DIABETES CLOSE UP

Diabetes Close Up, V3, #9
June 2, 2004
ADA Preview ~ New Classes of Diabetes Drugs

T h e s h o r t v e r s i o n

1. **ADA Preview – Get Ready for Orlando!**
   - **Rocking Schedule Afoot**: Besides Christmas week, this is my favorite week ("*Are you sure you want to admit that*?" asked my husband John.) I LOVE ADA. ADA begins on Friday and I love the lead up, love reading through all the abstracts and schedules and preparing my digital camera! There are so many fantastic sessions of interest and posters that intrigue and companies to watch – heady stuff. See our attached excel schedule, with five stars by the sessions that we think hold particular interest and/or promise.
   - **ADA Reports Offered**: As always, DCU receives many questions on what are *the* sessions to attend, please see our recommendations inside by area of interest (blood glucose monitoring, oral drugs, insulin, obesity). Cannot attend or just want another perspective? We'll do a five-pagish summary within six or eight weeks and that'll be on our site gratis, but DCU also provides a detailed 50-plus page conference report within two weeks of the conference and as well as on-site nightly updates for those who want the detailed scoop. Hit reply to sign up today. The price is $245 if you sign up before the close of ADA and $295 after. Healthcare professionals in full time clinical practice receive a price of $25 and a discount is available for private companies so if this applies, please inquire. If you aren't familiar with DCU conference reports here is a recent customer comment:
     - "*Diabetes 2004 Roundup provides an in-depth look at what has happened (and what is happening) in the diabetes 'space' over the last year. Kelly Close has synthesized a huge amount of information from multiple meetings, conferences, and key papers into a current and relevant view that is tempered by the perspective of both the analyst and a passionate consumer. This is valuable reading, particularly if you are trying to catch up on the field*." Alan C. Moses, MD, Associate VP of Medical Affairs, Novo Nordisk Pharmaceuticals, Inc
   - **Intriguing Abstracts**: Going to Orlando? We'll hope to see you there! Along with our schedule picks, we've included inside a selection of 25 abstracts (see separate PDF) that we think represent some of the most interesting posters at this year's ADA, from devices to drugs and back again. This PDF is under 20 pages, with a few lines of commentary on each – if you'd like our larger 100-page list, let us know – that was culled from thousands of abstracts, is organized by topic, and comes included with a conference report order.
2. **New Classes of Diabetes Drugs – GLP-1, DPPIV inhibitors, and PPAR**s. With all the hubbub of ADA, we've been asked several times in the past week or so what exactly all these new drug classes do. See this piece for our take on the new compounds.
3. **TIME on Obesity/Pump Update**: There's so much going on right now that we're publishing two newsletters concurrently. Please see accompanying PDF with the following stories:
   a. **TIME/ABC News Obesity Meeting** – going on now
   b. **Pump Industry Update** (Animas goes public, Medtronic MiniMed Reports, CozMonitor approved in win for Abbott Diabetes Care/Smiths Deltec)

Have an outstanding week!

T h e l o n g e r v e r s i o n

DCU Picks for key sessions to attend by topic (chronological order) – please see excel sheet for full details and please double-check all information before making firm plans. In addition to these sessions, there are some outstanding symposia going on, mostly in the drug world – pre-registration is required, so see http://www.diabetes.org/am04/symposia.asp to sign up. Information on speakers is not on the site, but is included on our excel sheet[1]:

1. **Continuous/BG Monitoring/A1C**:
    a. Glucose Monitoring and Insulin Delivery - Oral Abstracts – Friday, 2-4 pm, Conference Center (CC), Valencia A.
    b. New Approaches to Glucose Monitoring – Monday, 2:15 – 4:15, CC, Room 311-E-H
    c. Progress on the New Standardization and Values for the A1C Test, Tuesday, 10:15 – 12:15 pm, CC Room 209
2. **GLP-1, GIP, Gut Hormones**, **PPARs, TZDs**
    a. GLP-1, GIP and Gut Hormones - Oral Abstracts – Friday, 2-4 pm, CC, Room 224
    b. Use of Thiazolidinediones in Type 2 Diabetes – Friday, 4:15 – 6:15 pm, CC Valencia A.
    c. Metabolic Action of PPARs – Sunday, 8:00 – 10:00 am, CC, Room 230
    d. Islet and Gut Hormone Connections – Monday, 8:00 – 10:00 am, CC Room 304
    e. Adipokines: Recent Advances – Tuesday, 10:15 – 12:15, CC Room 414
3. **Insulin**:
    a. Practical Approaches to Insulin Therapy, Saturday, 10:15 – 12:15 pm, CC Valencia D
4. **Other drugs**:
    a. Pharmacologic Treatment of Type 2 Diabetes - Sunday, 2:00 – 4:00 pm, CC Auditorium
5. **Obesity/Metabolic Syndrome**:
    a. Bariatric Surgery: Before and After – Saturday, 8:00 – 10:00 am, Peabody, Orlando
    b. Dyslipidemia, the Metabolic Syndrome, and Cardiac Disease – Saturday, 2:45 – 4:45, CC room 414
    c. Fit-Fat Individual: At Increased Risk for Diabetes and Macrovascular Disease? - Sunday, 2:00 – 4:00 pm, CC Room 304
    d. Treatment of the Metabolic Syndrome – Monday, 8:00 – 10:00 am, Room 311 E-H
6. **Transplantation**:
    a. Islet Transplants for Type 1 Diabetes: From Clinical Research to Clinical Care – Sunday, 2:00 – 4:00 pm, CC 311, A-D
7. **Children**:
    a. Behavioral and Educational "Issues" in Youth - Oral Abstracts – Friday, 4:15 – 6:15 pm, CC, Room 207
    b. Children and Diabetes - Oral Abstracts - Sunday, 2:00 – 4:00 pm, CC Room 208
    c. To Treat or Not to Treat, That is the Question: Lipids and Diabetes in Childhood – Monday, 8:00 – 10:00 am, Room 230
8. **Complications**:
    a. Recent Advances in the Physiology of Hypoglycemia Counterregulation - Saturday, 8:00 am – 10:00 am, CC, Room 414
    b. Hypoglycemia - Oral Abstracts – Sunday, 2:00 – 4:00 pm, CC Room 230
    c. Hypoglycemia Unawareness – Monday, 8:00 – 10:00 am, CC Room 207
    d. Retinopathy: Experimental - 10:15 – 12:15 pm, CC 230
    e. Oxidative Stress and Lipids: What's the Connection? – Monday, 8:00 – 10:00 am, CC-Room 224
    f. Microvascular Complications in Clinical Studies - Oral Abstracts – Monday, 8:00 – 10:00 am, CC Room 311-A-D
    g. Preventing Cardiovascular Disease in Type 2 Diabetes: Trial Data – Monday, 4:30 – 6:30, CC Room 230

[1] Warning – the 5-page sheet is massive. To print, please hide rows in blue.

9. **Other**:
    a. Plenary - Michael Bliss, The Discovery of Insulin – Friday, 4:15 – 5:00 pm, CC Auditorium. *If you haven't heard Bliss, definitely go. On our website (www.closeconcerns.com) we have a review of his book and his talk at last year's AADE – very inspiring.*
    b. Epidemiology of Diabetes Complications: Changing Trends over Ten Years – Saturday, 8:00 – 10:00 am, Room 209.
    c. Late Breaking Clinical Trials – Sunday, 8:00 – 10:00 am, CC, Auditorium
    d. Novel Predictors of Type 2 Diabetes – Monday, 2:15 – 4:15 pm, CC Room 208
    e. ADA/IDF Joint Symposium: Diabetes Care in the Developing World, Tuesday, 8:00 – 10:00 am, CC Room 230
    f. Pay for Performance: Linking Reimbursement to Diabetes Outcomes, Tuesday, 8:00 – 10:00 am, CC Room 311, E-H

A Closer Look At New Classes of Drugs to Treat Type 2 Diabetes

New classes of diabetes drugs are making their way through the clinic. The genesis of these drugs was clearly sown in the advances of the 1980s in the fields of genetics, cell biology, and molecular biology. While none of these compounds will likely represent a panacea, all offer hope of supplementing and/or improving the care of patients with type 2 diabetes – at last count, 17 million in the US alone, and over 170 million worldwide[2]. It is estimated by Wild, et. al. in May's Diabetes Care that the total number of people with diabetes[3] would increase to 366 million in 2030; with such figures (which assume that obesity will remain constant and not increase – highly unlikely in our view), it is easy to see the source of the interest of Big Pharma.

With that in mind, as the ADA approaches, many are asking us about various new classes of diabetes drugs. We present the following as a basic primer, as our understanding of the new classes. The classes that we are particularly interested in at this point are GLP-1 analogs, DPP-IV inhibitors, and dual PPAR compounds.

