DIABETES CLOSE UP

Diabetes Close Up
December 2006, No. 64
Out of the Shadows

T h e S h o r t e r V e r s i o n

From the Editor:

Nothing's slowing down as the year draws to a close! Just this afternoon, we heard about an approved expanded indication for Byetta as an add-on therapy to thiazolidinediones (TZDs) – we got some quick opinions on this from some key thought leaders for our story below (see Quotable Quotes below for opinions from Drs. Steve Edelman and Orville Kolterman as well as our longer story). We think this is an excellent development for patients – this is a very complementary combo and Amylin and GSK and Takeda will all benefit, in our view, in addition to patients and healthcare providers and payors.

So, the world has really kicked into gear this month in the fight against diabetes. The United Nations on Wednesday (Dec. 20) passed a Resolution on diabetes – the grassroots path to this has really been awesome in the true sense of the word, and we see this as perhaps the beginning of some truly monumental change – the world is certainly waiting, as we saw last month in South Africa To start, the resolution recognizes diabetes as a worldwide threat, marking the *first* time the UN has made such a designation for a non-infectious disease. We believe it's a significant step that the global threat of diabetes has now been officially acknowledged and believe that the potential for the resolution could be enormous over time. Read more about this and how a mother-daughter team, diabetes advocates extraordinaire Kari and Clare Rosenfeld, along with new IDF President Dr. Martin Silink, and inspiration from many others, helped bring diabetes out from the shadows.

We're just back from IDF in South Africa and have been working through everything we learned... Results from ADOPT, the DREAM washout, and SERENADE were unveiled to eager eyes in conference halls and packed rooms. The sheer drama in terms of new data was really something, and we applaud all the investigators for their years-in-the-making, very significant work. We will remember for a very long time watching these doctors present and feeling that the face of diabetes could really be changing – UKPDS gave us, of course, the uncomfortable reality that diabetes is truly a progressive disease – there is now at least room to say that may not be so true and we expect to see much more on this front in the coming years. For now, we'd term our main takeaways that the TZD class came out looking stronger than expected, that potential for combo therapy with other new classes is striking, and that only better news awaits us.

Obesity is a very big topic this issue. We had a fascinating interview with obesity expert Dr. F. Xavier Pi-Sunyer recently in New York; we have posted the 7,000-word interview on our website for subscribers. Inside, we include highlights on Dr. Pi-Sunyer's views on currently approved drugs for obesity, the need for outcomes data, genes and neurophysiology, centrally acting obesity drugs, combination therapy, and the Look AHEAD trial for which he is co-chair of the executive committee. Look AHEAD is focusing on the disease most affected by being overweight and obesity, type 2 diabetes, and on the outcome that causes the greatest morbidity and mortality, cardiovascular disease. W**e** also give our take on two very interesting late October meetings - NAASO, the obesity meeting, and Amylin's first

annual R&D meeting, which also focused on obesity. Last, as a reminder of the burden of pediatric obesity, we also report below on England's public healthcare system's decision to begin paying for bariatric surgery in morbidly obese adolescents. That this got through NICE is confirmation of the gravity of just where we are with childhood obesity – a topic discussed at length by IDF attendees in Capetown lucky enough to hear Dr. Francine Kaufman's talks and to witness the latest, very disturbing statistics.

