DIABETESCLOSEUP

The Leading Source of Diabetes Business News

Strudel Rocks **September 2009 • No. 94**

From the Editor

So we're writing from Café Mozart in Vienna while we're here for EASD. We're eating strudel. Apple strudel. Because we can. My CGM says 91 and my blood glucose monitor says 93 and I just took Symlin. Yes, we've come a long way from the mid-1980s, when I was diagnosed, when doctors looked away when I said I wanted to have kids, when plenty of people in the waiting rooms of UMass and the Joslin were blind, had amputations, talked in hushed whispers. When I took 8 units of NPH and 4 units of regular every morning and every night, no matter what my blood glucose meter said, no matter what I was eating (carbs? I had no idea), no matter how stressed I was, no matter whether I was exercising or not (I wasn't). This evening, I'm eating strudel. My peak blood glucose isn't breaking 130 mg/dl (that's 7.3 mmol/l for those of us not stateside), and John and I walked two miles today between all the sessions and our little apartment that Alisa found on the edge of the city. I'm feeling on the positive side of this diabetes stuff.

But sometimes I wonder how much progress we've really made. On the plane over, Johnny and I sat next to a cardiologist who had just been to TCT in San Francisco, a major interventional cardiology meeting. We started chatting because I was calibrating my continuous glucose monitor (he was impressed with the accuracy) and finishing Dr. David Kessler's amazing "The End of Overeating: Taking Control of the Insatiable American Appetite," and I asked him if he had any people with diabetes in his practice. He just stared at me. I asked him again, and he sputtered, "Almost all my patients are diabetic! Almost all of them!" He then allowed that maybe the percentage was as low as 60-70%. I then asked if he knew what the problems were. He stared again. "Do they have normal A1cs?" I asked. He didn't know precisely (read: at all) but he said he was sure they were all out of control "or I wouldn't have met them in the first place!" What are their problems? Another stare. "Is it fasting blood glucose or post-prandial mostly?" He had no idea. I asked him if he prescribed incretins or metformin or SFUs. He said, almost disgustedly, "I stay out of all that. I'm busy. I have so many procedures to do. I get them to their endocrinologist as fast as I can! I don't have time to manage that."

I told him that it was because of him that people with diabetes cost insurers and taxpayers nearly $100 billion in hospitals last year, that it was a public health problem we could no longer afford, and that people with diabetes needed to get in control early and needed to have cardiologists talk about the importance of diabetes management so that the next procedures could be avoided. I asked, "Don't you care?" Well, he felt bad. He started talking about how he had no idea, that he was just so busy, with so many procedures. Surreal. PCPs aren't paid to teach the most basic care, endos and educators aren't paid for their time teaching patients to take care of themselves to avoid complications – and this is cheap! – and then our cardiologists are so busy that they can't think, because of all the people with diabetes who are overwhelming their practices, in dire need of once-unnecessary procedures.

So that's why I feel good at 93 mg/dl, but why I don't feel so great. Or put another way, I can eat half a strudel, but the glass is still half empty.

Here's another example. Last week, we went to a Drug Information Association Cardiac Safety Summit meeting in Washington, where the top guns at the FDA and prominent cardiologists and endocrinologists discussed how companies needed to gather cardiovascular data to get new drugs approved in light of new guidelines – write me for a copy of the detailed Closer Look notes if you don't know the background. We heard Dr. Allison Goldfine of the Joslin Clinic, and she gave an overview of the history of diabetes as a reminder of the progress that has been made in treating the disease since the discovery of insulin. She also highlighted the abundance of drugs that have been introduced with A1c-lowering effects since the approval of A1c as a surrogate endpoint for diabetes in 1995. According to Dr. Goldfine, even when that first drug was marketed, a number of clinical questions remained, including those about the long-term benefits, the long-term adverse effects, where the drug fits into a clinician's armamentarium, and what subpopulations are at greater risk for side effects. Dr. Goldfine emphasized the importance of monitoring CV risk in a post-marketing environment since 80% of all diabetic mortality can be linked to atherosclerosis. But from our view, this begs the question, shouldn't innovation in drugs continue so that patients can be treated early and aggressively and prevent or delay macrovascular disease? And if there is no incentive to develop innovative drugs, how will this happen?

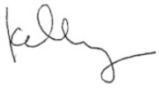
Then, Dr. Sue Kirkman of the American Diabetes Association delivered her own talk and emphasized the improvements of glucose control in US patients and said that the average A1c fell from 7.8% to 7.2% from 1999 to 2003 and that 57% of patients now meet the ADA target of 7%.

Maybe it's just me, but I'm still not so happy about only 57% of patients meeting that ADA target. First, this means that 43% of patients are NOT in control. Second, I've got to believe that the number has only come down because we are getting better at earlier diagnosis, so those newer patients have lower A1c. Third, why is 7% so good anyway? Normal cholesterol is normal cholesterol. If I have lipids that are 27% above normal (which is what 7% is to a normal A1c of 5%-6%), I go on a statin and I work out and I'm berated till I get to normal. If my blood pressure is 27% above normal, I go on meds to get to normal. In short, the diabetes drugs we have are good, but not good enough for the scope of the problem, and delay is one of our biggest enemies.

Consider this: TZDs were approved in the 1990s. Then no oral drugs were approved till Januvia in late 2006. A first generation incretin has been approved and one is delayed at FDA – again. A DPP-4 inhibitor that could be combined with a drug for insulin resistance got delayed last month. So when Dr. Goldfine discussed "the abundance of drugs that have been introduced to the market with A1c lowering effects," I just thought that was a little bit overstated since I don't think most who treat diabetes today feel there is an abundance of drugs that are highly efficacious, tolerable, easy to use, and safe. There are still 10 million people not at goal and another 10 million that are ostensibly at goal but who have major blood glucose swings every day and night. (Ask John. He loves my CGM but he also never sleeps more than four hours straight.)

It's worth noting that a number of doctors at DIA also lambasted the diabetes community for being glucocentric. True, wildly fluctuating blood sugars do tend to focus the mind on . . .wildly fluctuating blood sugars. So we'll stop being glucocentric when we have enough therapies and technologies and education to get patients to a normal A1c.

Best Wishes,



Kelly L. Close

Major Headlines

In This Issue

Videos

Below is our favorite video in diabetes this month:

- One Shot – A moving documentary of Team Type 1
  http://www.youtube.com/watch?v=72NCRWvFOxc&feature=fvsr

Coming soon in DCU…

There are several conferences coming up in October that we look forward to reporting from, including Cardiometabolic Health Congress in Boston, MA, International Diabetes Federation in Montreal, Canada, and The Obesity Society meeting in Washington, DC…

1. Quotable Quotes in Diabetes

Was the recent FDA Guidance an overreaction? (Sorry, Takeda…)

"While I don't think the guidelines are an overreaction [to Dr. Nissen's meta-analysis), it has only been nine to ten months since the new guidance was issued, and we are just beginning to see data following these new guidelines. None of us here at the FDA have written off the possibility that the guidelines could be modified and that there could be changes in what we ask for from companies"

— Mary Parks, MD (Director, Division of Endocrinology and Metabolism Products, Office of Drug Evaluation II, Office of New Drugs, CDER, FDA, Washington, DC) discussing the FDA cardiovascular draft guidance for assessing cardiovascular risk in anti-diabetic medications at the Drug Information Association's Cardiac Summit in Washington, DC.

Diabetes and Obesity

"[Type 2] diabetes and obesity go together like a hand in a glove."

— Donna Ryan, MD (Pennington Biomedical Research Center, Baton Rouge, LA) introducing the one-year interim results from the LOOK AHEAD trial at Cleveland Clinic's 4th Annual Obesity Summit.

Importance of the DCCT trial

"If you haven't seen these slides at least 1,000 times, you are in the wrong room."

— Denis Daneman, MD (Hospital for Sick Children, Toronto, Canada) speaking about the DCCT at the 8th annual joint meeting of the Lawson Wilkins Pediatric Endocrine Society / European Society for Pediatric Endocrinology.

Reimbursement for Obesity Therapies

"If we think about the obesity epidemic driving metabolic diseases, why aren't we talking more about obesity therapies? It is because diabetes drugs are the ones getting reimbursed, however, if we can make a real value proposition that if you treat one central risk factor (obesity), it will help future comorbidities as well as healthcare costs, it will help the obesity space. We need more outcomes studies."

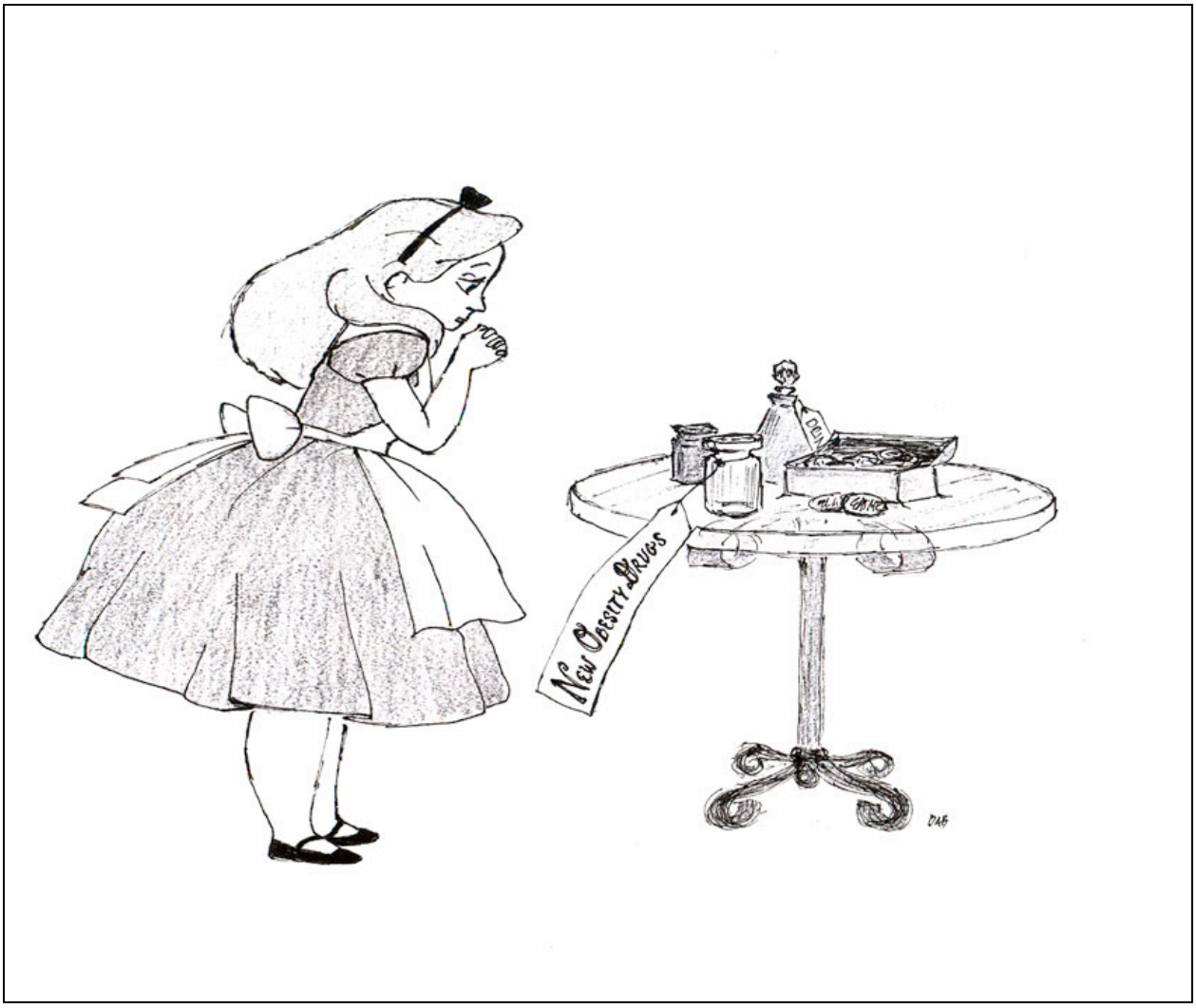
— Steven Chen, MD (Medical Affairs Director, Amylin Pharmaceutical, San Diego, CA) speaking on reimbursement and general market acceptance for obesity therapies at Cleveland Clinic's 4th Annual Obesity Summit.

Combating Obesity

"[Delos] Cosgrove says that if it were up to him, if there weren't legal issues, he would not only stop hiring smokers. He would also stop hiring obese people."

—Delos M. Cosgrove, MD (CEO, Cleveland Clinic, OH) was quoted in The New York Times ("Fat Tax", August 12, 2009). His controversial statements sparked heated debate at Cleveland Clinic's 4th Annual Obesity Summit. He subsequently apologized for his remarks to his own employees, clarifying that his statement was not meant to be hurtful or insensitive, but rather to spark discussion.

2. diaTribe FingerSticks



— by Daniel A. Belkin

3. DCU Company Watch

- **Bayer – Diabetes Care receives FDA approval for Contour USB blood glucose monitor:** On September 22, Bayer Diabetes Care announced the FDA approval of its Contour USB blood glucose monitoring system. Based on existing Contour technology, the Contour USB has the additional capability of connecting directly into a computer to facilitate downloading. Up to 2,000 test results can be stored on the device and transferred into Bayer's Glucofacts Deluxe software for analysis. The appearance and size of the device has been redesigned to resemble a USB thumb drive. In the press release, Bayer highlighted other additional features, such as the color screen that displays high, low, and average readings and pre- and post-meal marking. The company did not indicate when it plans to officially launch the Contour USB.

  Overall, we see this as a positive for Bayer Diabetes Care. In a weak blood glucose monitor market, the current Contour system has already shown above-market growth (169 million Euros or about $239 million, up 16.6% in 2Q09). The Contour USB is in line with the company's efforts to simplify diabetes management for patients – though it is presently unclear if the upgrade will provide enough benefit to convince patients to switch from their current meters. Bayer has been a pioneer on the software front and we believe its software provides very useful feedback on patterns for patients. Two problems with software persist: 1) few payers reimburse doctors and educators to view the results software provides; and 2) there isn't enough investment in patient education regarding software capabilities and interpreting results.

- **Arena – Announces BLOSSOM phase 3 data:** Arena's President and CEO, Jack Lief, led a conference call on September 18 announcing top-line data from the Behavioral modification and LOrcaserin Second Study for Obesity Management (BLOSSOM) trial, the final phase 3 study for lorcaserin, Arena's obesity drug targeting the serotonin 5HT2c receptor. The trial evaluated lorcaserin's potential to reduce weight and improve a multitude of secondary endpoints using 10 mg of lorcaserin once- or twice-daily in 4,008 obese or overweight patients, some suffering from at least one co-morbid condition (clinicaltrials.gov indicates patients were included if they had a BMI of 30-45 kg/m^2 with or without co-morbidity or 27-45 kg/m^2 with at least one co-morbidity). The results from the BLOSSOM trial are consistent with the BLOOM data: lorcaserin met the FDA's categorical efficacy benchmark while falling short of the average percent weight loss endpoint. The BLOSSOM trial showed that 47% of patients achieved ≥5% weight loss on an Intent-to-Treat Last Observation Carried Forward (ITT-LOCF) basis, with 63.2% of "completers" losing ≥5% body weight on lorcaserin 10 mg BID. Patients on the full dose of lorcaserin also experienced a mean weight loss of 5.9% on an ITT-LOCF basis and 7.9% on a per protocol basis compared to losses of 2.8% and 3.9%, respectively with placebo.