GLP-1 Overview

GLP-1 (Glucagon-like peptide), first identified in the 1980s, is an incretin[4] synthesized by the L cells of the intestine (L cells are endocrine cells in the intestine) and quickly degraded by dipeptidyl peptidase (DPP-IV). At present, there is only one known receptor of GLP-1, though anecdotal evidence has suggested that there may be a second[5]. While data continues to build on the wide range of biological activities of GLP-1 (including impacts on satiety and food intake), the most relevant activities to diabetes concern stimulation of glucose-dependent insulin secretion and biosynthesis, inhibition of glucagon secretion, and inhibition of gastric emptying and food intake.

In numerous studies conducted to date, GLP-1 has been shown to lower blood glucose in both Type 1 and Type 2 diabetes patients, despite the lack of any significant stimulation of glucose disappearance. While it seems unlikely that GLP-1 produces an insulin secretion effect in Type 1 diabetics (since most Type 1 diabetics have no beta cells left), it is more likely that the benefits seen in Type 1 patients derive from the delayed gastric emptying and the inhibition of glucagon secretion caused by GLP-1. Beta cell regeneration in this population remains a question.

On that note, budding evidence exists that GLP-1 regulates islet cell proliferation and neogenesis. GLP-1 seems to increase the size of islets and reduces the rate of beta cell apoptosis. In other words, GLP-1 may have a direct role in the death and regeneration of insulin-producing cells in the body. While its unlikely that this line of research would lead to therapies that could catalyze whole-scale reversals of Type 1 diabetes, it does offer an intriguing opportunity

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[2] Wild, Sarah, et.al. Diabetes Care, Volume 27, Number 5, May, 2004. "*Global Prevalence of Diabetes*."

[3] Including undiagnosed

[4] An incretin is a gut hormone that augments insulin, typically in response to nutrients.

[5] This evidence includes the observed activity of GLP-1 in tissues that have not been shown to express the GLP-1 receptor as well as the sometimes unusual binding and signal transduction behavior of GLP-1 and the fact that GLP-1 isn't always blocked by GLP-1 receptor antagonists like exendin.

to halt the progression of Type 2 diabetes and possibly stave off Type-1 disease if intervention occurs quickly enough.

Hypoglycemia is an ever-present concern with diabetes drugs and GLP-1 seems to be a very strong class of drugs in this regard. GLP-1 compounds seem to induce hypoglycemia only when combined with compounds that are known to cause hypoglycemia themselves (like sulfonylureas). Oddly, GLP-1 drugs have been associated with hypoglycemia in healthy recipients when administered in high doses, but, at least in monotherapy, not in patients with diabetes[6]. We see this glucose-dependent trait as a positive, as we believe some patients and healthcare professionals do not go on insulin due to hypoglycemia fears (combined with other factors such as mis-association with cardiovascular problems, fear, misunderstanding, etc.)

One complaint of various other oral classes of drugs as well as insulin has been associated weight gain; GLP-1 appears to be at least weight neutral or to prompt actual weight loss. We believe the power of the "weight factor" cannot be underestimated, particularly in the US.

There are several drugs in clinical development that propose to increase the level of a patient's GLP-1. Given that GLP-1 is naturally chewed up by DPP-IV, it is not surprising that those GLP-1 analogues that are resistant to cleavage by DPP-IV are more potent in the body. Drugs under development included human-derived (or modified) GLP-1 as well as non-human GLP-1 analogs. Interestingly, oral and buccal formulations of some GLP-1 compounds may be effective. While these drugs are still early in the development phase, historically, oral formulations have been preferable to subcutaneous injections when efficacy is equivalent. In those cases, however, weight impact may have been neutral.

Data on the side effect profiles of most GLP-1 compounds have not been comprehensive and we look forward to seeing more data at this year's ADA. We take it as a positive side that antibodies were reduced in Amylin's exenatide from over 50% in early trials to in the teens (at the one-year mark). Importantly, antibodies to date have been non-neutralizing.

The most oft-discussed negative associated with GLP-1 has been that injections are required. While see this as an obstacle – pills are just easier to take – it's not one that is impossible to overcome. If weight reduction is sustained, we think patients will see this as some solace for taking injections – additionally, we assume better and better pens will be developed.