The literature this month was remarkable. First, we share our thoughts in detail on ADOPT, the widely awaited outcomes trial presented in Capetown and published simultaneously in *The Lan*cet. We do see this trial as a real positive for the TZD class relative to expectations and of course for GSK's Avandia in particular. While Avandia and Takeda's Actos are certainly facing new competition in the DPP-4 inhibitors, we believe the mechanism of action is novel and that the new GLP-1 combination indication granted to Byetta will also provide a big boost for the drug in 2007 (while we wait to hear about potential for a pre-diabetes Avandia indication). We were also pleased to see diabetes and obesity highlighted in *Nature* this month – our monthly list of top 25 articles includes a sizeable number of excellent review papers from the Nature Publishing Group. Speaking of *The Lancet*, by the way, the December 8 issue included a heated debate about the results of the DREAM trial - we are *loving* correspondence lately – so often of late, it just shows what a dynamic field diabetes it. Commenter Dr. Steven Nissen, a very well known cardiologist from the Cleveland Clinic, raised interesting questions about whether rosiglitazone (Avandia) reduces cardiovascular disease, while Dr. Christian Herder outlined similarities between TZD therapy and lifestyle modification. Dr. John Yudkin questioned the outcome-benefits and cost-effectiveness of TZD therapy in pre-diabetes patients, while Drs. Jacobus Lubsen and Philip Poole-Wilson asked for clarification of mortality event rates in the study. In their authors' reply, Dr. Hertzel Gerstein, Dr. Salim Yusuf, and Jackie Bosch defended the trial as a study designed to detect progression to diabetes, not cardiovascular disease. They suggested that perhaps the link between TZDs and lifestyle modification is insulin sensitization, pointed out that further data are forthcoming about rosiglitazone's role in disease progression and long-term outcomes, and provided the requested numbers in reply to Drs. Lubsen and Poole-Wilson. We think all of this correspondence aptly demonstrates how controversial diabetes is, particularly as it relates to cardiovascular disease – we'll be seeing more and more of this over time and we can't imagine debates will slow down anytime soon.

Please vote for us! On Close Concerns news, we're excited on a number of fronts! The maiden issue of our patient newsletter *diaTribe* met with great feedback, particularly our stories for patients on GLP-1 and continuous monitoring as well as our interview with star diabetes educator Davida Kruger. Our second issue will be out in early 2007. If you haven't yet seen it, take a look at www.diatribe.us. Also we've been nominated for "Best Diabetes News Blog" in the Diabetes O.C. Blog Awards for 2007! Voting is going on only this month, at diabetesoc.blogspot.com, and we'd love if you would vote for us as a year-end present! We salute Allison Blass for her work creating this oh-so valuable patient site. Please click and vote for us as "best diabetes news blog" - thank you for your consideration and please click! http://diabetesoc.blogspot.com/1990/01/2nd-annual-diabetes-oc-blog-awards.html

MAJOR HEADLINES, DCU #64

And very best wishes to all our readers in 2007. I have loved seeing so many of you this year, meeting many of you for the first time, and corresponding often with new and old friends. Thank you for so much wonderful support and encouragement this year and as always, please write me at Kelly@closeconcerns.com if you have anything in diabetes you'd like to talk about or see us cover differently or better (we so appreciate your suggestions how). We are sending very warm wishes to you and yours, the world over, and in Clare's words, diabetes is coming out of the shadows – thank you, and here's to doing our very best in 2007 to propel better care for everyone.

—Kelly L. Close

In this issue:

Quotable Quotes from October's DCU:

Dr. Steve Edelman, VA San Diego Healthcare Center, TCOYD Director, on Byetta + TZDs:

- *"The newly approved combo of TZD/Byetta represents an excellent combination of two powerful drugs that attack some of the main defects of type 2 diabetes … The combination is safe and effective without hypoglycemia or weight gain. Many caregivers have been using the two together off label and for the cautious prescriber this opens the door for using both of these effective therapies together."*

Dr. Orville Kolterman, Amylin Senior Vice President, Clinical and Regulatory Affairs, on Byetta + TZDs:

- *"The inclusion of 'use with TZDs' in the label allows all patients treated with TZDs to use Byetta as a labeled-indication. Thus, another barrier to coverage by 3rd party payors has been removed."*
- *"Pick your combo of choice, Byetta and the combo will beat the DPP-4 inhibitor and the combo any day …"*

Dr. Xavier Pi-Sunyer:

- *"I think there's a bit of nihilism from the point of view of both the [obese] patient and the doctor, saying that there really isn't very much to help me…If you don't have a pharmaceutical base and you're uncomfortable with a behavior base, then you're going to ignore the problem. I think that's what's happening."*
- *"[The Look AHEAD trial] is more translatable in a way than the DPP, because we're doing all the behavior change by groups rather than by individuals. And I think it's an important trial, because it will show whether there's a rationale for telling diabetic patients to lose weight. Right now, we're telling them to do that, but we don't have really good evidence that it's going to improve their prospects."*
- *"As we learn more, we'll be able to design molecules that would target specific receptors or block specific receptors that would affect behavior. I mean, that's been the whole breakthrough in psychiatry in the last 25 years, the change from the idea that you're going to analyze a patient to the idea that you're going to get drugs that are biologically active that will change behavior and improve the way people's minds and brains work."*
- *"The future of pharmacotherapy for obesity is going to be a combination of medications. Much as has been the case with diabetes and with hypertension…"*
- *"It's clear that there is enormous propensity to gain weight by the human species if the environment is correct…And I think it makes some sense biologically that the body really defends against underweight but doesn't defend much against overweight, since most of the survival problems in the past eons have been famine, not over-eating. So, we've built up some very good defenses against famine, but not very good defenses against overweight."*