  Lorcaserin appears to have an impressive safety profile based on this data. Dropout rates due to adverse events were very low at 6-7% in the treatment arms and 5% in the placebo group. However, these rates were not entirely reflected in the overall completion rates, which were 57-59% for the lorcaserin groups and 52% for the placebo group. While these completion rates are relatively low, they are on par with most other obesity medication trials that have been done thus far. The weight loss data fell short of the Vivus Qnexa data also recently released (see below). In the EQUIP trial, Qnexa showed a mean weight loss of 14.7% in the high-dose completers, with an indication that the drug could improve cardiovascular risk factors. Overall, we believe these data are positive, especially in regards to safety, but assuming that Qnexa and Contrave make it through the FDA, lorcaserin will have significant competition. We look forward to lorcaserin's NDA being filed by year's end, as well as to a more detailed analysis of the BLOSSOM trial.

- **Novo Nordisk – Announces plans for new chronic inflammatory disease research center in Seattle:** Novo Nordisk announced, on September 18, that it plans to open a new

chronic inflammatory disease center in Seattle, Washington. Novo Nordisk currently has four projects in early clinical development on rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus. There was no mention of intentions to conduct diabetes research at the center, but we are curious to see if Novo Nordisk will eventually diversify its diabetes portfolio to include research that targets the anti-inflammatory pathways implicated in diabetes pathology. From what we understand, the inflammatory component of type 2 is something already being studied at the company, primarily in Denmark.

- **Intarcia – Begins enrolling patients for phase 2 trials of ITCA 650:** On September 17, Intarcia Therapeutics, Inc. (Hayward, CA) initiated enrollment for phase 2 trials of ITCA 650, a novel product for the treatment of type 2 diabetes. ITCA 650 provides continuous delivery of exenatide for extended periods of time using the DUROS technology platform, which draws on a proprietary formulation technology and a device that consists of an implanted subcutaneous pump (http://www.durect.com/pdf/duros_fact_sheet2001.pdf). The phase 2 trial will investigate the two doses that achieved the best results in the phase 1b study in a larger population with an extended duration of treatment. Patients will be recruited from 50 clinical trial sites in the US and will be randomized to receive either one of two doses of ITCA 650 or twice-daily injections of Byetta (Amylin). The company hopes to include 150 sub-optimally controlled type 2 diabetes patients in this 12-week trial. An extension study is also planned, in which patients in all three arms will be re-randomized to receive higher doses of ITCA 650 for an additional 12 weeks of study. The extension arm is designed to evaluate the tolerability of ITCA 650 at higher doses and to help the company select doses for phase 3 trials, which are expected to begin in the second half of 2010. This extension study should also provide information on the clinical utility of switching patients from Byetta to ITCA 650.
- **Baxter – Announces novel therapy for type 1 diabetes in preclinical stages; human studies expected to begin in 2011:** CEO Robert Parkinson led Baxter's 2009 Investor Conference Call on September 16. Notably, he announced a recent collaboration with Children's Hospital Pittsburgh to combine their microsphere formulation technology (PROMAXX) with antisense oligonucleotides (ASO), to create a novel treatment for type 1 diabetes. In the accompanying presentation, slides showed that the antisense technology targets three co-proteins that play an important role in immune activation CD40, CD80, and CD86. Their hypothesis is that down-regulating these proteins and blocking activation of the immune system will inhibit the mechanisms leading to beta cell destruction and type 1 diabetes progression. In a study by Phillips et al. (*Diabetes*, 2008) PROMAXX microspheres carrying these ASOs prevented type 1 diabetes in 80% of mice and also had the ability to reverse new-onset type 1 diabetes in non-obese diabetic (NOD) mice. Kenneth Burhop, VP of Global Pharmaceuticals R&D Medication Delivery, noted that Baxter's PROMAXX-ASO microspheres is still in preclinical stages and that Baxter plans to begin a single dose-escalating human clinical study in 2011. How excellent - we look very forward to following Baxter's entry into this aspect of diabetes.
- **Transition Therapeutics - Reports F4Q09 results; strong hopes for gastrin and gastrin/GLP-1 combination therapies:** In a call led by CEO Tony Cruz on September 16th, Transition Therapeutics announced fiscal 2009 year-end results (for a period ending June 30, 2009). Though little new information was reported, Cruz reviewed the year's developments for TT-223, Transition's lead gastrin-based compound. Gastrin is a hormone that plays a key role in gastric motility and has also been shown to have a role in regenerating beta cells. In F3Q09, the company initiated a phase 2 clinical trial to evaluate the safety and efficacy of TT-223 in patients with type 2 diabetes; results are expected early in F1Q10 (in Q&A he clarified that results wouldn't be seen before January). Additionally in F3Q09, Transition and partner Eli Lilly moved a combination of TT-223 and LY2428757 (once-weekly GLP-1) therapy into phase 1b trials. Cruz

reiterated from F3Q09 that other longer-acting gastrin-based therapies have been developed through this partnership – with the potential to move some into further stage development – though specific compounds were not mentioned. At the end of fiscal year 2009, Transition had cash, cash equivalents, and short-term investments of 45.6 million CAD ($39.1 million USD) and Cruz suggested that this was sufficient to continue operations at least until mid-fiscal year 2011.

- **Lexicon Pharmaceuticals – Begins phase 2 trial of its SGLT2 inhibitor, LX4211:** On September 15, Texas-based Lexicon Pharmaceuticals announced the completion of phase 1 studies of its SGLT2 inhibitor, LX4311, and the initiation of a phase 2 clinical trial. The SGLT2 protein is responsible for the majority of glucose reabsorption in the proximal tubule of the kidney. Inhibition of SGLT2 enables secretion of excess glucose into the urine. Results from the phase 1 trial demonstrated that LX4211 was well tolerated at all dose levels, resulting in dose-dependent urinary glucose excretion. Adverse events were mild and observed in all dose groups, including the placebo group. Further details of phase 1 data have not yet been released. Lexicon is currently initiating a four-week phase 2 trial (n=36) evaluating the safety and tolerability of two dose levels of once-daily LX4211 for the treatment of type 2 diabetes (dose levels have not been specified). Lexicon is one of several companies pursuing an SGLT2 inhibitor—Bristol-Myers Squibb/AstraZeneca's dapagliflozin is currently the farthest along in development, now in phase 3 trials. Among thought leaders, concern regarding the side effects of SGLT2 inhibitors appears to be mixed, especially regarding the risk of increased rates of urinary tract infection. From completed trials of other SGLT2 inhibitors, the risk of urinary tract infections has not been shown to be markedly increased in the treated groups.
- **Eli Lilly – Announces new operating model and names Enrique Conterno the head of the diabetes unit**: On September 14, Eli Lilly announced a major reorganization of its pharmaceutical business and named new leaders of each business unit. The company's pharmaceutical business will be organized into four units: oncology, diabetes, established markets, and emerging markets. The head of the diabetes unit will be Enrique A. Conterno, currently the president of Lilly USA. As part of this company-wide reorganization, Eli Lilly is also establishing a Development Center of Excellence (COE), which will aim to streamline the development of late-stage pharmaceuticals. Dr. Tim Garnett, MD, will oversee medical, regulatory, global product safety, translational medicine, and global health outcomes at the COE while Tom Verhoeven, PhD, will be responsible for the clinical development organization, product R&D, toxicology/ADME, and project management. Lastly, the company announced a goal of cutting costs by $1 billion and reducing its workforce to 35,000 by the end of the year (according to Thompson, the current headcount is 40,500). We look forward to hearing more details about this reorganization and cost structure reduction during Eli Lilly's upcoming investment community day on December 10, 2009.
- **Amylin – Developing anti-diabetes "phybrid" with Biocon:** Amylin Pharmaceuticals announced on September 10 that it will jointly develop, commercialize, and manufacture a novel anti-diabetes therapeutic with India-based biotechnology company Biocon. The two companies have entered into an exclusive agreement to collaborate on the development of a novel peptide compound—a phybrid, or peptide hybrid molecule, combining the pharmacological effects of two unique peptide hormones with additive or synergistic therapeutic attributes into a single molecular entity. According to the agreement, Amylin will be responsible for providing expertise in peptide hormone development and harnessing the power of their phybrid technology in designing the novel compound. Biocon will offer expertise in recombinant microbial expression technology for the manufacturing of the compound and will also employ its experience in preclinical and clinical development of diabetes products. No details have been disclosed about the identity of the compound, but we suspect that it could be Amylin's AC-164209, purported to

be a peptide hybrid linking a GLP-1 agonist to an amylin mimetic, or a variation of this compound. The companies may choose to differentiate from drug classes already in development, but we would be surprised if they do not tap into at least one of their peptide franchises for the combination (amylin, leptin, and PYY). Combination therapies have the potential to alleviate the effects of parallel pathway compensation that work against the efficacy of monotherapy agents. Uniting two agents into a single molecular entity could streamline the manufacturing process, simplify drug delivery, ease the regulatory path, and increase patient convenience and tolerability due to the tendency for these drugs to have fewer side effects. However, the generation of any novel entity also carries the potential for unforeseen side effects. This is clearly an ambitious endeavor, but Amylin seems to be taking steps to position itself advantageously through a partnership with Biocon. We are intrigued by this development and look forward to gathering more information.

- **Oramed Pharmaceuticals – Begins clinical trials with oral GLP-1 analog, ORMD 0901:** Oramed Pharmaceuticals, Inc. announced on September 10, that it had received Institutional Review Board (IRB) approval to commence human clinical trials of its oral GLP-1 Analog, ORMD 0901. This approval follows Oramed's favorable pre-clinical results. The clinical trials will be conducted on healthy volunteers at Hadassah University Medical Center in Jerusalem, Israel. Currently available GLP-1 analogs are all injectable drugs, and patient ease of use is an important factor in the success of type 2 diabetes drugs as the market expands to include novel classes of drugs (at least nine by our current count). Other companies pursuing oral GLP-1 formulations include Novo Nordisk working with Emisphere and Merrion Pharmaceuticals and Unigene. Oramed is also currently conducting Phase 2b clinical trials for its flagship product, an oral insulin capsule, ORMD-0801.

- **Vivus – Announces striking phase 3 EQUIP and CONQUER results for Qnexa:** In a conference call on September 9 led by President and CEO, Leland Wilson, Vivus announced impressive results from two phase 3 trials evaluating the safety and efficacy of low, medium, and full doses of Qnexa (phentermine + topiramate): EQUIP (OB-302) and CONQUER (OB-303). The two trials were placebo-controlled, double blind, and randomized, and included over 3,750 morbidly obese patients (BMI >35 kg/m^2) at 93 sites over a 56-week period. In the EQUIP study, 1,297 morbidly obese (BMI >35 kg/m^2) patients were treated with placebo, low-dose (3.65 mg phentermine/23 mg topiramate) Qnexa, or full-dose (15 mg phentermine/92 mg topiramate) Qnexa for 52 weeks after a four-week titration period. Patients treated with both the low-dose and full-dose Qnexa met the FDA's categorical and mean efficacy endpoints. Based on the ITT-LOCF (intent-to-treat last observation carried forward) data analysis, patients on low-dose Qnexa achieved 5.1% (13 lbs) mean weight loss and patients on full-dose Qnexa achieved 11% (28 lbs) mean weight loss, while placebo patients lost 1.6% (4 lbs). Nearly 45% of low-dose Qnexa patients and 67% of full-dose Qnexa patients lost 5% or more of their weight in the intent-to-treat group, compared to 17% of placebo patients. Of completers, 26% of placebo lost 5% of weight, 59% on the Qnexa low dose, and 84% on the Qnexa high dose. From a commercial perspective, we believe percentages of patients losing 10% or 15% of their weight are far more important than the 5% group. 12% of placebo patients lost 10% of their weight or more, compared to 27% on the Qnexa low-dose and 60% on the Qnexa full-dose. 5% of placebo patients lost at least 15% of their weight, compared to 11% on the Qnexa low-dose and 43% on the Qnexa full-dose.

  In the CONQUER study, 2,487 obese patients with two or more co-morbidities were treated with placebo, mid-dose (7.5 mg phentermine/46 mg topiramate) Qnexa, or full-dose Qnexa for 52 weeks after a four-week titration period. The majority of patients in this study had prediabetes (16% of patients had diagnosed diabetes), hypertension, and/or dyslipidemia. Using ITT-LOCF analysis, patients treated with both mid- and full-dose Qnexa also met both the categorical and

average weight loss endpoints as defined by the FDA. Mid-dose Qnexa patients achieved weight loss of 8.4% (19 lbs) and full-dose Qnexa patients achieved weight loss of 10.4% (24 lbs),compared to weight loss of 1.8% (4 lbs) with placebo. In the categorical response, 62% of mid-dose and 70% of full-dose Qnexa patients had weight loss over 5%, compared to 21% of placebo patients. The response was more robust, as expected, in the completed patient data analysis, representing patients completing 56 weeks of treatment, with weight loss of 10.5% (24 lbs) in the mid-dose Qnexa group and weight loss of 13.2% (30 lbs) in the full-dose group, compared to weight loss of only 2.4% (6 lbs) with placebo. Ten percent of placebo patients lost at least 10% of their weight compared to 49% on the Qnexa low-dose and 64% on full-dose. Four percent of placebo patients lost at least 15% of their weight, compared to 26% on the Qnexa low-dose and 39% on the full-dose. Regarding secondary endpoints, for full-dose patients, a significant reduction in systolic blood pressure of 20.4 mmHg was observed as well as a 95-98 mg/dL decrease in triglyceride levels in the mid- and full-dose treatment groups. Both doses significantly improved diabetes risk factors over placebo including significant reductions in A1c of 0.5-0.6% from a ~7% baseline with virtually no (less than 1%) hypoglycemia. Notably, both doses also showed marked improvement over placebo in inflammatory risk factors including decreased CRP and increased adiponectin.

The most commonly reported side effects for high dose Qnexa in both studies were dry mouth (17-21%), tingling sensation (19-21%), constipation (14-17%), upper-respiratory tract infection (12-13%), and altered taste (8-10%) with the majority of cases characterized as mild. The combined study completion rate for Qnexa full-dose was 62%, Qnexa mid-dose was 69%, and Qnexa low-dose was 57%, compared to 53% completion in placebo (9-18% ended the trial for reasons related to side effects and we wonder what else led people to discontinue). Qnexa used also showed no association with suicide – due to CNS issues with former obesity drugs, this is being followed very closely.

We look forward to more detailed analyses at The Obesity Society in late October. The company plans to submit the data to the New England Journal of Medicine and to show it at major diabetes, obesity, cardiology, and primary care provider meetings. Vivus is still on track for an NDA submission to the FDA by the end of 2009 and is currently looking for collaborators for the rollout and launch of the drug, pending approval. We predict, assuming no surprise safety issues, strong partner interest will ensue given the positive efficacy data and reassuring safety data profile. Even if not every patient experiences positive results with Qnexa (~30-40% did drop out of the trial), clearly there are more than enough obese patients who could potentially benefit. Broadly speaking, we also believe these results bode well for the pursuit of combination therapies, particularly therapies previously unsuccessful at high doses but that might be more successful at lower doses. If the drug could ultimately be viewed as cardioprotective, this would considerably increase the potential commercial success of the drug.