GLP-1 Candidates

1. Amylin is working on its version of synthetic exendin-4, **exenatide**, and has partnered with Eli Lilly to develop the compound, which is the furthest along on the regulatory path – it's finished Phase 3 trials and is expected to be submitted to the FDA mid-year. Exendin-4 is a naturally occurring and extremely potent agonist for the mammalian GLP-1 receptor that has merited considerable clinical and scientific attention. Exendin-4 occurs naturally in the saliva of the *Heloderma* genus of lizards (the venomous Gila Monster and Beaded Lizard). What makes Exendin-4 particularly interesting is that it is highly resistant to DPP-IV cleavage – because of the structure of exendin-4, DPP-IV cannot bind to it and "chop it up". Primarily for this reason, Exendin-4 is considerably more effective in vivo than naturally occurring GLP-1. Prior to partnering with Amylin, Lilly had been developing its own DPP-IV resistant compound LY315902. This compound showed encouraging efficacy and safety in early stage trials, but was associated with cutaneous irritation. With the partnership with Amylin in place, Lilly has chosen to discontinue development of this compound[7].
2. **Liraglutide** (NN2211) is a compound under development by Novo Nordisk. Liraglutide is an acylated albumin bound GLP-1 analog. Novo Nordisk has completed Phase 2 studies of Liraglutide and as we understand it, intends to initiate Phase 3 studies sometime in mid-2004. Liraglutide has been formulated as a once-daily injection and has shown a half-life of approximately 12 hours and an effective duration of roughly 24 hours. Interestingly, Novo Nordisk's own research has shown the

[6] Edwards T, Ghatei, Bloom. Subcutaneous glucagon-like peptide-1 amide is insulintropic and can cause hypoglycemia in fasted healthy subjects. Clin Sci (Lond) Dec 1998; 95 (6): 719-24.)
[7] Source: Amylin, Eli Lilly

above-discussed increase in beta-cell mass. In the case of Liraglutide, it is the binding to serum albumin that enhances the compound's longevity and partially contributes to the resistance to degradation by DPP-IV. Studies thus far have shown prolonged decreases in glucose and glucagon in the 24 hours following administration of the drug and the most dramatic side effects include nausea and vomiting[8].

3. Conjuchem is developing **CJC-1131** (or DAC GLP-1), a human DPP-IV resistant GLP analog. This drug is presently in mid-Phase 2 studies, with final results expected mid-year. Unlike some other GLP-1 compounds, CJC-1131 has been purposely modified to be resistant to DPP-IV cleavage. In trials conducted to date, this drug has produced significant reductions in glucose levels (both daily mean and fasting), a long duration after administration, and an average weight loss of 3kg. The company's Phase 2 study is designed to enroll 196 patients into a two-stage trial. In the first stage, the patients received escalating daily doses of the drug for 28 days. In the second stage, patients will be randomized into five different administration groups (once/day, 3/week, 2/week, 1/week, and no treatment). Interim results (after the first stage of therapy) has shown a 0.8% reduction in HbA1c levels, a mean weight loss of 2.3kg, 26% mean reduction in average daily glucose level, and 24% mean reduction of average fasting glucose level. Absence of a control group made it difficult to analyze these results, and we look forward to seeing more data in short order. Primary side effects have been nausea and vomiting[9].
4. Aventis is developing its own exendin-4 derivative -- **ZP10**, also known as AVE-0010. This compound was licensed to Aventis by Zealand Pharmaceuticals (a Danish biotechnology company) in mid-2003 and is presently in Phase 2 testing. In very early stage testing (Phase 1/2), Zealand reported dose-dependent lowering of plasma glucose concentrations with no side effects. While initial testing has centered around a twice-daily injection, there are plans to develop and test once-daily and long-acting formulations[10].
5. **BIM51077**, a human GLP-1 derivative, is under development at Roche. The compound was licensed from Ipsen late in 2003 and is presently in early stage testing. As a human GLP-1 derivative, this compound has been modified in an effort to achieve greater half-life in vivo[11].

DPP-IV Overview

In addition to supplementing or stimulating the body's production of GLP-1, diabetes drug researchers have focused attention on inhibitors of DPP-IV. As we understand it, in a sort of mirror image to GLP-1 therapy, DPP-IV inhibitors enhance the action of GLP-1 and GIP (gastric inhibitory polypeptide – an incretin secreted by the K cells of the intestine) by blocking or slowing the natural degradation of them by the DPP-IV pathway. In other words, DPP-IV inhibitors improve glucose control by "getting out of the way" of GLP-1 and GIP and allowing those incretin molecules to do their job. Studies have shown that DPP-IV inhibitors can lead to a two-to-four-fold increase in GLP-1. What's more, the natural degradation of GLP-1 produces GLP-1 (9-36) amide – an antagonist that hampers the function of GLP-1. When DPP-IV inhibitors are introduced, the levels of GLP-1 (9-36) amide decrease significantly and GLP-1 can more effectively operate.