Dr. Barry Goldstein, Jefferson Medical College of Thomas Jefferson University, on ADOPT:

- *"Ultimately, people should not argue over which drug [metformin or rosiglitazone] is better. When the study was developed, the authors were taking monotherapy very seriously … we are no longer treating diabetes that way – or at least, we no longer should be…"*
- *"Positive for diabetes… is the arsenal of drugs being built that normalize glycemia without hypoglycemia, including both DPP-4s and rosiglitazone."*

Dr. Anne Phillips, GlaxoSmithKline, on ADOPT:

- *"We have the indication for Avandia to be used as monotherapy; it is up to doctors to understand new data and decide how relevant it is to their practice. I think that the numbers for Avandia in*

terms of the risk of monotherapy failure are striking, given the 32% and 64% risk reductions for Avandia compared to metformin and glyburide."

- *"Doctors need choices, and patients need choices, so it is important that sulfonylureas are available. That said, it's very clear - it doesn't matter if you look at fasting or postprandial blood glucose or an A1c - the results here were consistently in favor of Avandia, then metformin."*

Blogwatch - See below for blogs since our last monthly newsletter. You can see any update online at http://www.closeconcerns.com/ as well as subscribe to the RSS blog feed. Our blog was recently nominated as a top news blog - please vote for Close Concerns as a top diabetes news blog at http://diabetesoc.blogspot.com.

- **December 18: NYT on Lilly's Zyprexa - unsettling at best**
- **December 17: Seattle Times on Medtronic - Not a case...**
- **December 7: Lilly discusses new GLP-1**
- **December 7: IDF Day #4 + #5: Final thoughts**
- **December 5: IDF Day #2 and #3**
- **December 3: IDF Day #1: "...what has really captured the hearts and minds of US physicians…"**

T h e L o n g e r V e r s i o n

1. DCU Company Watch

- **Amylin—FDA approves label expansion for Byetta as an add-on therapy to TZDs**: Amylin and Lilly announced today (December 22) that Byetta has been approved as an add-on therapy for type 2 diabetes patients who are not at glycemic goal on a thiazolidinedione (TZD). See below for our in-depth story on this breaking news, including opinions from Dr. Steve Edelman (UC San Diego) and Dr. Orville Kolterman (Amylin) on the implication of this combination.

- **Novo Nordisk—Novo achieves big win in hiring Dr. Nathanial Clark:** Highly regarded endocrinologist Dr. Nathanial Clark, formerly of the ADA, has recently joined Novo Nordisk – what a win for Novo! We imagine all of Dr. Clark's vast experience (clinical, political, and commercial) will be a major asset to Novo. That was fast action and says a lot about Novo's aggressive pursuit of top talent. Novo will provide a broad platform for Dr. Clark, who will have the chance to work on many innovative fronts – insulin, GLP-1, insulin pens, maybe insulin pumps - and given Novo's recent pledge to expand its sales force by 60%, we assume Novo's endocrinologists will be busy.

- **United Nations—A diabetes resolution:** What welcome news for the entire diabetes community in the UN's passage of a diabetes resolution (December 20), highlighting the global epidemic. It's also a victory for the Rosenfelds, an Oregon family that triggered the idea. Get set to descend on New York for National Diabetes Day, 2007 next November. See our in-depth story on page ten.