- **Takeda – Receives complete response letter from FDA on the fixed dose combination therapy of alogliptin plus Actos:** On September 4, Takeda announced its receipt of a formal response letter from the FDA on its fixed dose combination therapy consisting of alogliptin and Actos. According to management, the response letter is consistent with the response letter issued by the FDA on June 26, 2009 for alogliptin monotherapy. As for the monotherapy, the FDA seems to be looking for a larger study with more CVD deaths so it can assess whether alogliptin has a safe CVD profile. This response letter follows up the recent approval of Takeda's new safety trial, EXAMINE, designed to satisfy the FDA's requests for more safety data on alogliptin (for more information on EXAMINE, see "Takeda – Initiates EXAMINE Cardiovascular Study of Alogliptin" below). The latest full response letter comes as no surprise as any combination therapy is typically judged heavily on its monotherapy components. Takeda

announced that it believes the results from the EXAMINE study will support the resubmission of both the alogliptin monotherapy and the alogliptin plus Actos combination therapy. Takeda recently made clear through patent suits against Torrent Pharmaceuticals that it intends to defend the Actos patent for as long as possible by claiming infringement on its combination therapies containing Actos. Overall, we feel very disappointed for Takeda on the turn of events at FDA. The drug seems very comparable to Onglyza and Januvia and certainly not different enough to prompt such a completely different regulatory path pre-approval. FDA hasn't provided any public rationale and we hope the new approach doesn't cause companies and investors to turn away from developing innovative new therapies. Although this DPP-4 inhibitor itself may not be novel, we believe potential combinations could be.

- **Sanofi-aventis – Grants awarded to improve diabetes management in the Middle East:** On September 3, Sanofi-aventis announced that five doctors in Bahrain and the United Arab Emirates (UAE) were awarded grants to implement new research projects to improve diabetes screening and care in the Persian Gulf. This region has been particularly hard hit by diabetes; in the UAE, for example, approximately 25% of all adults have diabetes (including 40% of people over 60 years old). This is estimated to be the second highest prevalence worldwide; the first is Nauru, followed by the UAE, Saudi Arabia, Bahrain, Kuwait, Oman, Tonga, Mauritius, Egypt, and Mexico. The awards are part of Sanofi-aventis' DEVOTED initiative, aimed at improving diabetes care in the Middle East. Grants were distributed in June 2009. We applaud Sanofi-aventis for funding the DEVOTED initiative – the prevalence of diabetes has been gradually increasing in the Middle East, with over three million people diagnosed in the Persian Gulf region, and thus a clear need exists for more prevention and awareness programs.
- **Diamyd Medical – Four-year follow-up with Diamyd vaccine shows positive results; expanding into phase 3 trials in the US:** In a press release on September 3, Diamyd Medical announced positive results from the four-year follow-up of a phase 2 trial with Diamyd (rhGAD65), its vaccine for type 1 diabetes. The Swedish-based trial examined nearly 70 patients recently diagnosed with type 1 diabetes (within 18 months); participants were treated with two injections of 20 μg Diamyd four weeks apart. The primary endpoint of interest was residual insulin secretion as measured by fasting serum C-peptide levels. While detailed results were not reported, the company indicated treated patients had "a clearly better diabetes status" compared to the placebo group at the four-year follow-up with no serious adverse events reported. As a reminder, initial results from the trial presented at this year's ADA (also in print; NEJM 2008) suggested a significantly slower decline in fasting C-peptide levels from baseline in patients from the treatment group after 30 months; however, no corresponding change in insulin requirement was evident. We are waiting for more detailed commentary than "clearly better" since this phrase is hard to interpret meaningfully. This phase 2 trial lasted seven years and two-thirds of participants elected to stay enrolled until the trial was completed; this is characterized as a positive in the press release although we think that losing so many of the original participants is disappointing given that follow up was likely straightforward (that said, we realize loss to follow up is complicated due to moves, patients not staying in touch, etc.)

  A global phase 3 program (in nine European countries and a parallel study in the US) with the Diamyd vaccine is currently underway and aims to include a total of 640 children and adolescents recently diagnosed with type 1 diabetes. As of September 1, 2009, the US-based trial will examine children ages 10-20, expanded from the initially designated limits of 16-20 years. This follows the FDA's decision in June to decrease the lower age limit. Diamyd Medical is also in negotiations to increase the number of participating clinics from 13 to 40. The company hopes to achieve market approval for the Diamyd vaccine in 2012. While the drug still seems far from achieving the ultimate goal of preventing the onset of type 1 diabetes, evidence of a slower decline in fasting C-

peptide levels and comparatively better diabetes status four years after treatment suggests beta cell protection could be occurring. We think this is a step towards eventually reaching the final goal of preventing type 1 diabetes and we look forward to the results of this phase 3 trial.

- **Amgen – TREAT study of Aranesp shows no significant difference versus placebo in cardiovascular and renal endpoints:** Amgen released topline results of its Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) for patients with type 2 diabetes on August 25. Aranesp (darbepoetin alfa, marketed by Amgen) stimulates the production of red blood cells and is currently used to treat anemia. In patients with chronic kidney disease, cells that secrete erythropoietin (which promotes the production of red blood cells) may be damaged, and patients often become anemic. Anemia puts additional strain on the cardiovascular system of patients with chronic kidney disease, which can lead to heart failure. The randomized, controlled, phase 3 trial of Aranesp involved 4,044 patients with type 2 diabetes, anemia, and chronic kidney disease without dialysis. The treatment group was titrated on Aranesp until their hemoglobin was elevated to 13 g/dl (which is within the normal biological range for men and women). Primary outcomes of the study were a composite cardiovascular endpoint (cardiovascular morbidity or all-cause mortality) and a composite renal endpoint (time to all-cause mortality or chronic renal replacement therapy). With both endpoints, no significant difference was detected between the treatment and placebo group. Two previous studies had shown increased rates of all-cause mortality and cardiovascular morbidity in patients titrated to target hemoglobin concentrations >13 g/dl compared to those with targets of <13 g/dl. This new information suggests that Aranesp may be safely titrated to help patients achieve closer to normal hemoglobin levels, which are typically 12-16 g/dl for women and 13-18 g/dl for men.
- **Piramal Life Sciences – Completes two phase 1 trials with novel insulin sensitizer:** On September 2, India-based Piramal Life Sciences announced its novel anti-diabetic P1736 successfully completed two phase 1 trials. The trials, conducted in the Netherlands, included a single ascending dose study (up to 1600 mg P1736) in 30 healthy volunteers and a multiple ascending dose study (200 and 1000 mg P1736) in 22 healthy volunteers. The company reported that the compound was well tolerated in both studies, with no serious adverse events. Additionally, P1736 did not demonstrate any adverse effects on liver function or cause blood plasma volume expansion or weight gain. As a reminder, P1736 is an oral drug shown to increase insulin sensitivity and lower blood glucose in animals. Unlike the thiazolidinediones (TZDs), the compound does not activate PPARγ. While initial animal studies have demonstrated less of an insulin-sensitizing effect compared to the TZDs, these phase 1 results suggest a possible lower side effect profile; we suspect the compound will likely be used in combination, if approved. We look forward to hearing more about the efficacy of P1736 in human trials; Piramal is currently planning further studies to assess safety and efficacy in patients with diabetes.
- **Medtronic – Undergoes major organizational and leadership changes while the Paradigm Veo is launched in over fifty countries:** Medtronic announced, on September 2, several internal leadership and organizational changes designed to promote the company's One Medtronic initiative, and better leverage technologies and customers. The company's various businesses will be consolidated into two operating groups; one operating group will consist of the Diabetes, Surgical Technologies, Spinal and Biologics, and Neuromodulation businesses while the other operating group will be comprised of the Cardiac Rhythm Disease Management (CRDM), CardioVascular, and Physio-Control businesses. In terms of management changes, Chris O'Connell will be leaving his position as president of the Diabetes business to assume the newly created position of executive vice president and group president for the new operating group containing the Diabetes business. Katie Szyman will be replacing O'Connell as the President of Medtronic Diabetes. Szyman has been with Medtronic since 1991, when she started as an internal

auditor; she has since served in international finance positions for the company and most recently as the senior vice president of Strategy and Innovation for the company's Cardiovascular business unit. As we understand it, she knows the hospital glucose monitoring area well and backed a major investment in this space last year.

These changes come amidst the widespread launch of Medtronic's new CGM-ready low glucose suspend insulin pump, the Paradigm Veo—now launched in over 50 countries across Europe, Asia, Africa, Canada, and Latin America. The Veo is the first sensor integrated pump with an automatic basal insulin shut-off mechanism, which could prevent severe hypoglycemia. Chris O'Connell has called the device revolutionary and suggests that it is the next step in the quest for a closed-loop system. The automatic shut-off mechanismsuspends basal insulin delivery for two hours if the user is not responsive to hypoglycemia alarms from the CGM component of the device. Medtronic is currently working with the FDA to gain approval to market the product in the US; in the meantime, it plans to release the Revel later this year in the US, which has all the same features as the Paradigm VEO except the LGS, with the major new difference being that it has predictive alerts.

- **Takeda – Initiates EXAMINE cardiovascular study of alogliptin:** On August 31, Takeda received approval from the FDA for a cardiovascular study of alogliptin, which they have titled EXAMINE (EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome). Presumably, results of this trial are needed before the FDA will approve alogliptin. We imagine approval for alogliptin is sought as soon as possible since Actos goes generic in 2011. Following evaluation of alogliptin's NDA, the FDA requested further cardiovascular safety studies based on its new cardiovascular guidance for antidiabetic therapies (for more information on the formal FDA response letter, see "Takeda – Receives Complete Response Letter from FDA on the Fixed Dose Combination Therapy of Alogliptin Plus Actos" above). Nancy Joseph Ridge, MD, General Manager of Takeda's Pharmaceutical Development Division, stated that they anticipate interim results from EXAMINE to be submitted to the FDA in two years. The study is scheduled to begin in September 2009 and end in December 2014, with an expected cohort of approximately 5,400 patients with type 2 diabetes. As we understand, the patients sought for the trial will have had a cardiovascular event already; in our view, although DPP-4 inhibitors are often aimed at those newly diagnosed, in order to get through a trial of this length, patients who have had CVD events will help the trial gather the required amount of events as well as proceed at a faster pace. The primary outcome of the study will be the time from randomization to the occurrence of a "primary major adverse cardiac event," defined as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The time from randomization to the occurrence of a secondary major adverse cardiac event will serve as a secondary outcome. While Takeda will face tough competition entering the US market if and when EXAMINE is completed (in addition to Merck's Januvia, BMS/AZ's DPP-4 inhibitor Onglyza recently received FDA approval on July 31st), we do feel the potential to combine alogliptin with a TZD in one pill offers a potentially unique advantage – and also that the potential DPP-4 inhibitor market itself is quite big.
- **Ipsen – Reports 1H09 results:** Ispen announced first half-year 2009 results in a call on August 28 led by CEO Jean-Luc Bélingrad. While no developments were mentioned in terms of either the GLP-1 analog taspoglutide (being developed in partnership with Roche) or the melanocortin receptor 4 (MC4) agonist BIM-22493 for the treatment of obesity, management noted that the company has received €10.9 million ($14.6 million USD) in milestone payments in 1H09, mainly driven by partnerships with Roche for taspoglutide and a treatment for cervical dystonia. As a reminder, at an investor day held in January, Ipsen indicated taspoglutide would be a once-weekly injection using a 29-gauge needle, considerably smaller than the anticipated 23-

gauge needle for exenatide LAR. The drug is currently in phase 3 trials, with initial results expected by 4Q09 or 1Q10. BIM-22493 remains in preclinical studies as far as we understand it.

- **Abbott – Submits 510(k) for updated FreeStyle and FreeStyle Lite test strips:** In a press release on August 28, Abbott announced its submission of 510(k) applications to the FDA for the clearance of its new FreeStyle and FreeStyle Lite blood glucose test strips. The updated test strips will use the glucose dehydrogenase flavin adenine dinucleotide (GDH-FAD) enzyme rather than the controversial glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) enzyme that is used in current strips. As the new strips will be compatible with all FreeStyle systems, the company indicated that patients need not switch from their current meters; Abbott also noted that patients can continue to use their current strips as long as they are not using an interfering drug product or therapy. This announcement comes at the heels of the FDA's public health notification on August 13 regarding errors that can occur for the population of patients (estimated by the FDA at 40,000) who are taking therapies that interfere with the GDH-PQQ enzyme. We believe Abbott had already begun shifting in manufacturing toward the GDH-FAD enzyme some time ago – though the FDA's notification likely accelerated the 501(k) filing. We expect Roche and HDI, which both currently market strips using the GDH-PQQ enzyme, to follow suit and file similar 501(k) forms soon (as we understand, both companies also indicated previously initiating shift in manufacturing). Overall, we appreciate that the affected companies are addressing the problem quickly.
- **Aegis Therapeutics – Announces joint commercialization agreement for anti-obesity OB-3 peptide with Albany Medical College:** On August 26, Aegis Therapeutics and Albany Medical College announced a joint commercialization agreement to advance the clinical development of the OB-3 peptide, Albany's patented anti-obesity therapy. This is an expansion of the license agreement made in May 2005; under the new agreement, Aegis will be responsible for finding a partner to commercialize the novel drug. The OB-3 peptide was discovered by researchers at Albany Medical College in 2000 and consists of a small portion of leptin, a protein hormone involved in appetite control. The formulation in development makes use of Aegis' Intravail delivery technology to improve the oral bioavailability of the peptide, leading to greater than 50% of the bioavailability of the injectable formulation. Initial studies in animal models have suggested both a reduction in caloric intake and possible effects on glucose metabolism, indicating potential applications in diabetes. Oral formulations of peptide drugs typically prove ineffective – however, success with Intravail technology could indicate broader applications, given the increasing use of peptide-based therapies in diabetes and obesity care.
- **Medtronic — Reports F1Q10 results and announces restructuring of R&D model:** In a call led by CEO Bill Hawkins on August 25, Medtronic reported its fiscal 1Q10 results, announcing insulin pump and CGM revenue of $295 million, up 10% (15% on constant currency basis), from $269 million a year ago. This reflected effectively flat revenue versus a quarter ago (fiscal 4Q09) overall; we think CGM growth is positive and pump revenue is down slightly, which most likely reflects some accounting for the infusion set recall last quarter. Notably, US revenue of $193 million grew 15% compared to a year earlier while no change occurred in international revenue from 1Q09, with $102 million reported this quarter. Management cited solid CGM and insulin pump sales as drivers of growth, especially in light of the challenging economic climate. (These growth rates are unsurprising given that the comparison was an easy one in the US versus 1% growth a year earlier and a challenging one internationally given over 30% growth a year earlier – though knowing precisely how to account for CGM hardware vs. sensors is difficult.) The recall of Quick-set infusion sets was only briefly mentioned; management noted its aggressive response, with over 158,000 patients reached for replacement in the first few days of the recall. The recall amounted to a $16 million charge on the income statement; next quarter, we expect a lower

charge. We also expect the total charge (which is expected to be reimbursed) to be in the ballpark of $30 million. Management noted that the Revel, its new sensor-augmented insulin pump for the US market, is on target to be released in the US later this year.

Medtronic will have to strategically navigate the pump market, even if the Paradigm Veo is approved. In 2010-2011 in the US, Medtronic will face increased competition from Insulet and Animas, which are both planning to submit a sensor-integrated CGM/OmniPod by end of year or early next year and from other companies breaking into the pump market such as Medingo with its new Solo MicroPump. Generally, we feel that the disposable, patch, and detachable pumps will expand the pump market; the integrated pumps (and to a lesser extent, the disposable, patch, and detachable pumps) could be an opportunity for competitors to take share from Medtronic, although Medtronic's new pump platform is also an opportunity for the leader to take share from traditional competitors. This market is highly dynamic in our view, and we look forward to even faster innovation as the players battle for market share.