Given that DPP-IV naturally degrades GLP-1 and GIP, it is not surprising that knockout mice studies have confirmed that DPP-IV inhibitors do not work in the absence of functional GLP-1 and/or GIP receptors. In plainer terms, DPP-IV inhibitors allow whatever GLP-1 and GIP that is in the body to work longer, but it cannot and does not create what doesn't already exist in the body. At present it appears that DPP-IV inhibitors are a viable therapy for cases of mild or moderate resistance but are ineffectual (or at least sub-optimal) in patients with severe insulin resistance.

While research is ongoing as to possible side effects of DPP-IV inhibitor therapy, one immediate concern revolves around the patient's autoimmune system. Because DPP-IV inhibitors appear to have some affect on T-cell signaling, it is not unreasonable to be concerned about possible adverse reactions – the "what else is being inhibited?" query often arises. What's more, as GLP-1 is produced in the brain, there is concern as to whether or not DPP-IV inhibitors will penetrate the blood-brain barrier and induce some sort of side effect(s).

[8] Source: Novo Nordisk
[9] Source: Conjuchem
[10] Source: Aventis
[11] Source: Roche

Although there is some encouraging (though very early) data on oral and buccal formulations of GLP-1 analogs, most GLP-1 therapy must be injected. What's more, many GLP-1 compounds have a relatively short half-life in the body, a fact that necessitates larger and/or more frequent dosing. In addition to an easier administration schedule (virtually all DPP-IV inhibitors under development are administered orally), there is budding research suggesting that DPP-IV inhibitors may be combined with GLP-1 analogs to produce an even greater effect. We don't know too much here yet but will be watching closely.

DPP-IV Candidates

Several companies have a variety of DDP-IV inhibitor compounds under development:
1. **LAF237** from Novartis appears to be the furthest along in development (Phase 3);
2. Merck has its own compound (**MK0431**) in Phase 2 studies (with plans to enter Phase 3 in mid-04)
3. **Glaxo SmithKline** has at least three different DPP-IV inhibitors in early development.
4. Sanofi-Synthelabo has identified one such compound (**SSR-162369**) in pre-clinical testing[12].

PPAR Overview

PPAR's (Peroxisome Proliferator-Activated Receptors) are ligand-activated nuclear transcription factors that increase the transcription of targeted genes. These receptors were first identified in the early 1990's by Isseman and Green. At present, three PPAR's have been identified and described in detail – PPAR-alpha, PPAR-gamma, and PPAR-delta (also called PPAR-beta). While the biochemistry around PPARs is very new (and extremely complex) and considerable research is still ongoing, it is clear that all of the PPARs are extensively involved in how the body produces and processes fatty acids.

PPAR-alpha is known to regulate fats in the blood and liver by regulating enzymes that breakdown lipids. PPAR-gamma enhances the expression of numerous genes involved in glucose and lipid metabolism. Accordingly, PPAR-gamma regulates lipid synthesis, carbohydrate metabolism, and leads to differentiation of adipocytes.

In the case of diabetes, both PPAR-alpha and PPAR-gamma have been shown to be active in glucose control, though the role of PPAR-gamma looks to be considerably clearer in this regard. The expression of PPAR-gamma is highest in adipose tissue, which may offer a partial explanation of the link between obesity and Type 2 diabetes. Targeting one PPAR is not really anything new in diabetes – the TZD (thiazolidinedione) class of drugs works because they are ligands for the PPAR-gamma, while fibrates (clofibrate, fenofibrate, bezfibrate) target PPAR-alpha and were developed as hypolipidemic agents.

For some time now, drugs targeting PPAR-gamma have been successfully used to help control Type 2 diabetes. These drugs – thiazolidinedione (TZDs) or glitazones – bind with PPAR-gamma to enhance insulin-mediated glucose transport into adipose tissue (fat cells) and skeletal muscle. In plainer English, they work by moving glucose from the blood stream into muscle and fat tissue – essentially helping the body make better use of the insulin that it still produces. Additionally, TZD's decrease hepatic glucose output. TZD's also appear to impact beta cells directly – increasing secretion rates, maintaining cell mass, and reversing the intrinsic dysfunction that leads to the worsening of Type 2 diabetes over time. TZDs have been extremely successful commercially, with over $3.5 billion in worldwide revenue for 2003.