- **Medtronic—BD test strips to remain available; GuardControl study results published in *Diabetes Care*:** Medtronic announced December 15 that BD has sold its blood glucose monitoring business to Sanvita, a medical supply distribution company. BD had previously pledged to make strips available through December 2007, but Medtronic has now notified customers that Paradigm Link meter strips will be available "well into the future" from Medtronic or other supply distributors. They also noted that they are "making progress" on a meter replacement option and hope to announce one in 2007. This is a positive outcome for Medtronic, given that partnering with three of the top four manufacturers would have meant partnering with a direct competitor on the pump (J&J Animas or Roche) or glucose monitoring front (J&J LifeScan, Abbott Diabetes Care, or Roche). Positive results from the GuardControl Study were published November 27 in the December issue of *Diabetes Care*. The paper showed that use of Medtronic's Guardian REAL-Time Continuous Glucose Monitoring System improves glycemic control in poorly controlled type 1 patients. This study, conducted in eight European centers and originally presented at EASD 2005 in Athens, evaluated 162 type 1 patients (half adult, half pediatric) over 12 weeks. Participants were randomized into three arms: arm one used the Guardian continuously, arm two used it for three days every other week, and the control arm used only SMBG. At baseline all participants were poorly controlled, with mean A1C of 9.6% despite fingerstick testing ~five times a day. All were on insulin pumps or MDI (multiple daily injections). In arm one, A1c fell 0.6% at one month and 1.0% from baseline at three months compared to 0.2% and 0.4% in the control arm. Surprisingly, there was no statistical difference in A1c lowering between arm two and the control arm. These improvements were achieved with no changes in total daily insulin dose – this seems to demonstrate clearly that for these patients, the inability to lower their A1c stemmed from suboptimal management of insulin administration, and that having continuous glucose information helped them improve their regimens. Interestingly, at three months, half of the patients in arm one had A1c reductions >1% (37% in arm two and 15% in control arm) and 26% had reductions >2% (9% in arm two and 4% in control arm). This suggests to us that there are specific patients who may benefit more from using CGM – it would be interesting to learn whether there are ways to predict who will improve more or less – but this study is a good example of the kind of outcomes work that needs to be done to show the benefits of CGM to the payer community. Dr. Irl Hirsch noted

in a recent meeting that anecdotally it seemed that patients who did the best were ones who watched their continuous monitors frequently – we have certainly noted improvements from making ongoing small corrections throughout the day. It's great to see this study published and we look forward to seeing more of its kind. In the meantime, Medtronic is developing the next generation of the Guardian RT – we learned at TCOYD last month that it will be available in "select markets" this January. The new version looks more like a pump and is smaller than the last generation – smaller is always better, to us. The last bit of news on Medtronic is that it will be hosting a half-day investor day in New York City on January 19. Taking a leaf from Morgan Stanley Unplugged, the popular investor conference that takes place each May in Miami, this event will be called "Medtronic Unplugged" and will feature brief addresses by each of Medtronic's presidents followed by Q&A. We look very forward to hearing MiniMed's new President Chris O'Connell.

- **New Leadership at MiniMed, J&J LifeScan, and Abbott Diabetes Care:** On that management note – change is certainly in the air; as of the first of the year, there will be new top leaders at MiniMed, LifeScan, and Abbott Diabetes Care – Chris O'Connell (coming from Medtronic PhysioControl), Don Casey (coming from J&J Vistakon), and Chip Hance (coming from Abbott Vascular). Top medical device analyst Thom Gunderson of Piper Jaffray, who covers Medtronic, talked to us about the changes at Medtronic, noting that Chris O'Connell did a good job cleaning up PhysioControl, a $400 million business at Medtronic where revenues rose nearly 40% last quarter. Gunderson feels the management move should be a positive one for Medtronic and we agree, having watched O'Connell take on and pretty much wildly succeed at a very high-profile job at Medtronic some years back as a young rising star (when we co-covered Medtronic in our old Wall Street days, O'Connell had just been tapped as head of sales for Medtronic's all-important cardiovascular risk management.) We look forward to seeing how all three new leaders will be pushing forward diabetes care, as they take on leadership of these businesses. Our biggest wish is for more resources (financial, management, mindshare) to be devoted to planning and executing important regulatory trials – from patient and provider perspectives, the planning and execution and publishing of such trials couldn't be more important for reimbursement (the word that continues to spell brass ring).

- **Diamyd—Pre-IND briefing package submitted to FDA**: Diamyd announced December 15 that it is submitting a Pre-IND/End of Phase 2 Briefing Package with the FDA for proposed type 1 diabetes clinical trials in the US. The briefing package is being submitted in support of a January 29 meeting with the agency. The Swedish company currently has an ongoing phase 2/3 trial testing its product, Diamyd, in 160 patients with autoimmune type 2 diabetes (LADA). CEO Anders Essen Möller expressed hopes that the January meeting will provide "valuable guidance" toward building a US clinical program for the development of Diamyd as a therapy for type 1 diabetes.