- **Verva – Announces licensing agreement with Isis Pharmaceuticals:** On August 20, Verva Pharmaceuticals, an Australian-based clinical-stage pharmaceutical company focused on novel diabetes and obesity therapies, announced an exclusive licensing agreement with Isis Pharmaceuticals regarding Verva's Fibroblast Growth Factor Receptor (FGFR) antisense therapy (FGFR4) for the treatment of metabolic disorders, particularly obesity. The license grants Isis exclusive intellectual property rights for the therapy and a right of first refusal to license the intellectual property. In return, Verva has received an upfront payment (undisclosed amount) and is eligible for future milestone and royalty payments. FGFR4 utilizes antisense technology to inhibit gene targets in the FGFR pathway, which includes the family of FGF receptors and other biological targets associated with obesity. Inhibition of the FGFR pathway has already been shown to prevent fat cell formation, lower body weight, and improve insulin sensitivity in animal models. Currently, FGFR4 is in the preclinical stage of development. Overall, we believe that this is a beneficial partnership, as Isis is heavily focused on antisense technology drug development, with multiple drug candidates for the treatment of diabetes. We look forward to hearing future developments from this partnership, particularly early-stage clinical trials.
- **FDA – Issues public health notification regarding certain blood glucose meter test strips associated with maltose:** On August 13, the FDA issued a public health notification regarding potentially fatal errors that can result from using glucose test strips incorporating the GDH-PQQ enzyme. These errors are relevant to patients who are taking interfering therapies (largely dialysis-related therapies) containing specific non-glucose sugars, which can artificially elevate blood glucose readings three to 15 times laboratory readings. While the FDA estimates the at-risk patient population to be 40,000, executives at a couple of organizations have pointed out the population is actually likely closer to 70,000-110,000. Since the at-risk population is meaningful from an absolute perspective, because it only affects a small percentage of SMBG users, we don't expect major implications for patients nor do we do expect meaningful share shifts. While some higher costs will be incurred by companies undergoing manufacturing shifts to address this problem, Abbott has already submitted 510(k) applications for updated strips (for more information on Abbott's response, see "Abbott – Submits 510(k) for updated FreeStyle and FreeStyle Lite test strips" above). We believe this news signals a stricter FDA; we also look for the agency to reduce margin of error for glucose meters from 20% to the 10-15% range in the near future. Overall we believe Abbott and Roche are taking proactive, responsible measures.

— *by Sanjay Trehan, Eric Chang, Tony Sheng, Jessica Swiencowski, Nick Wilkie, and Kelly Close*

4. DCU Interview with Dr. David Maggs, Senior Director of Medical Affairs at Amylin Pharmaceuticals

In the midst of the engaging ADA's 69th Scientific Sessions in New Orleans, LA, Dr. David Maggs (Amylin Pharmaceuticals, Inc.) sat down with us to discuss conference trends and prospective therapies in Amylin's pipeline. Dr. Maggs noted that the evolving metabolic vision for diabetes seen at this year's ADA complimented the broad hormonal effects observed with GLP-1 agonists. He went on to describe the broader, neural effects of GLP-1 agonists, the potential for Byetta use in patients with early onset type 2 diabetes, and the safety profile of Byetta with respect to thyroid carcinoma. He also reflected on the potential hormonal effects underlying bariatric surgery (widely characterized as diabetes surgery at this year's ADA).

Dr. Maggs described the current status of obesity therapies in development at Amylin, including davalintide and pramlintide/metreleptin combinations. While most excited about the prospect of exenatide once weekly, a therapy for the treatment of type 2 diabetes currently under FDA review, Dr. Maggs also expressed cautious enthusiasm about alternative routes for exenatide administration including nasal and transdermal routes. Broadly, he said, Amylin's robust pipeline includes several diabetes and obesity candidate therapies that have great potential. We look forward to the FDA's decision on exenatide once weekly, which has a PDUFA date of March 5th 2010, and look forward to further data emerging from the Amylin pipeline.

We were particularly taken by promising preliminary data from the 28-week, phase 2 dosing trial of its pramlintide/metreleptin obesity therapy. The study found that patients with a baseline BMI <35 kg/m2 treated with the highest pramlintide/metreleptin doses (360 mcg/5 mg, respectively) experienced an average weight loss of 11%, or 22 lbs (10 kg), compared to placebo. While these data are promising, we are interested in understanding whether leptin resistance is affecting efficacy in more severely obese patients. We look forward to hearing future developments regarding the pramlintide/metreleptin therapy, as Amylin hopes to finalize its funding and development strategy for its obesity program by the end of 2009.

PATHOPHYSIOLOGY OF BODY WEIGHT CONTROL

KELLY CLOSE: There has been a lot of talk about weight control and obesity at this year's ADA – even more than last year. Can you talk a little about this shift and about body weight control specifically for people with diabetes?

DR. DAVID MAGGS: We initially thought that there wasn't enough focus on weight control, particularly when we saw that the focus of attention regarding the VADT and ACCORD trials emphasized concerns regarding neuropathy and hypoglycemia, and little mention of the body weight effects in the trials. However, it has been encouraging in the meeting as a whole that there has been a focus on the wider metabolic defects associated with diabetes and the importance of body weight control, not just the glucose-centric view. The question of body weight control is really a question of having to consider lipotoxicity as well as glucose toxicity, and if you think about where the type 2 diabetes world is going right now, there will be an increasing focus on body weight control coupled with efforts to improve glycemia. The message is no longer simply the glucose-centric "give insulin back" view; it's more about the wider metabolic effect of excess adiposity and its relation to hyperlipidemia, proinflammatory states, and vascular endothelial function. GLP-1 agonism is set up beautifully to address the metabolic disarray of type 2 diabetes: it takes the burden off of the beta cell, corrects abnormal glucagon secretion, impacts food intake and body weight control, and possibly has positive effects on lipids and the cardiovascular system.

KELLY: We certainly see a greater focus this year on correcting the underlying pathophysiology of diabetes, rather than simply lowering glucose. Can you talk a little more about the focus on glucagon?

DR. DAVID MAGGS: Excess postprandial glucagon is a well recognized problem in diabetes, but may be recognized by only a small group of physicians. When you go outside of this group to the wider group of physicians, many think that diabetes is a state of glucagon deficiency; glucagon deficiency is indeed observed in type 1 patients, but only during hypoglycemia. In fact, excess postprandial glucagon is present in patients with both type 1 and type 2 diabetes, it's a key contributor to hyperglycemia, and it's likely an earlier defect within the islet - where some have reported that you see elevated glucagon levels before you see subtle changes in insulin secretion.

KELLY: That's really interesting. Insulin resistance has commonly been thought of as the first defect – do I have that right? If so, could you address where the insulin resistance defect is coming from and its relation to glucagon?

DR. DAVID MAGGS: Generally insulin resistance is seen as a separate entity, a background defect that manifests itself in a quarter to a third of the general population. However, you can accelerate the manifestations of insulin resistance by becoming overweight early in life, which is increasingly the case with the younger population. Then there is a sizeable subset of individuals with insulin resistance who also have defective beta cell function. The combination of these two defects, with more severe insulin resistance burdening the defective beta cell, results in type 2 diabetes being seen now in 13-year-old kids rather than your 70-year-old grandfather. Glucagon comes into the picture with the interaction between the beta cell and the alpha cell. Under normal conditions, the beta cell helps regulate the alpha cell where insulin release suppresses glucagon release. So, if the beta cell, after working upstream against the increased demands of insulin resistance starts to fail, one of the first things that you see is that the alpha cell starts to release too much glucagon. So, glucagon excess is actually one of the earlier defects seen in patients with diabetes.

HORMONAL EFFECTS OF BARIATRIC SURGERY

JOHN CLOSE: Fascinating. We are also covering bariatric surgery, which some experts are now calling metabolic/diabetes surgery. Could you talk about whether this surgery is causing remission from type 2 diabetes and associated conditions such as dyslipidemia? It seems like the underlying mechanism is less about the "re-plumbing" of the surgery and more about subsequent changes in hormonal regulation. Is that an appropriate way to think about it?

DR. DAVID MAGGS: This is actually a very interesting story if you look at it from a GLP-1 perspective as an example. Let's just say that GLP-1 levels in a healthy individual are around 10-20 pmol/L and the levels of exenatide you achieve when taking Byetta are in the range of 50 pmol/L. If you measured GLP-1 levels in patients within days or weeks of bariatric surgery, their GLP-1 levels would be up around 100-150 pmol/L. So what we're seeing after surgery is an incretin hypersecretion that has also been reported to be present years after surgery. The short answer to your question is that the sudden improvement in metabolic state in diabetics who have had surgery has been solely attributed to incretin hypersecretion. However, this may be overly simplistic as many other hormonal changes occur following surgery, such as changes in PYY levels, and the mechanism is likely to be more complex.

There is also a subset of patients who get significant refractory hypoglycemia around two to four years after surgery. These patients have been reported to have very high GLP-1 levels around 200 pmol/L or more—far higher than the GLP-1 levels seen with DPP4 inhibition or the exenatide levels seen with either Byetta or exenatide once weekly. It is speculated by some that these excessive GLP-1 levels may be solely responsible for such hypoglycemia but again this may be overly simplistic — remember patients have had

surgery, there is now disturbed anatomy and not every surgery has the same outcome, and again there are many other neurohormonal changes that occur as a consequence of the surgery.

KELLY: How hard is it to measure these effects, and what do you do after you identify refractory patients? And do you have a sense how common this is?

DR. DAVID MAGGS: It is relatively straightforward to identify patients with this problem by measuring blood glucose when symptoms arise. As this is a relatively new clinical phenomenon, treatment options are still being explored but in very severe cases surgery may have to be considered. To your second point, it is not clear how common this is but it is seen in small numbers of patients in large centers where a high volume of surgery is being carried out.

JOHN: If bariatric surgery-induced weight loss is largely mediated by hormones, do you think the amount of weight loss from combination hormone therapies will ever approach what can be accomplished with bariatric surgery?

DR. DAVID MAGGS It is hard to say right now. No one fully understands the hormonal, or should I say neurohormonal, disturbance that occurs through bariatric surgery—a combination of altered anatomy and changes in hormonal and neural signals between the gut, fat stores, and the brain. I think our data in rodents and now in humans showing that the combination of a gut signal like amylin and leptin, a fat borne protein, results in impressive weight loss may be just scratching the surface. As we learn more about this field, it is conceivable that the extraordinary weight loss seen with bariatric surgery could be harnessed in some pharmacologic platform.

AMYLIN'S PIPELINE PROSPECTS

KELLY: Switching gears, could you just talk about which prospects you are most excited about in your pipeline given how robust it is across a number of areas?

DR. DAVID MAGGS: First and foremost, we are most excited about exenatide once weekly, as it has the potential to be a paradigm shifting therapy. We also cannot ignore other explorations with the exenatide molecule. We have been looking at alternative delivery routes such as the nasal platform, which is of particular interest to us. We also have some very preliminary data suggesting that exenatide gets into the bloodstream through transdermal administration using the Altea technology. However we don't have enough data yet to know whether these two alternate platforms are ready for more rigorous experimentation.

JOHN: I'd like to ask you to talk a little bit about Amylin's integrated neurohormonal approach to the treatment of obesity. We've been impressed by the rat data that Amylin has published regarding weight loss with a combination therapy consisting of PYY, leptin and pramlintide. Can you speculate as to how this research might translate to humans, as this combination is not being tested in human trials that we know of?

DR. DAVID MAGGS: In obese patients, leptin resistance is common, so if you administer leptin alone you do not see any weight loss. However, giving leptin with a gut-brain signal in the form of amylin (or its analog pramlintide) seems to sensitize the brain to leptin and induce weight loss. This is the foundation for the pramlintide/metreleptin anti-obesity combination we are currently working on [Editor's note: top-line data for this study was announced shortly after the time of this interview. As previously reported in Closer Look, the pramlintide/metreleptin combination was shown to produce an average weight loss of 11%, or 22 lbs (10 kg), in patients with a BMI <35 kg/m^2].

With regard to the triple combination therapy, we have been looking at PYY over the years, and you are correct that the triple combination of leptin, amylin and PYY looked very promising in rodent studies. We

hope to first demonstrate that significant weight loss is associated with the pramlintide/metreleptin combination. If so, it opens a path to pursuing an actual anti-obesity indication. It, of course, also opens the door to exploring the possibility of the triple combination therapy further down the road.

JOHN: Is there any talk of a partner for the metreleptin/pramlintide combination therapy, or of any alternative methods for administration?

DR. DAVID MAGGS: It is no secret that we have been in partnership discussions concerning this opportunity, but there is no news on anything concrete yet. Regarding methods for administration, we are currently focused on the injectable form, but plan to explore alternative delivery options that would offer patients convenient dosing frequency and delivery later on.

KELLY: Can you also talk about the prospects of davalintide (next-gen Symlin)?

DR. DAVID MAGGS: The amylin agonism pathway is very important to us firstly of course with Symlin, and secondly with the potential of the pramlintide/metreleptin combination. Davalintide is a molecule that is very similar to native amylin that also has similarities to calcitonin. Amylin is part of the calcitonin peptide family, along with other peptides CGRP and adrenomedullin, which means that these molecules are somewhat similar in their structure and sequence, and they all bind to the same family of receptors. Preliminary data has shown that davalintide has a longer biologic action than pramlintide, which allows better BID administration. It may also be better suited for a longer-action administration like once-a-day or once- a-week. So in general, davalintide is an interesting molecule and we will have a read-out of it later this year from our phase 2 study. We are excited by this because it may open new opportunities with our obesity aspirations.

KELLY: Is davalintide going to be developed as a standalone therapy?

DR. DAVID MAGGS: If we see good efficacy data in the early davalintide trials then yes it is a possibility. But for now we see this molecule as being a potential superior analog to pramlintide that may offer advantages in either efficacy or possible delivery in a variety of indications, alone or in combination with other molecules. We will be better able to assess its potential utility once we see the results of our ongoing study in 4Q09.

IMPLICATIONS OF GLP-1 AGONISM

JOHN: Switching gears, there has been a lot of discussion here at ADA about liraglutide and thyroid issues. Can you discuss whether there is reason to think these could or should be considered to be a class effect of GLP-1 therapies?

DR. DAVID MAGGS: First, you have to remember that Byetta does not have a thyroid signal; either in the early animal studies where no thyroid cancer was seen and in the more recent safety reporting. So the idea of a "class effect" for GLP-1 therapies would have to be more explicitly focused on long-term, continuous GLP-1 agonism rather than the intermittent agonist delivery seen with Byetta. Regarding long-term GLP-1 agonism, the issue is somewhat uncertain. We do know that liraglutide has documented thyroid cancer in the animal studies, occurring in two species and at exposure levels close to human use. We also know that in the exenatide once weekly animal studies we saw thyroid cancer, but at much higher multiples of human clinical exposure (nearly 30 times higher than what would be used in humans). We will wait to see how the FDA deals with this matter in their discussions with Novo Nordisk.

JOHN: Given the presence of GLP-1 receptors in the brain, could you explain a little bit about the known psychological effects of GLP-1 agonists?

DR. DAVID MAGGS: The neurocircuitry around GLP-1 is becoming better understood. Rat studies indicate that GLP-1 may operate in centers that are involved in higher functioning but little more is understood for now. There are soft anecdotes of a "feel-good" phenomenon with exenatide use in the clinic but this has not been substantiated with the right clinical trial measures.

