltec's Cosmo generated a lot of attention and positive comments at the meeting. Doctors praised it because you can enter carbohydrate ratios and let the device do the figuring. A source said, "It takes away the calculations." The one criticism was that it could be smaller.

Other Interesting News

Lilly's Zyprexa (olanzapine) vs. Bristol-Myers Squibb's Abilify (aripiprazole)

A Bristol-Myers Squibb poster suggested that there is a higher CHD event rate with Zyprexa than Ability. The retrospective

Measurement	Zyprexa	Abilify	p-value
Estimated change in one-year risk (n=91)	+0.02	-0.06	p=.005
Estimated change in five-year risk (n=91)	+0.16	-0.42	p=.005
Estimated change in 10-year risk (n=91)	+0.41	-0.92	p=.005

analysis was made from data from an ongoing Phase III head-to-head trial of the two agents. Researchers concluded, "If 75 patients were on treatment for 10 years on Abilify instead of Zyprexa, you could expect one less patient with a CHD event, which is clinically meaningful."

GLAXOSMITHKLINE'S Avandia (rosiglitazone)

A six-month, prospective, randomized study from Korea found that in-stent restenosis is significantly reduced when diabetic patients took a loading dose (8 mg) of Avandia prior to PCI and a maintenance dose of 4 mg daily for six months. None of these patients were on a TZD prior to the trial. The findings are intriguing, and the ADA highlighted them by including them in an ADA press conference, but several questions remain, including:

- Will the data hold up longer-term (at 12-24 months)?
- Can non-diabetics benefit in a similar manner?
- Will patients experience "rebound" restenosis if they stop taking Avandia?
- Do patients who are already on Avandia or another TZD benefit as well?
- Do patients already on Avandia or another TZD need a loading dose?
- If a patient is on 2 mg a day Avandia, for how long should they increase the dose to 4 mg?

Measurement	Avandia N=47	Placebo N=48	p-value
Binary restenosis per patient	11.4%	44.7%	p<.05
Binary restenosis per stent	10.2%	36.0%	p<.05
% stenosis	28.6%	41%	p<.05
MLD	2.25 mm	1.7 mm	p=.003

ISIS'S PTP-1B antisense

A Phase I trial in normal volunteers started in May 2003, and a Phase II trial is due to start in September 2003. It does not appear to cause hypoglycemia at any dose, does not change body weight, causes no change in serum chemistry, and has no overt toxicity.

ASTRAZENECA'S Crestor (rosuvastatin)

Crestor will be considered by an FDA advisory panel, and an expert at the ADA meeting suggested one of the issues the panel will be discussing is the interaction of Crestor and fibrates. He said, "Rosuvastatin looks like cerivastatin (Bayer's Baycol) in terms of interaction with gemfibrozil. It is almost exactly like cerivastatin. The panel may consider how to use it with gemfibrozil available." Despite this, he predicted the lower doses of Crestor would be approved, but he expressed concern that post-approval problems could arise from off-label use with gemfibrozil. ♦