- **Novo/Pfizer—Injunction to block Exubera sales denied:** US District Judge Leonard Sand ruled December 14 that Pfizer may continue to sell Exubera, denying an injunction by Novo Nordisk to block sales of the product as part of its August patent-infringement case. As a reminder, Novo Nordisk claimed that Exubera infringed on its patents for inhaled insulin and that the market launch of Exubera before AERx, its own inhaled insulin, would harm its status and market position. AERx is not expected to enter the market for several more years. Judge Sand explained, "Novo's attempts to show irreparable harm in the future for both its current market standing and for the future sales of AERx fail as, paradoxically, they are readily determinable for the purposes of monetary damages and at the same time speculative." We agree – Exubera sales and any potential decline in Novo's sales will be easy to track, for the purposes of awarding monetary damages, if Novo wins the trial, which we don't expect. We are surprised to see so much effort into this fight by Novo.

- **Bristol-Myers Squibb—Nonexclusive DPP-4 licensing deal signed with OSI:** BMS licensed OSI's DPP-4 inhibitor patent portfolio on December 13. OSI's development of this patent portfolio had

been on hold as of the company's last investor call in November due to shortage of capital. The company has recently dropped development on DPP-4 inhibitor PSN 9301 (phase 2). We think this is a potentially interesting deal for BMS (it also covers a patent portfolio from German company Probiodrug), and note that BMS probably got a pretty good deal if there is any value there, because OSI's diabetes area has essentially been halted. This is a non-exclusive deal, and it will be interesting to see what BMS is doing with saxagliptin (phase 3), which they have been very quiet on since the muraglitizar blow-up last year. We note that this is the first year in a very long time that BMS didn't have an investor meeting (typically held in Nov/Dec). OSI Pharma already has some non-exclusive agreements in place (Merck and an undisclosed Japanese company). Overall, this is a positive for OSI only because it is desperate for cash; the value for BMS is less clear.

- **MicroIslet—Planning investigational NDA filing for encapsulated islets in Q307:** MicroIslet announced December 13 that it had a "positive" pre-investigational new drug application (NDA) meeting with the FDA on plans for beginning clinical trials with its microencapsulated islet-cell transplantation technique for type 1 diabetes. CEO James Gavin (whose recent arrival at the company has prompted significant interest) noted that MicroIslet hopes its encapsulation technique will protect allotransplantation (same-species) islet cells from immunorejection and allow recipients to avoid the hard-core, chronic immunosuppressant regimens currently required by islet transplantation techniques such as the Edmonton Protocol. We thought this was a highly ambitious claim – a huge advance if they can manage it, but potentially very difficult to carry out. MicroIslet plans to file its Investigational NDA in Q307.

- **Merck—Announcing Janumet as Januvia sales soar:** Despite the Januvia launch late this year, Merck's December 12 analyst day was very quiet in terms of diabetes and obesity. Merck gave virtually no data on the launch, though it sounds as though it has been quite positive. The company also did not respond to unanswered questions regarding Januvia, including low potency in monotherapy, various trial designs, and uncertainty of long-term safety and durability. R&D is studying Januvia in combination with insulin and pioglitazone (as an add-on and in combo) – we believe they had the request to study Januvia with SFUs and insulin from the FDA. Janumet, a combination of metformin and Januvia, has been submitted to the FDA and a response is expected in the first half of 2006. According to data presented at IDF, in one study, Janumet dropped A1c 2.2% from baseline 8.8%, and reduced both PPG and FPG, with side effects similar to placebo (i.e., not many). In that trial, there had been questions about wash-out, etc., but this was a fast presentation in this meeting, so the trial design was not reviewed in depth. The company did try to distance itself further from Novartis' Galvus skin lesion issues in monkeys, making clear that it had completed a three-month safety trial in monkeys with Januvia where no skin lesions were observed. From a comparison perspective, management cited Januvia's better selectivity for better toxicity results. Merck is also trying to show beta cell function improvement with Januvia. We are surprised they would push this message without more long-term durability data – although we have heard even some early type 1 excitement about this (notably, not from management, who hasn't said anything about testing type 1s at this stage). In other drugs, Merck plans to move its CB-1 receptor inverse agonist into phase 3 with an NDA filing planned for 2008. Management said it was not aware of any significant increase in depression in active trial arms, but declined to answer most of the other questions about the compound including those about its comparison to Sanofi's rimonabant. Merck also announced the day before the meeting that it has teamed up with Healthy Interactions Inc. to make "Conversation Map" tools, an innovative approach to self-management education, available across the U.S. in 2007, in an effort to encourage patient empowerment in managing diabetes. We think anything Merck could do to partner with AADE (we believe they are doing extensive work on conversation maps) is certainly smart, especially if it involves getting the Januvia word out and supporting the association.