JOHN: Given the broad range of effects the GLP class has, have you explored the use of Byetta in early onset type 2 diabetes patients as a way to increase rates of remission?

DR. DAVID MAGGS: This is a great question. If you look all the way back to UKPDS it was estimated that you've lost about 50% of beta cell function by the time diabetes is being diagnosed. More precise measures of beta cell function reported recently by Ralph DeFronzo and Ele Ferrannini in individuals with blood glucose levels only inching up above the normal range to the high 90s and low 100s, showed beta cell function is as low as 20% of normal. So understanding how Byetta is currently used, in patients already failing one or two oral agents, you are already far down the track in terms of declining beta cell function. It is speculated by some that exenatide may have a more powerful effect on the beta cell if used earlier.

For Byetta currently, it's not possible to encourage such use until the monotherapy indication is attained; it would also be an interesting discussion for the average primary care physician to have with patients – an injectable treatment that may have important effects on the beta cell, versus the currently available oral therapies. If exenatide once weekly becomes available for use in the future then the value proposition changes significantly. There are a number of progressive thinking doctors who are already looking forward to that discussion with patients – a once-a-week injection with all its positive effects versus the currently available oral therapies.

KELLY: Is it possible that if you were given exenatide and still had normal endogenous GLP-1 levels that you could have adverse effects from having too high GLP-1 levels?

DR. DAVID MAGGS: No real evidence for that. There is increasing evidence that type 2 diabetes isn't really a state of reduced GLP-1 levels as has been stated in the past. If you look at GLP-1 levels in type 2's all the way to late disease, GLP-1 levels are thought to be actually pretty normal. The problem with type 2 diabetes is that the beta cell becomes less responsive or resistant to GLP-1. So you are secreting GLP-1 at mealtime normally, but your beta cell is not responding to GLP-1 as it should. However, when you give a more pharmacologic dose of GLP-1 in the form of exenatide, you get the really nice, robust effect we've seen. In a recent study we actually measured GLP-1 levels during Byetta administration and GLP-1 levels were no different to the control study.

PROSPECTS OF EXENATIDE ONCE WEEKLY

KELLY: There are so many ways that exenatide once weekly seems transformational. What do you think would make exenatide once weekly more commercially successful than twice-daily Byetta: the convenience of it being once-weekly, the weight loss, the significantly fewer instances of nausea, or its significant effect on lowering A1c?

DR. DAVID MAGGS: I would say it's mostly convenience. At the end of the day it's all about how primary care physicians are better armed to stem the type 2 diabetes tide and a treatment like this could be transformational. One should not diminish the actual clinical profile of exenatide once weekly either: potent glucose lowering properties, an attractive effect on body weight, and a more tolerable profile than that of Byetta.

KELLY: After we surveyed our diaTribe patients' responses about twice-daily Byetta there were two primary concerns: 1) the high cost of the drug, and 2) how big the nausea issue is for so many patients.

Given that there is a 30% reduction in nausea seen with exenatide once weekly, it would seem that this would be a very significant improvement.

DR. DAVID MAGGS: I think you are right. Nausea is clearly a barrier but how physicians handle it is very mixed. To many endocrinologists it is easy to manage patients through the nausea, whereas for many other physicians it is just too time consuming to handle—it simply means a longer conversation with the patient concerning practical guidance. Exenatide once weekly having a more tolerable profile will be a clear advantage for all.

— by Mark Sorrentino, Jen Lesser, Brendan Milliner, John Close, and Kelly Close

5. In the News: Insulin, pumps, CGM – learn all about it!

We recently had the opportunity to try out a wonderful new online Continuing Medical Education (CME) program on the use of insulin, insulin pumps, and continuous glucose monitoring (CGM) that was created by Dr. Irl Hirsch (University of Washington). The program is available on the website of the American Association of Clinical Endocrinologists at http://www.aace.com/cme/ under the link "Improving Glycemic Control with Insulin" and is available to anyone who is interested.

This interactive case-based program is organized into three hour-long modules on insulin therapy, insulin pumps, and continuous glucose monitors. While the program qualifies for CME credit for physicians, it is really ideal for anyone who is interested in learning more about how to use insulin and technology to improve glycemic control in type 1 and type 2 diabetes patients. Each module begins with a series of introduction slides that gives a concise but comprehensive overview of the topic being covered and reviews some of the supporting literature to guide clinicians in making evidence-based treatment decisions. This is followed by a series of three patient cases that simulate typical scenarios that a clinician might encounter in practice. These cases cover both type 1 and type 2 diabetes patients in a range of ages and circumstances.

The case-based format of the modules is the main forte of the program, as they are extremely well-designed to facilitate clinical learning and help the user develop specific clinical reasoning skills – i.e. calculation of insulin doses, use of insulin pump features to optimize glycemic control, how to make therapeutic adjustments based on self-monitoring or CGM results, etc. Each of the patient cases comes complete with a patient-narrated history, an interactive exam room in which the user can click on various objects in the room to learn about the patient's physical exam or test results, and a series of multiple choice questions on the best way to make treatment adjustments both at the initial visit and at follow-up visits. Each of the multiple choice questions is accompanied by a detailed explanation of what the best treatment strategy would be and why. In addition, after each treatment adjustment is made the case continues on with what happens at the next follow-up visit so that the user can see how the adjustments affected the patient's clinical course. The cases are populated with a number of helpful features, such as simulated SMBG charts for review. There is also a very helpful case summary at the end of each case that reviews the main teaching points from the case. Each module concludes with a ten-question review quiz that the user must complete to receive CME credit.

The only downside to the program is that the modules must be completed in order, so users cannot skip the preceding module(s) if they are only interested in the second or third module. We understand the rationale behind this, as each module builds upon clinical information taught in the earlier modules, but clinicians who are interested in reviewing only pump therapy or CGM are out of luck!

Overall, we thought this program was extremely well done and an excellent resource for clinicians or anyone who want to learn more about which patients are candidates for insulin, insulin pump therapy, or

CGM; how to start them on the therapy, and how to optimize that therapy to improve their glycemic control. As well, we liked the extensive information on how to use Symlin (pramlintide) as an adjunct to insulin therapy, both for patients on multiple daily injection (MDI) and pump (CSII) therapy. We also particularly liked the case on the use of insulin pumps for type 1 diabetes control during pregnancy – an important topic that many clinicians may be less familiar with. And for users who want to review or read further about the topics addressed during the program, a pdf transcription of each module, complete with references, can be downloaded for future study.

We think that this program is an extremely worthwhile (and free!) resource and we highly recommend it for anyone interested in learning more about insulin technologies.

— by Jenny Jin

6. Conference Pearls: Keystone—Practical Ways to Achieve Targets in Diabetes Care

July 17-19, 2009 • Keystone, Colorado • http://www.childrensdiabetesfdn.org

The University of Colorado Denver and the Children's Diabetes Foundation's Conference held in Keystone, CO, entitled "Practical Ways to Achieve Targets in Diabetes Care," brought together some of the most important names in diabetes—Drs. Richard Bergenstal, George Eisenbarth, Ralph DeFronzo, Satish Garg, David Harlan, Irl Hirsch, David Owens, David Schade, and Jay Skyler —to name just a few. The presenters shared with doctors, nurses and educators insight into patient care based on the most recent research. With striking clinical, scientific, and public health implications, the talks were not only important for the everyday practice of diabetes care, but also for the field as a whole. Below we review the conference's most compelling sessions.

- **Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL) presented several powerful theses on controversies in diabetes.** He drew six main conclusions in his presentation: 1) rosiglitazone does not cause heart disease, 2) tight glycemic control does not kill but unwarranted overaggressive treatment (i.e., not backing off treatment when patients are not responding) could, 3) stricter FDA guidelines based on flawed studies could make it much harder for companies to bring products to market, thus putting patients at a disadvantage, 4) glucose control in the hospital is still needed but hypoglycemia must be carefully monitored, 5) exenatide does not cause pancreatitis, and 6) insulin glargine does not cause cancer. He concluded by strongly advising the diabetes field against allowing medical journals to facilitate media coverage, thereby encouraging sensational reporting instead of careful analysis.
- **Dr. Skyler, Irl Hirsch, MD (University of Washington, Seattle, WA), Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), Ralph DeFronzo, MD (University of Texas Health Sciences Center, an Antonio, TX), David Owens, MD (Cardiff University, Penarth, UK), David Schade, MD (University of New Mexico, Albuquerque, NM), Satish Garg, MD (University of Colorado Denver, Aurora, CO) hosted a widely-awaited panel on current controversies in diabetes.** Audience members questioned the panel on the implications of recent headlines. From our view, the most important information delivered was that insulin glargine (Sanofi's Lantus) cannot be definitively associated with cancer (this was in line with what we have reported of late; but all attendees have not necessarily been following all editorials and expert opinion closely so we felt this was critical). Yet, the panel noted that does not mean that insulin in general does not have oncogenic properties, and thus doctors should exercise judgment and take into account patients'

medical histories when making decisions regarding insulin usage. A very poignant point was made that despite the controversies surrounding insulin analogs, therapies should be continued because diabetic patients are ultimately dying of heart disease and stroke—not of cancer. No consensus was reached on a timeline for insulin initiation, with several panel members advocating starting insulin therapy earlier to preserve beta cell function, while others held that there is no evidence insulin does this and we should thus focus on GLP-1s and TZDs. (We look very forward to seeing results from a trial being led by Dr. DeFronzo whereby newly initiated patients receive a combination therapy of metformin, a TZD, and Byetta.)

- **Steve Edelman, MD (University of California at San Diego, San Diego, CA) and Irl Hirsch, MD (University of Washington, Seattle, WA) discussed the merits of continuous glucose monitoring (CGM) at a DexCom sponsored corporate symposium.** Dr. Edelman noted that current glucose monitoring technology is still imperfect even when a patient follows all of the rules because it can only give a snapshot in time, not trends or long-term data. According to Dr. Edelman, those who are most likely to benefit from CGM would be persons with severe hypoglycemia unawareness, elevated A1cs or wildly fluctuating glucose levels, and pregnant patients with diabetes. Ultimately, Dr. Edelman said CGM is most important for the patient—it can help the patient better understand their diabetes and thus improve everyday glucose variability. Dr. Hirsch discussed the importance of CGM in the intensive care unit (ICU). He defined the concept of malglycemia, which encompasses hyperglycemia, hypoglycemia, and glucose variability—all predictors of poor outcome for ill patients. Malglycemia, he said, can only be avoided in the hospital with frequent checking of blood glucose; thus, euglycemia will only be achieved when CGM is integrated into the hospital setting.
- **Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), emphasized that we must shift our thinking on self-monitoring of blood glucose (SMBG), putting emphasis on glucose management rather than just passive monitoring.** While some studies showed improvements in glucose control with SMBG (an A1c change of -0.42 over control in a meta-analysis of eight randomized controlled trials with 1,307 patients), other studies found no obvious effect of monitoring on A1c. Dr. Bergenstal attributed the difference between success and failure of SMBG in the studies to patients knowing how to respond to their readings. SMBG will be most beneficial if patients are educated about nutrition, exercise, and adjustments in therapy according to readings, are given feedback about their readings, and agree on glycemic goals, he said. We assume there may have been an effect of glycemic variability in these trials though the impact may be unknown as CGM has only become accurate enough as of late to measure. We look forward to seeing CGM integrated in more trials to better understand how therapies affect control, variability, and "time in zone".
- **David Schade, MD (University of New Mexico, Albuquerque, NM) touched upon some of the barriers to adoption of self-monitoring of blood glucose (SMBG) in populations with type 2 diabetes not on insulin.** He noted that the high costs of testing supplies (about $100 per month), which are often not reimbursed by insurance companies, are a major barrier to SMBG adoption. As we understand it, Medicare reimburses one strip per day; those that want to test more must pay out of pocket. Dr. Schade said finger-stick testing can be inconvenient, painful, and can cause scarring, but there is little on the horizon, he said, that will give equally accurate readings. He said that compliance to SMBG in populations with type 2 diabetes not on insulin is low and the discontinuation rate, even in clinical trials, is high. Given that studies have failed to show benefits of SMBG in these populations, Dr. Schade questioned whether resources would be better-spent putting patients on other regimens, such as once-weekly exenatide. Notably, he forecast that CGM will soon replace SMBG.

- **Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), David Schade, MD (University of New Mexico, Albuquerque, NM), Irl Hirsch, MD (University of Washington, Seattle, WA), and David Owens, MD, (Cardiff University, Penarth, UK) held an impromptu panel discussion on the timeline for the phasing out of self-monitoring of blood glucose (SMBG) and the dominance of continuous glucose monitoring (CGM).** Dr. Hirsch noted that the accuracy of CGM needs to improve before it is completely adopted over SMBG, but that CGM will grow quickly for patients with type 2 diabetes and gestational diabetes. Several doctors commented that SMBG is inadequate for patients with type 2 diabetes not on insulin because the snapshot it provides is not enough to help patients understand and monitor their diabetes, but the trends CGM provides are key. Dr. Owens held that because CGM gives so much more information, diabetes technology will go heavily in that direction.
- **Marian Rewers, MD, PhD (University of Colorado Denver, Aurora, CO) said that the incidence of coronary artery disease (CAD) is not improving in patients with type 1 diabetes and that coronary artery calcification is a great test for determining the short risk prognosis of CV events.** CAD has become the leading cause of death among patients with type 1 diabetes, surpassing nephropathy. The coronary artery calcification (CAC) test is a noninvasive test measuring the extent and progression of atherosclerosis. Dr. Rewers suggested that better control of A1c, blood pressure, cholesterol, and vitamin D can lower the risk of CAD but that additionally, all asymptomatic patients with type 1 diabetes older than 30 should be screened for CAC. Those with scores over 400 should be further tested and those with perfusion defects or CAD symptoms should undergo proper treatment.
- **Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York, NY) outlined prospects for the development of an artificial pancreas, i.e., the "closed loop."** He defined the goals of the JDRF-sponsored Artificial Pancreas Project as accelerating the availability of the artificial pancreas, ensuring wide availability and reimbursement of its components, and creation of a thriving, robust artificial pancreas market that gives patients with diabetes many choices. Dr. Kowalski emphasized that the first-line goal of the project was to create a device that could prevent severe hypoglycemia by ceasing insulin delivery when patients are no longer responsive to "low" alarms. This is akin to the new Medtronic pump that has already been approved outside of the US. The hypothetical pathway to an artificial pancreas will likely progress through 1) a pump that ceases delivery when glucose is very low, 2) a pump that ceases delivery when glucose is trending low, 3) a pump that minimizes both hypo and hyperglycemia, 4) an automated basal/hybrid closed loop, 5) a fully automated closed insulin loop, and finally 6) a fully automated multi-hormone (insulin and anti-insulin) closed loop. Dr. Kowalski said it was imperative that the industry now "takes the bull by the horns" to ensure eventual commercialization of the artificial pancreas. We heartily agree. We had never quite heard a pathway as explicit as this; we found Dr. Kowalski's presentation particularly helpful and very inspiring. We thought the last step was particularly interesting and wonder whether he was referring to glucagon, pramlintide, etc.
- **Richard Bergenstal, MD (International Diabetes Foundation, Minneapolis, MN), David Owens, MD (Cardiff University, Penarth, UK), and Jay Skyler (University of Miami Miller School of Medicine, Miami, FL) made clinical recommendations based on the findings of the ACCORD/ADVANCE, VADT, APOLLO, 4T, ORIGIN, and Heart T2D trials.**
- **Dr. Bergenstal reviewed the results of ACCORD presented at this year's ADA, which suggested a higher risk of mortality associated with intensive glucose control.** He

noted that this increased risk was not necessarily due to hypoglycemia, and could be associated with "pushing too hard" on patients who were not responding to their therapy. Additionally, the risk of mortality was lower with lower A1cs. In light of these results, intensive glycemic control and a target A1c of <7% still make sense, but doctors must carefully monitor their patients' responsiveness to treatment.