More recently, it's been suggested that co-activating both PPAR-alpha and PPAR-gamma works better than activating just one of the two. While PPAR-gamma agonists help re-sensitize the recipient to insulin, the PPAR-alpha component provides beneficial lipid-modulation. What's more, PPAR-gamma can have the unwelcome side effect of weight gain. PPAR-alpha, though, reduces appetite and stimulates lipid oxidation, which reduces obesity. A dual-PPAR, then, should help address hyperglycemia, insulin resistance, and dyslipidemia – helping to alleviate the complications of elevated blood glucose and the cardiovascular co-morbidities of diabetes. Neat.

[12]Source: Company websites

Despite the promising aspects of dual PPAR therapy, clinical programs have faced some significant challenges. In particular, there seems to be a disconcerting trend toward unusual cancers in rodents exposed to these compounds. Whether the compounds are exclusive to murine biology hasn't been explored yet, but of course the FDA will not allow any compound that shows rodent cancer to progress until the companies in question can completely satisfy the FDA that the cancers are exclusive to rodents.

PPAR Candidates:

1. Kyorin Pharmaceuticals and Merck pharmaceuticals had been jointly developing a compound (**KRP-297** in Japan, **MK-767** in the U.S.) and had advanced it as far as Phase-3 studies in the United States. The trial was stopped in late 2003 because a rare form of malignant tumor was seen in mice. Ragaglitizar (NN622) was suspended in Phase 2 due to bladder tumors in rodents. Licensed from Dr. Reddy's – a large Indian pharmaceutical company, ragaglitizar had shown significant efficacy in regulating blood glucose and controlling diabetic dislipidemia.
2. **Muraglitizar** is a dual PPAR agonist in Phase 3 trials. The drug was originally discovered and developed by Bristol Myers, and Bristol recently (April 2004) formed an alliance with Merck for global commercialization. The agreement also included a so-called backup compound that is currently in Phase 2 testing. We do not know if Muraglitizar has shown any murine cancer issues, nor do we know the details of the backup compound (or whether it's a dual PPAR agonist as well).
3. Ligand Pharmaceuticals has an impressive suite of PPAR compounds under development – almost all of which are partnered with Eli Lilly. One compound, **LY818**, has advanced into Phase 3 trials and another, LY929, is still in early-stage studies.
4. Aventis currently has two relevant compounds in Phase 2 studies. **AVE-8134** is a PPAR-alpha agonist while **AVE-0847** is a dual PPAR-alpha/gamma agonist.
5. Glaxo SmithKline is also involved in PPAR research, with the compound **677954** currently in Phase trials. This compound is described by Glaxo as a PPAR pan-agonist. We do not know at present if this means a dual alpha/gamma agonist or if it's truly a pan-agonist (covering all three PPAR versions). We will be looking for data at the ADA on this compound in particular.
6. Johnson and Johnson is presently developing Isaglitazone, also known as **MC-555**, an agonist of PPAR-gamma. This is currently in Phase 2 studies.
7. **JTT-501** (PNU 182716) from Japan Tobacco and Pharmacia was a PPAR alpha/gamma that was terminated after phase 2, c. 2002. While there was not an "official" reason, carcinogenicity is suspected.

There have been some disconcerting side effects seen in the PPAR class that were detailed in key *Circulation/ Diabetes Care* pieces in late 2003 (see a summary on the piece in DCU, V3, #4, January 22). Specifically, recent studies show an increased occurrence of edema, or buildup of fluid in the blood vessels, among patients with diabetes using TZDs. This occurrence increases susceptibility to congestive heart failure (CHF), for which patients with diabetes are already at a high risk. We'll be watching closely to see if dual PPARs are less at risk.

The ADA should hold much interest in 2004 on the drug side in particular; we look forward to learning more!

References

www.glucagon.com
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--By Stephen Simpson and Kelly Close

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Many thanks to Melissa Ford, Stephen Simpson, and Jennifer Wei in researching and writing this newsletter.

Diabetes Close Up is a newsletter highlighting notable information and events related to selected companies with diabetes/obesity businesses. This newsletter is put forth as an unbiased commentary on the industry. If you have any suggestions or comments regarding content, please contact info@closeconcerns.com. If you would like to 1) unsubscribe; 2) receive a monthly digest rather than real-time updates; 3) add a name to the DCU mailing list; or 4) offer any suggestions or comments regarding content, please contact info@closeconcerns.com.

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