- **Dr. Owens described the 4T's findings that improvements in A1c were best with prandial and biphasic insulin therapy for patients with baseline A1cs >8.5%. Patients with A1cs <8.5% at baseline were equally likely to see A1c improvements with biphasic, prandial, or basal insulin.** In general, adding insulin to oral therapies proved to have suboptimal responses in type 2 diabetic patients (A1c drop of 0.8% to 1.4%) and prandial and biphasic insulins were associated with more hypoglycemia and weight gain. Overall the results suggested that complex, multi-insulin regimes may be needed to achieve target glucose levels and years two and three of the 4T study will explore this (4T was first reported at EASD nearly two years ago; we had assumed the trial was finished by now). He also touched upon APOLLO's findings that insulin glargine and insulin lispro are essentially equivalent in their lowering of A1c and blood glucose, but that insulin glargine is associated with less hypoglycemia.
- **Dr. Skyler recapped ACCORD, ADVANCE and VADT's findings, including that lowering A1c below 7% reduces the risk of microvascular complications and CVD risk in diabetic patients, thus making an A1c target of 7% reasonable.** Along with discussing various suggestions regarding blood pressure, LDL cholesterol, and aspirin therapy, he made recommendations for a pathophysiologically based treatment algorithm focusing on lifestyle change, TZD, metformin, and exenatide (Amylin's Byetta) therapy (this combination was discussed in Dr. DeFronzo's Banting Lecture in 2008 at ADA) that would ideally bring A1cs below 6.0%. We thought it was notable to hear a clinician like Dr. Skyler talking again so openly about the virtues of A1cs under 6.0% for at least some patients; we haven't heard this since prior to when ACCORD was first released. We applaud this direction since from our view, patients are likely better off the closer they can get to normal blood glucose levels safely.
- **Peter Gottlieb, MD (University of Colorado Denver, Aurora, CO) emphasized that curing type 1 diabetes will mean successfully preventing loss of beta cell mass and outlined immunotherapeutic approaches to this goal.** After going through some of type 1 diabetes' basic immunology, he described several strategies currently aiming to preserve beta cells: therapies that block the activation of autoreactive T-cells, which ultimately kill beta cells, a pro-insulin DNA vaccine that would prevent autoimmunity, antigen-specific therapy that would block insulin being presented to T-cells, and anti-GAD, anti-thymocyte globulin, and anti-Interleukin-1 (a cytokine) therapies. He detailed many of the immunotherapy trials currently underway and said that the best hope for remission or prevention will probably be an approach combining several immunotherapeutic options so that immunosuppression is lessened while positive effects are maximized. An important aspect of many of these therapies is that their greatest potency will be very early—either before disease onset or during honeymoon phases.
- **George Eisenbarth, MD, PhD, (University of Colorado Denver, Aurora, CO) discussed our genetic understanding of diabetes and how we can hopefully use this knowledge to cure and prevent the disease.** He began his lecture with some practical aspects of type 1 diabetes genetics, encouraging referrals to TrialNet for relatives of patients with type 1 diabetes and suggesting several assays that could detect autoantibodies. He also recounted the immune basis of type 1 diabetes, explaining that certain HLA genes are highly associated with disease formation; as a reminder, HLA is the human molecule that allows for insulin recognition by autoreactive T-cells in diabetes. Because of type 1 diabetes' genetic basis, patients are very

likely to develop autoimmunity if their parents have diabetes or they share high-risk genes with siblings. Through creation of animal models mimicking type 1 pathogenesis and trials such as the DAISY trial (which looks at the development of diabetes in genetically susceptible children), we will hopefully one day be able to predict and therefore treat or prevent type 1 diabetes, Dr. Eisenbarth said.

- **Boris Draznin, MD (University of Colorado School of Medicine, Denver, CO) gave hope for the prospects of islet transplants from pigs.** Because of the very limited supply of transplantable human islets and the extremely strong immunosuppressive regimes used for current transplantation protocols, another transplant method needs to be found, he said. His talk focused on the use of porcine islets, which can be isolated in large quantities and have the same physiological response to glucose as human islets. Some serious cons to use of porcine islets include the risk of animal virus transmission and strong immune rejection of the islets. Yet a solution may have been found in specific pathogen free pig populations found on Auckland Island and in the encapsulation methods of a New Zealand company. The company has conducted trials with infusion of encapsulated porcine islets and had positive results in terms of A1c and mean glucose reduction. There are still many, many questions about this technology and Dr. Drazinin noted that maybe patients will one day receive these islet infusions on a yearly basis for maximum efficacy. We aren't sure how broad the patient population would be. While we'd very much like to see this come to fruition, we feel the technology still has numerous challenges to overcome but are excited for future results.
- **David Harlan, MD (National Institutes of Health, Bethesda, MD) shared realistic, though not overly promising information about islet and pancreas transplantation.** While there was lots of hope for the field following publication of the Edmonton protocol in 2000 (New England Journal of Medicine) and evidence that islet transplant reliably stores insulin independence (at least for the first year), this is no longer necessarily the case, Dr. Harlan said. It has been shown that the immunosuppressants given post-transplant significantly worsen renal function and that the risk of patient mortality never decreases post pancreas-alone transplantation. Thus, given the success of current insulin therapies and the low mortality rate associated with type 1 diabetes, any transplantation therapy will have to better patients' lives beyond what current methods can do. Other interesting facts from Dr. Harlan's lecture were that there is evidence that the native pancreas still secretes insulin many, many years after type 1 diagnosis, but that exogenous insulin therapy can actually suppress native insulin production, and that beta cells do not regenerate after age 30. We believe this information was gleaned, at least in part, from a failed NIH trial testing exenatide in type 1 patients. We wonder if there are plans to try exenatide in patients at risk of type 1 or who have it and are younger than 30.

— by Lisa Rotenstein and Kelly Close

7. Literature Review: Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years' Duration: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005) – Archives of Internal Medicine

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Arch Intern Med, 2009, 169 (14): 1307-1316.
http://archinte.ama-assn.org/cgi/content/abstract/169/14/1307

Although there have been recent studies suggesting that rates of complications for patients with type 1 diabetes have been decreasing, these reports have been from single centers or anecdotal. In the present study, the authors compare the frequencies of serious complications 30 years after diagnosis in patients randomized to the intensive or conventional treatment arms of the Diabetes Control and Complications Trial (DCCT) plus its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) , as well as a subset of the cohort of the separate Epidemiology of Diabetes Complications (EDC) study treated according to similar guidelines as the conventional arm of the DCCT/EDIC. As the treatment guidelines of the "intensive" arm of the DCCT/EDIC have largely become standard therapy, this comparison provides an updated view of outcomes of patients with type 1 diabetes today as compared to in the past. The data show dramatic improvements in outcomes for people with type 1 diabetes today.

The authors describe that the cumulative proportions of participants experiencing proliferative retinopathy, nephropathy, and cardiovascular disease (CVD) at 30 years duration of diabetes are 50%, 25%, and 14% in the conventional arm of DCCT/EDIC, and 47%, 17% and 14% in EDC (statistically similar). In contrast, the intensive arm of the DCCT/EDIC study shows rates of 21%, 9%, and 9% for proliferative retinopathy, nephropathy, and CVD respectively (all statistically significant). An associated commentary along with this article notes that these figures are drastically improved since cohorts with onset of diabetes in the 1950's to 70's. Specifically, they cite that the 30% and 12% cumulative incidences of proliferative retinopathy and nephropathy are far less than the rates of proliferative retinopathy of 40% to 53% and rates of nephropathy of roughly 35% in studies with onsets of diabetes 10 to 20 years before that of DCCT/EDIC or EDC.

"Now in the modern era, knowing how to use insulin more physiologically has led to really dramatically different outcomes," said David Nathan, one of the study chairs for DCCT/EDIC.

- **Data from the cohort of the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) as well as a subset of the cohort of the separate Epidemiology of Diabetes Complications (EDC) study, are reported to provide an updated view of clinical care, metabolic results, and outcomes of patients with type 1 diabetes.** As a reminder, the DCCT randomized 1441 patients to either a regimen of conventional (one or two daily insulin injections) or intensive (at least three daily injections of insulin and at least four self-tests of blood glucose) glycemic control. One hundred and sixty-one subjects from the EDC study were also included due to the similar timing of the study and the similarity in treatment to the conventional arm of DCCT/EDIC.
- **At the onset of DCCT, the average duration of diabetes was 5.6 years (range 1-15 years), and at year 12 of EDIC the average duration was 24.3 years (range 17-37 years).** Although the A1c of the intensive arm of DCCT had a significantly lower A1c than the conventional arm, all participants were offered intensive therapy at the end of the study and the two groups became roughly equivalent after five years.
- **This study calculated the morbidities of patients relative to their duration of diabetes, rather than the time since randomization.** Thus, the data presented here reflect current outcomes at different durations of diabetes rather than the time course of a particular treatment.
- **Rates of events (per 100 patient years) were also reported for hypoglycemia or coma, requirement for assistance, and diabetic ketoacidosis (DKA).** During DCCT, the rates for these complications were 5.4, 18.7, and 1.8 in the conventional arm, and 16.3, 61.2, and 2.0, respectively, in the intensive arm. At year 12 of the EDIC follow-up study, the rates were 9.2, 39.6, and for the conventional arm and 13.6, 48.4, and 0 in the intensive arm.

- **An associated commentary notes that these figures are drastically improved since cohorts with onset of diabetes in the 1950's to 70's.** Specifically, they cite that the 30% and 12% cumulative incidences at 25 years diabetes duration of proliferative retinopathy and nephropathy in the intensive arm of DCCT/EDIC are far less than the rates of proliferative retinopathy of 40% to 53% and rates of nephropathy of roughly 35% in studies with onsets of diabetes 10 to 20 years before that of DCCT/EDIC or EDC (note: the duration of 25 years was chosen for this comparison to match current findings with those of previous studies). They also point out that the standardization of intensive control is not the only factor leading to superior outcomes in patients with type 1 diabetes: they point to the advent of statins, angiotensin-converting enzyme inhibitors (ACE inhibitors), more attentive surveillance, and the increased use of aspirin as factors that have likely lowered rates of complications. They predict, however, that intensive therapy should result in a >50% reduction in the rates of complications for people with type 1 diabetes, particularly with early intervention. The authors conclude that prospects for patients with type 1 diabetes have greatly improved, but that the issues of hypoglycemia and low implementation rates must be addressed to fully realize the benefits of intensive control.

— by Nicholas Wilkie and Kelly Close

8. Conference Preview: Obesity Society 27th Annual Meeting

October 24-28, 2009 • Washington, DC • http://www.obesity.org/obesity2009

In late October, the Obesity Society will hold its annual meeting in Washington, DC. The conference will include scientific sessions, oral and poster presentations (over 900 abstracts have been submitted!), key lectures, and symposia. More than 2,500 researchers, clinicians, educators, and professionals are expected to attend the meeting. The meeting will be organized into five thematic tracks running concurrently: cell and molecular biology, integrative biology, clinical studies, population studies, and clinical/professional practice. This meeting is sure to be packed with cutting-edge scientific research, and the latest treatment, trends, education, news, and developments in the field of obesity. We expect all three major players with new weight-loss drugs in late stage development, Vivus, Arena, and Orexigen, to present data for their respective drug candidates Qnexa, Lorcaserin, and Contrave – we look forward as well from hearing from other obesity leaders such as Amylin. While the details of the oral presentations have not yet been released and abstracts are embargoed until the meeting, we provide you with a collection of symposia and key lectures we are particularly looking forward to below.

Highlights

Saturday (October 24)

- **Pharmacotherapy Update.** There will be a pre-conference session on the state of pharmacotherapy for diabetes led by Drs. Ken Fujioka, MD (Scripps Clinic, San Diego, CA), Louis J. Aronne, MD (Weill-Cornell Medical College, New York, NY), and Richard E. Pratley, MD (Vermont College of Medicine, Burlington, Vermont). Every year this is usually very, very good – we are especially interested to hear views this year given so much more phase 3 data has been released.
- **President's Address.** Robert F. Kushner, MD (Northwestern University, Chicago, IL), the current president of the Obesity Society, will deliver the opening address. (We interviewed Dr. Kushner last year – let us know if you'd like a copy of this interview.)

Sunday (October 25)

- **New Mechanisms for Regulating Adipogenesis.** Ormond A. MacDougald, PhD (University of Michigan Medical School, Ann Arbor, MI) and Sean Adams, PhD (Amylin Pharmaceuticals, San Diego, CA) will chair this symposium in the Cell and Molecular Biology track. Highlights include a talk by Jacqueline Stephens, PhD (Louisiana State University, Baton Rouge, Louisiana) titled "Novel Effectors of Adipogenesis" and a talk by Susanne Mandrup, PhD (University of Southern Denmark, Odense M, Denmark) on the "Regulation of Adipocyte Genes by PPAR-Gamma".
- **Weight Loss-Independent Effects of Intestinal By-Pass Surgery: Fact or Fiction?** This symposium in the Integrative Biology track will be chaired by Bruce M. Wolfe, MD (Tufts University, Boston, MA). We are very much looking forward to talks by Naji Abumrad, MD (Vanderbilt University School of Medicine, Nashville, TN) on the "Short-Term Metabolic Effects of Bariatric Surgery Versus Caloric Restriction" and by Elisa Fabbrini, MD, PhD (University of Rome La Sapienza, Rome, Italy) on the "Long-Term Metabolic Effects of Bariatric Surgery".
- **Drugs: Past, Present, and Future.** In a symposium from the Clinical/Professional Practice track led by chair Dr. Fujioka, Steven B. Heymsfield, MD (Columbia University, New York, NY) will talk about "Failed Drugs" and Frank Greenway, MD (Pennington Biomedical Research Center, Baton Rouge, Louisiana) will discuss "Drugs for Tomorrow".
- **Molecular Physiology of the Weight-Reduced State.** This key lecture from the Integrative Biology/Clinical Studies track is co-sponsored by the Society for the Study of Ingestive Behavior (SSIB) and will be chaired by Martin Myers, MD, PhD (Sunnybrook Health Science Center, Toronto, Canada) and delivered by Rudy Leibel, MD (Columbia University, New York, NY).
- **Medication and Obesity Comorbidities.** In this symposium in the Clinical/Professional Practice track, Louis J. Aronne, MD (Weill-Cornell Medical College, New York, NY) will deliver a talk on "Drugs Causing Weight Gain", Richard Lutes, MD, FAAFP (Central Ohio Nutrition Center, Columbus, OH) will speak about "Medication Management During Weight loss", and Caroline Apovian, MD, FACP, FACN (Boston University School of Medicine, Boston, MA) will discuss "Medical Considerations in Obese Patients with Comorbidities".
- **Setting Up an Obesity Practice.** This symposium in the Clinical/Professional Practice track, chaired by Peter Vash, MD, MPH (Century City Hospital, Los Angeles, CA), will include talks by Nikhil Dhurandhar, PhD (Louisiana State University System, Baton Rouge, LA) on "The Clinic Environment", Robert Kushner, MD (Northwestern Memorial Hospital, Chicago, IL) on "Patient Evaluation", and Kenneth Storch, MD, PhD (Storch Medical Nutrition Center, Florham Park, NJ) on "Reimbursement Issues".

Monday (October 26th)

- **Spotlight on 5HT2C.** In this symposium in the Clinical Studies track chaired by Jonathan Purnell, PhD (Oregon Health & Science University, Portland, OR) and Robert Berkowitz, MD (The Children's Hospital of Philadelphia, Philadelphia, PA), we are looking forward to talks by Laurence Tecott, MD, PhD (University of California, San Francisco, CA) on the "Neuroscience of 5HT2c", Steven Smith, MD (Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA) on "Lorcaserin Clinical Results", and Neil Weissman, MD, FACC (Washington Hospital Center, Washington, DC) on "A Primer of Valvulopathy in Obesity".
- **Adipose Tissue in Health and Disease: What's the Connection?** Chaired by Harold Bays, MD, FACP (Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY), this symposium in the Clinical/Professional Practice track will include talks by Michael D. Jensen, MD (Mayo Clinic, Rochester, MN) titled "What is Good about Fat?" and Dr. Bays on "How Does Obesity Cause 'Sick Fat'. In this session, Lewis Landsberg, MD (Beth Israel Hospital, Boston, MA)

will also speak on Hypertension and Henry Ginsberg, MD (Columbia University College of Physicians and Surgeons, New York, NY) will speak on lipids.

- **Mitochondrial Dysfunction and Obesity.** We are looking forward to the talks in this session, which will be chaired by past NAASO President Barbara Corkey, PhD (Boston University School of Medicine, Boston, MA) and David Wright, PhD (University of Plymouth, Plymouth, UK) including "The Role of Mitochondrial Adaptation in Human Muscle for Diet and Exercise" by Bret Goodpaster, PhD (University of Pittsburgh, Pittsburgh, PA).
- **Fat Additions and Subtractions.** Marc Reitman, MD, PhD (National Institutes of Health, Bethesda, MD) will chair this symposium in the Integrative Biology track. C. Ronald Kahn, MD (Joslin Diabetes Center, Boston, MA) will deliver a talk on the "Beneficial Effects of Subcutaneous Fat Transplantation on Metabolism" among others.

Tuesday (October 27)

- **Multidisciplinary Treatment of the Bariatric Surgery Patient.** This symposium in the Clinical/Professional Practice track will be chaired by Stephanie Sogg, PhD (Harvard Medical School, Boston, MA). Edward Livingston, MD, FACS, AGAF (University of California-Los Angeles Bariatric Surgery Program, Los Angeles, CA) will discuss "What's New in Surgical Techniques?" and Dr. Kushner will speak about "Postoperative Management".
- **Neuroimaging in Obesity.** Dr. Purnell will chair this Clinical Studies Track symposium. Nora Volkow, MD (National Institute on Drug Abuse, Bethesda, MD) will educate the audience about "Reward Pathways", Joy Hirsch, PhD (Cornell University Medical College, New York, NY) will speak about "Leptin and Weight Loss", and Eric Stice, PhD (University of Texas at Austin, Austin, TX) will discuss "Using FMRI to Study Obesity".
- **Advances in Obesity and Nonalcoholic Fatty Liver Disease.** In this symposium in the Integrative Biology Track, we will hear about "New Therapies for NASH" from Elif Oral, MD (University of Michigan School of Medicine, Ann Arbor, MI) and "Cellular Mechanisms Responsible for Nonalcoholic Fatty Liver Disease" from Gregory Gores, MD (Mayo Clinic College of Medicine, Rochester, MN). This session will be chaired by Edward Doo, MD (National Institutes of Health, Bethesda, MD) and Elizabeth Parks, PhD (University of Texas Southwestern Medical Center, Dallas, TX).
- **Emerging Concepts in Devices as Alternatives to Drugs and Surgery.** In this Key lecture from the Clinical Studies track chaired by Lee Kaplan, MD, PhD (Massachusetts General Hospital, Boston, MA), Dr. Wolfe will discuss "Devices in the Treatment of Obesity".

Wednesday (October 28)

- **Lipokines: Hot Topics in Diabetes and Obesity Research** This symposium in the Cell and Molecular Biology track chaired Jenifer Fenton, PhD, MPH (National Cancer Institute, Bethesda, MD) will feature intriguing talks by Jonathan Graff, MD, PhD (University of Texas Southwestern Medical Center, Dallas, TX) on "Harnessing the Power of Stem Cells to Cure Obesity and Diabetes" and Daniele Piomelli, PhD (University of California, Irvine, CA) on "The Lipid Mediator OEA Links Fat Absorption to Satiety".
- **Advances in Chemoreception.** This key lecture in the Integrative Biology track titled "Taste Receptors in Gut Regulate Endocrine Function" will be delivered by Robert Margolskee, MD, PhD (Mount Sinai School of Medicine, New York, NY), and chaired by Samuel Klein, MD (Washington University School of Medicine, St Louis, MO).

- **Assessment Tools for Obesity: Beyond BMI.** This Clinical/Professional Practice track symposium chaired by Jack Yanovski, MD, PhD (National Institutes of Health, Bethesda, MD) will include talks by Nancy Sebring, RD (National Institutes of Health, Bethesda, MD) on "Body Composition: Practical Considerations" and Kong Chen, PhD, MSCI (Vanderbilt University, Nashville, TN) on "Measuring Energy Expenditure in Humans".

— by Jessica Swienckowski

9. Conference Preview: International Diabetes Federation's 20th World Diabetes Congress

October 18 – 22, 2009 • Montreal, Canada • www.worlddiabetescongress.org

The IDF's 20th World Diabetes Congress in late October will be packed with fascinating talks on the latest scientific and clinical advances in diabetes and obesity. From novel pharmacotherapies and recent clinical trials to prevention interventions, this meeting will cover some very hot topics in diabetes and obesity. In particular, we're really looking forward to hearing the final 4T data – should be very interesting. At IDF this year, one very big deal will be hearing new global guidelines for self-monitoring of blood glucose in type 2 patients. Interestingly, there seems to be a special emphasis on prevention of metabolic diseases, reduction of cardiovascular risk, and early lifestyle interventions. Below, we have highlighted certain talks of particular interest; however, this is by no means an exhaustive preview so look forward to our conference highlights!

Highlights

Monday (October 19)

- **Is Anti-Obesity Drug Treatment Appropriate for Treatment of Obese Patients with Type 2 Diabetes?** Luc Van Gaal, MD (Antwerp University, Edegem, Belgium) and John Buse, MD (University of North Carolina School of Medicine, Chapel Hill, NC) will debate the use of anti-obesity drugs in obese patients with type 2 diabetes: Dr. Buse will argue "no" and Dr. Gaal will argue "yes". Dr. Gaal will mainly draw upon data from sibutramine and orlistat in patients with type 2 diabetes and Dr. Buse will cite the complexity, cost, risks, and discomfort associated with obesity therapies as reasons to avoid the use of drugs for which there is no clear evidence showing benefits beyond modest weight loss. We very much hope they will talk about future therapies such as Vivus' Qnexa, Orexigen's Contrave, and potential obesity therapies in development from Amylin – we don't think more discussion on sibutramine and orlistat alone is really very interesting, especially because neither Roche nor Abbott is even spending resources marketing either therapy.
- **PPAR-Agonists 10 Years On.** Bart Staels, PhD (Institut Pasteur de Lille, Lille, France) will begin this session by reviewing the physiological mechanisms and effects of PPAR agonists, including PPAR-gamma agonists and dual PPAR agonists. Henning Beck-Nielson, DMSC (Odense University Hospital, Odense C, Denmark) will present on the results of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial. Lawrence Leiter, MD (St. Michael's Hospital, Toronto, Canada) will review data from long-term trials that have assessed the safety of TZDs, specifically with respect to cardiovascular disease. Lastly, Ian R Reid, MD (University of Auckland, Auckland, New Zealand) will discuss the effects of TZDs on bones from a scientific and clinical perspective.

- **What is Obesity and Why?** Dennis Richard, MD (Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec, Canada) will review the hormonal regulation of appetite. Brent Wisse, MD (University Washington School of Medicine, Seattle, WA) will cover data in animals and humans regarding the regulation of energy expenditure. Tony Lam, PhD (University of Toronto, Toronto, Canada) will be discussing central and peripheral regulation of metabolism. Finally, Francesco Giorgino, MD, PhD (University of Bari School of Medicine, Bari, Italy) will provide an overview of the role of the adipocyte, focusing on its role in visceral adiposity.
- **Where Now for Diabetes Genetics?** Mark J McCarthy, MD (University of Oxford, Oxford, United Kingdom) and Constantin Polychronakos, MD (McGill University Healthcare, Montreal, Canada) will speak about whole-genome analyses to identify genetic loci responsible for predisposition to developing type 2 diabetes and type 1 diabetes. Ewan R Pearson, MD (University of Dundee, Dundee, United Kingdom) will talk about the potential for pharmacogenetics to be used as a guide for treatment decisions.
- **Diabetes and Hyperglycemia: The Size of the Problem.** Jeffery A Johnson, PhD (University of Alberta, Edmonton, Canada) will start this session with an epidemiologic and economic review of diabetes worldwide. Pablo Aschner, MD (Universidad Javeriana and Asociación Colombiana de Diabetes, Bogotá, Colombia) will present evidence for a population shift to the right in the glucose distribution of the normal glucose tolerance (NGT).

Tuesday (October 20)

- **Diabetes and Obesity Management: Fat Distribution, Bariatric Surgery, Obesity Drugs as Glucose-Lowering Drugs, and Appetite Control in Diabetes.** Francesco Rubino, MD (Weill Cornell Medical College, New York, NY) will begin by discussing the effect of gastric bypass surgery on hormones in type 2 diabetes. Jean-Pierre Després, PhD, FAHA (Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec, Canada) will review the stage of proposed additional markers for diagnosing visceral adiposity. Samuel Klein, MD (Washington University School of Medicine, St Louis, MO) will provide an eye-opening talk on the metabolic consequences of bariatric surgery.
- **Prediabetes: which organ is the culprit?** In this symposium that makes us think of Dr. Ralph DeFronzo's memorable 2008 Banting Lecture, speakers will give detailed presentations on the role a particular organ plays in the development of prediabetes; organs include the beta cell, muscle, liver, adipocyte, and brain as well as one presentation on an integrated approach. Speakers include Steven E. Kahn, MB, ChB (VA Puget Sound Health Care System and University of Washington, Seattle, WA), Gerald Shulman, MD (Yale University School of Medicine, New Haven, CT), Michael Roden, MD (German Diabetes Center, Duesseldorf, Germany), Takashi Kadowaki (Graduate School of Medicine, Tokyo, Japan), Silvana Obici, MD (University of Cincinnati, Cincinnati, OH), and Linong Ji (Peking University People's Hospital, Beijing, China).
- **Type 1 Diabetes: From Pathogenesis to Intervention Trials.** Immunology expert Kevan Herold, MD (Yale University, New Haven, CT) will present experimental results on the immunological effects of anti-CD3 monoclonal antibody therapy in type 1 diabetes. Wow we are keen to get his updated thinking.
- **Primary Prevention of Type 2 Diabetes: Drugs versus Lifestyle.** This session will cover important findings and takeaway messages from multiple large-scale trials such as the Diabetes Prevention Program (DPP) trial (presented by the national chairman, David M Nathan, MD [Massachusetts General Hospital, Boston, MA]), the Indian Diabetes Prevention Program (IDPP), and the Prevention Program in Finland (FIN-D2D). We are looking very forward to hearing Dr. Nathan's updated thinking.

Wednesday (October 21)

- **Insulin Resistance, Islet Beta Cells, and Mitochondrial Dysfunction.** In this "Teaching Lecture", Dr. Roden will discuss the science behind insulin resistance on a cellular level, specifically noting the role of mitochondrial function and normal levels of ATP production.
- **Prevention of Type 2 Diabetes and CVD: Diabesity.** In another teaching lecture, Nigel Unwin, MD (Newcastle University, Newcastle, United Kingdom) will present on the evolving relationship between obesity and risks for type 2 diabetes and cardiovascular disease from an epidemiological standpoint.
- **Prevention Initiatives for Type 1 Diabetes and Type 2 Diabetes.** Maurizio Vanelli (University of Parma, Parma, Italy) will present his research findings from "the Parma Campaign", which proposed a set of cost-effective, simple strategies for the diagnosis of type 1 diabetes. Abdulla Ben-Nakhi, MD (The Dasman Center for Research & Treatment of Diabetes, Kuwait, Kuwait) will speak on the risks and preventative strategies for type 2 diabetes in the Gulf region.
- **Assessment of Cardiovascular Risk in Type 2 Diabetes.** James Meigs, MD (Harvard Medical School, Boston, MA) will focus on recent clinical studies such as STENO-2 and UKPDS follow-up study to illustrate the effect of metabolic risk factors on type 2 diabetes.
- **In-Hospital Glycemic Management of Diabetes.** In this meet-the-expert session, Guillermo Umpierrez, MD (Emory University School of Medicine, Atlanta, GA) will provide a thorough review of evidence supporting improving in-hospital glycemic control for inpatients with hyperglycemia and the recommended glycemic targets in various populations.
- **Is Self-Monitoring Useful in Type 2 Diabetes: What is the Evidence? In Whom?** In this meet-the-expert session, Oliver Schnell, MD (Munich Diabetes Research Institute, Munich, Germany) will discuss data leading to the new global guidelines for self-monitoring of blood glucose in type 2 diabetes patients.
- **Diabetes and the Brain.** Elizabeth Seaquist, MD (University of Minnesota, Minneapolis, MN) will kick-off this symposium with a lecture on brain glucose and glycogen metabolism in diabetes and hypoglycemia unawareness. Dianne Figlewicz Latemann, PhD (VA Puget Sound Health Care System, Seattle, WA) will review the basic mechanisms involved in hypoglycemia-associated autonomic failure (HAAF). Lastly, Roger McIntyre, MD, FRCPC (University of Toronto, Toronto, Canada) will talk about depression associated with insulin resistance and a comprehensive management approach for such disorders.
- **Novel Therapeutic Approaches To Prevention and Management of Type 1 Diabetes.** Rebecca L. Hull, PhD (VA Puget Sound Health Care System and University of Washington, Seattle, WA) will discuss challenges facing islet cell transplantation and the effects of amyloid deposition on islet transplantation outcomes. Camillo Ricordi, MD (University of Miami, Miami, FL) will review the challenges and advances of stem cell therapy in type 1 diabetes.
- **Ectopic Fat and Cardiometabolic Risk in Type 2 Diabetes – EAS/ICCR Joint Symposium.** Theodore Mazzone, MD (University of Illinois, Chicago, IL) will talk about the effects of visceral fat on lipoprotein and inflammatory markers of cardiovascular disease risk. Jean-Pierre Despres, PhD (Centre de Recherche, Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec, Canada) will speak on therapeutic agents that specifically target visceral fat.

Thursday (October 22)

- **Extrapancreatic Effects of the Incretins.** Yutaka Seino (Kansai Electric Power Hospital, Osaka, Japan) will review the basics of two major incretin hormones, GIP and GLP-1, focusing on the extrapancreatic effects, which differentiate them. Randy J. Seeley, PhD (University of Cincinnati, Cincinnati, OH) and Daniel J. Drucker, MD (Mount Sinai Hospital, Toronto, Canada) will discuss the effects of incretin hormones on the brain and the skeleton and cardiovascular systems, respectively.
- **Inflammation and Diabetes.** We look forward to hearing Steven Shoelson, MD, PhD (Harvard Medical School, Boston, MA) talk about the role of innate immunity in insulin resistance and type 2 diabetes. Allison Goldfine, MD (Joslin Diabetes Center, Boston, MA) will continue this session by reviewing clinical trials of anti-inflammatory agents. Lastly, Vivian Fonseca, MD (Tulane University, New Orleans, LA) will present on the association between inflammation and cardiovascular disease.
- **Latest Clinical Trials.** In this symposium, we will hear reviews of results from the latest clinical trials including 4T final results, an update on ACCORD, and the results of the ONSET trial of sensor-enhanced CSII in children with new onset type 1 diabetes. In addition, John Chalmers, MD (George Institute for International Health, Camperdown, Australia) will provide new analyses and results from the ADVANCE trial.

— by Sanjay Trehan

10. Conference Preview: Diabetes Technology Society 9th Annual Meeting

November 5-7, 2009 • San Francisco, CA • http://www.diabetestechnology.org/index.html

Each year, we look forward to the Diabetes Technology Society's annual meeting, which brings together corporate and clinical leaders to discuss the latest developments and controversies in the realm of diabetes technologies. This year, the conference comes to Close Concerns' home in San Francisco, and we could not be more excited – the agenda promises strong presentations and panel discussions on every aspect of diabetes technology, from basic research to clinical guidelines, reimbursement issues, and approval procedures. Broad perspectives will be presented as well, with speakers ranging from certified diabetes educators to well-known diabetes bloggers and representatives from the FDA. Below we present our anticipated highlights of the more corporate and clinically relevant discussions.

Highlights

Thursday (November 5)

- **Insulin and Metabolic Peptide Delivery.** This pre-meeting workshop panel will discuss the advantages and disadvantages of insulin pump therapy with respect to both patient and physician preferences. The panel – which includes star speakers John Pickup, MD, PhD (Guy's Hospital, London, UK) and Gloria Yee, RN, CDE (University of California at San Francisco, San Francisco, CA) – will also delve into the potential of insulin pump therapy in patients with type 2 diabetes, a growing application.
- **Hemoglobin A1c: Laboratory and Clinical Advances.** This workshop will congregate two panels of speakers to compare advances in the use of A1c as a treatment tool in the laboratory and in the clinic. We are particularly looking forward to the presentation by Robert Cohen, MD (University of Cincinnati, Cincinnati, OH) on "Biologic Variability in Hemoglobin A1c and its Implications for Estimated Average Glucose and the Diagnosis of Diabetes" on the laboratory side and the session with George Cembrowski, MD, PhD (University of Alberta, Edmonton, Canada) entitled "Toward More Rational Utilization of Hemoglobin A1c" on the clinical side.

- **Future Drugs for Diabetes/Future Drugs for Obesity.** Building upon the presentation by Robert Rushakoff, MD (University of San Francisco, San Francisco, CA) on current diabetes drugs and their limitations, we expect these two sessions will recap the diabetes and obesity drug pipelines. Presented by Alexander Fleming, MD (Kinexum, Harpers Ferry, WV) and Frank Greenway, MD, FACP (Louisiana State University, Baton Rouge, LA), we hope to hear opinions on the "drugs to watch", as well as their anticipated impact on the field. We really look forward to this session and expect it to be one of the best of the meeting.
- **Will Bariatric Surgery Replace Drugs for Type 2 Diabetes?** While the title of this presentation is intriguing enough to turn anyone's head, we hope Albert Wetter, MD (Mills-Peninsula Health Services, Burlingame, CA) will discuss the future implications of bariatric surgery and its potential applicability within the type 2 diabetes population. We have certainly heard a lot of thinking in this area recently – hopefully Dr. Wetter will be able to provide some further insight on the topic.

Friday (November 6)

- **Technologies for Metabolic Monitoring.** This session will feature presentations on many of the latest innovations in the field of glucose monitoring, including "tattoo" technology, Raman spectroscopy, continuous glucose monitoring using glucose binding protein, and sensor-augmented pump therapy. The session will open with a keynote address from Alfred Mann, MS (MannKind Corporation, Valencia, CA) on "Diabetes in the 21st Century," surely not to be missed – we really hope to hear focus on where Mr. Mann thinks all of diabetes care will go, in addition to his current focus on inhaled insulin.
- **Artificial Pancreas – Continuous Glucose Monitoring Alarms.** This session will include presentations from the "big three" in continuous glucose monitoring, DexCom, Abbott, and Medtronic. Given the recent international release of Medtronic's Paradigm Veo, we hope to hear some updates on the benefits of the low-glucose suspend technology from John Mastrototaro, PhD (Medtronic Diabetes, San Diego, CA) who will speak on "Real-time Continuous Glucose Monitoring Alarms and Considerations for Patients."
- **Overnight Closed-Loop Insulin Delivery.** The final talk in the "Artificial Pancreas – Continuous Glucose Monitoring Alarms" session will be given by research leader Roman Hovorka, PhD (University of Cambridge, Cambridge, UK) – we expect to hear a review of the latest research in the progress towards closed-loop delivery from this top researcher.
- **Artificial Pancreas – The Food and Drug Administration's Point of View.** As the Artificial Pancreas becomes more and more of a reality, we continue to hear about the anticipated complications in the approval process. As many speakers have noted in the past, most models of closed-loop technology would require approval for over six separate components, which could severely delay the availability of the technology. This session will feature more than an hour of discussion from a panel of four representatives from the FDA on the topic – we always appreciate when the FDA publicly divulges their perspective, so we will really be looking forward to this session.

Saturday (November 7)

- **Alternative Delivery Routes for Insulin and Metabolic Peptides.** This session will discuss various aspects of insulin delivery techniques, from the controversial ("The Technology and Clinical Aspects of Nasal Insulin Therapy") to the clinical ("When to Add Insulin in Type 2 Diabetes Patients Who Are Failing Oral Agents and/or Glucagon-Like Peptide-1 Therapy"). We are particularly looking forward to Kenneth Ward, MD (Oregon Health Services University, Portland, OR)'s presentation, which will discuss the role of insulin kinetics in the development of

closed-loop therapy – we hope to see some discussion of how newer faster-acting analogs in development may alter the field.

- **Hospital Technology.** This session will focus on the highly debated topic of intensive insulin control and glucose management in the intensive care setting. We expect a review of results from large clinical trials (possibly opinions on NICE-SUGAR) as well as some updates on technologies in the space – Thomas Peyser, PhD will be presenting on Glumetrics' novel fluorescent intravascular sensor, which showed some positive results in a late-breaking poster at this year's American Diabetes Association Scientific Sessions.
- **Efficacy of Continuous Glucose Monitoring in Patients with Type 2 Diabetes Mellitus.** A part of the US Army's history of sponsorship for the meeting, this presentation will feature Robert Vigersky, MD (Walter Reed Army Medical Center, Washington, DC) discussing the benefits of CGM for patients with type 2 diabetes. Throughout conferences this year, we have heard strong support for this application in aside comments from many leading physicians and researchers – we look forward to a presentation focused solely on the topic.
- **Panel Discussion: A Challenge to Industry – What Technology Do We Need for Improving Adherence and Outcomes?** This should be a fantastic closing session - we look forward to hearing different perspectives on this very important unsolved issue of adherence. The diverse panel will include a very plugged-in physician (Daniel Crowe, MD), a keyed-in researcher (Brian Hipszer, PhD), a very highly regarded diabetes educator (well-known Neesha Ramchandani, PNP, CDE), and a top diabetes blogger (star Amy Tenderich, MA, of Diabetes Mine).

— by Eric Chang and Kelly Close

11. Diabetes Comings and Goings

- **Enrique A. Conterno** was promoted to head of the new Diabetes Business Unit of Lilly USA on September 14 – it is a big promotion and move by Lilly to dramatically increase focus on diabetes. Previously, Conterno was President of Lilly USA, which oversaw the company's US business operations.
- **David Ricks** was promoted to the President of Lilly USA on September 22. Mr. Ricks was previously the general manager of Lilly China and will replace Enrique Conterno, who was recently appointed the head of Lilly's new Diabetes Business Unit on September 14 (see above).
- **Dr. Mark Erion** resigned as the CEO, CSO, and member of the Board of Directors of Metabasis Therapeutics to join Merck as vice president and worldwide basic franchise head of Diabetes and Obesity. **David Hale**, the current chairman of the board, has been appointed as the CEO of Metabasis, effective October 31, 2009.
- **Dr. Claude Bertrand** was appointed Executive Vice President, Chief Scientific Officer of Ipsen on September 22. Dr. Bertrand was previously a Senior Vice President at AstraZeneca R&D. He will join Ipsen on November 2 and will replace Jacques-Pierre Moreau (see below).
- **Jacques-Pierre Moreau** was appointed as the Chief Scientific Advisor to the Executive Committee at Ipsen on September 22. He was formerly the Executive Vice President, Chief Scientific Officer and is transitioning into more of an advisory role within the company.

- **Hubert C. Chen, MD** joined Regulus Therapeutics as Vice President of Translational Medicine on September 16, 2009. Previously, he was a Senior Director of Clinical Research at Amylin, where he focused on preclinical and clinical programs in obesity and type 2 diabetes. We view this as a major positive for Regulus Therapeutics as well as for Dr. Chen, who is clearly gaining increased responsibility.
- **Dr. Marijn E. Dekkers** was voted the new CEO of Bayer on September 15 by the Bayer Supervisory Board. Dr. Dekkers is currently the President and CEO of Thermo Fisher Scientific.
- **Werner Baumann** was named the new CFO of Bayer on September 15. Mr. Baumann currently serves on Bayer's Board of Management and the Executive Committee of Bayer HealthCare.
- **Dr. Tim Garnett** and **Dr. Tom Verhoeven** were named the co-heads of Eli Lilly's new Development Center of Excellence.
- **June D. Ameen** was named the Vice President, Corporate Development of MDRNA on September 8. In this role, Ms. Ameen will report directly to the President and CEO on alliance management, business development, technology evaluation and strategic partnering efforts for the company. Previously, Ms. Ameen was the Vice President, Business Development and Alliance of Entelos, Inc.
- **Roche's Board of Directors appointed multiple new executives on September 7 – all appointments are effective January 1, 2010:**
    - **Pascal Soriot** was appointed Chief Operating Officer Pharma Division. Mr. Soriot is currently the CEO of Genentech.
    - **Jean-Jacques Garaud** was appointed Member of the Enlarged Executive Committee. Mr. Garaud is currently the Head of Pharma Development and will be responsible for Roche Pharma Research and Early Development as of January 1, 2010.
    - **Dan Zabrowski** was voted Head of Pharma Partnering as well as Member of the Enlarged Executive Committee. The Head of Roche Diabetes Care, Burkhard Piper, will report directly to Mr. Zabrowski.
    - **Daniel O'Day** was appointed Chief Operating Officer Diagnostic Division and Member of the Executive Committee.
    - **Ian Clark** was appointed CEO of Genentech. Currently, Mr. Clark is Head of Global Product Strategy Pharma and will report directly to Mr. Soriot in his new position.
- **Dan Cohen** was named the Senior Vice President for Government Relations and Health Policy at EnteroMedics on September 24.
- **Bob Finder** was appointed an independent director of Living Cell Technologies' board of directors on September 23. Previously, Mr. Finder was the CEO of GroPep and Novozymes GroPep, the Australian subsidiary of Novozymes
- **David McAuliffe** was also appointed an independent director of Living Cell Technologies' board of directors on September 23. Mr. McAuliffe was the founder of NeuroDiscovery.
- **Dr. David Brookes** was elected as the new chairman of Living Cell Technologies' board of directors on September 23 after Simon O'Loughlin stepped down due to other commitments. Dr. Brookes was appointed as an independent director for LCT in August 2007.

12. DCU Stock Chart and Final Thoughts

	28-Sep-09	28-Aug-09		27-Mar-09		29-Sep-08		IPO		Market Cap
ALKS (Alkermes)	9.33	9.37	0%	12.10	-23%	13.35	-30%	5	87%	884.2M
AMLN (Amylin)	13.13	12.91	2%	12.00	9%	19.36	-32%	14	-6%	1.9B
ARNA (Arena)	4.58	4.70	-3%	4.15	10%	5.24	-13%	18	-75%	424.2M
BIOD (Biodel)	5.08	5.04	1%	4.94	3%	3.41	49%	15	-66%	120.9M
DXCM (DexCom)	7.98	7.95	0%	4.26	87%	-	-	5.33	50%	366.3M
ETRM (EnteroMedics)	5.40	3.90	38%	1.47	267%	6.01	-10%	12	-55%	162.2M
GSK (GlaxoSmithKline)	39.67	39.14	1%	29.49	35%	3.20	1140%	8	396%	102.9B
HALO (Halozyme)	7.42	7.47	-1%	5.68	31%	42.08	-82%	-	-	665.7M
HDIX (Home Diagnostics)	6.84	6.02	14%	5.30	29%	6.70	2%	6.27	9%	115.4M
HGSI (Human Genome Sciences)	18.90	19.80	-5%	0.97	1848%	10.50	80%	7.68	146%	2.6B
ISIS (ISIS Pharmaceuticals)	15.05	16.15	-7%	15.12	0%	6.39	136%	21.5	-30%	1.5B
MBRX (Metabasis)	0.39	0.47	-17%	0.48	-19%	16.23	-98%	10	-96%	13.7M
MNKD (Mannkind)	9.80	7.93	24%	3.39	189%	3.85	155%	2.31	324%	1.0B
NVO (Novo Nordisk)	63.68	61.06	4%	48.85	30%	51.98	23%	14	355%	44.7B
OREX (Orexigen)	9.69	8.13	19%	2.89	235%	10.65	-9%	29.2	-67%	449.9M
OSIP (OSI Pharmaceuticals)	35.08	34.15	3%	38.74	-9%	48.50	-28%	12	192%	2.0B
PODD (Insulet)	10.80	9.29	16%	4.39	146%	13.86	-22%	170	-94%	301.5M
TTHI (Transition Therapeutics)	8.36	5.03	66%	4.04	107%	5.09	64%	15	-44%	194M
VVUS (Vivus)	10.41	6.31	65%	3.61	188%	7.96	31%	1.25	733%	728.3M
XOMA (XOMA Limited)	0.81	0.86	-6%	0.56	45%	2.11	-62%	14.25	-94%	133.5M
S&P 500	1028.12	982.18	5%	752.83	37%	1271.51	-19%	-	-	-
NASDAQ	2024.43	1967.89	3%	1391.47	45%	2361.97	-14%	-	-	-

Index Value = 144.1

There was a lots of movement in diabetes and obesity companies this month, primarily concentrated on a few companies – overall, the index has moved substantially since we started it several months ago. Notably, there were 14 companies that increased in value from a month ago versus just seven that fell and overall, the diabetes and obesity stocks moved up considerably, even compared to the positive broader market in July to date. Major movements in Vivus' stock price reflected positive phase 3 data for Qnexa, its leading obesity candidate. Arena's stock price remained relatively flat despite the release of phase 3 data for lorcaserin. The Close Concerns diabetes and obesity index increased 16% in September to date to 144.1 from August, the S&P500 increased 5% and the NASDAQ increased 3% over the same period. In general, we expect clinical regulatory updates to continue to drive major changes in many stocks in the coming months, including Novo Nordisk, MannKind, Biodel, Amylin, Orexigen, and Arena, to name a few.