- **Lilly—Anticipated launch of HumaPen Memoir, expanded diabetes sales force, and annual analyst meeting:** Impressively ahead of schedule, Lilly is launching a new insulin "smart" pen in February 2007. HumaPen Memoir electronically records the time and amount of the previous 16 insulin doses; it is the first insulin delivery pen that does this, and we're very excited to see it (Kelly is in love with her Omnipod pump but looks forward to taking a day off bolusing to try it, as soon as possible!) This launch is part of a larger pen initiative for Lilly, which is planning to market three new pens next year – the other two are Memoir, a long-awaited half-unit pen for pediatrics, and a new pre-filled pen. We talked to Scott MacGregor, a manager and spokesman at Lilly about the pen just after EASD. It sounds like Lilly has received strong feedback, especially from CDEs, regarding the pen's unique characteristics, namely the memory. While it won't be a smart pen *quite* like a smart pump – it's not a math wizard yet, where targets can be input and insulin doses created – a memory is the first step! This pen has been on the market since mid-2005 in Finland and the Netherlands, where a number of patients have embraced it according to a couple of CDEs with whom we've spoken. In our interview, MacGregor emphasized the accuracy of dosing – we weren't really aware that was a problem in other pens, but that was interesting to hear and we do agree it will be nice for patients to see their previous doses and to be as exacting as possible. One of the recent critical breakthroughs in insulin dosing has been the "insulin on board" feature for pumps that allows one to avoid "stacking" – it would be terrific if at some point this could be available in pens, but we're sure it is a tradeoff as to how many features are included in this first-generation smart pen. In pumps, "IOB" is now just software and represents a major advantage over syringes and pens. Back on the Memoir pen – thousands of patients now use it in Europe, which is exciting. Critically, we see this new pen as perhaps helping encourage people to move to basal-bolus therapy, which we are convinced would be useful. We're convinced that many, probably all, with A1c's over 9 need insulin, and we're also convinced many may be on only one shot a day, which might be simple, but also ineffective. All good new alternatives should help. There was no mention of timing for Lilly's other two new pens, but mid to late 2007 is our guess, once the company gets beyond manufacturing and quality control hurdles. Earlier in 2006, Lilly spoke about re-energizing its insulin franchise, and it is nice to see movement toward that end. We are always concerned about reimbursement and hope that Lilly has done its work to ensure coverage for these new devices; historically, weak reimbursement has deterred pen use. On a related note, at the IDF meeting in Cape Town, IDF and Lilly announced the Bringing Research In Diabetes to Global Environments and Systems (BRIDGES) program; a $10 million gift from Lilly will fund the BRIDGES grant program to support translational research projects. These projects will "translate" clinical research into real health care models and programs. BRIDGES will ask for grant proposals in 2Q07, and the first awards will be announced by the end of 2007. We don't see translational research garner extensive funding and see this as great news for researchers like star PhD Linda Siminerio of the University of Pittsburgh Diabetes Institute, who has done significant translational research over time and was very excited about this new program at IDF. In other news, Lilly had its annual analyst meeting in December and gave a little more detail on its diabetes business. Notably, in 2007, Lilly will increase by 40% the insulin-marketing portion of its U.S. sales force. Lilly said it will also increase its diabetes sales force worldwide to encourage Byetta growth – we don't foresee any slowing, despite the chatter about DPP-4 inhibitors, which we feel will also be a great new class, but which won't impact Byetta too much, given the vast need for help (we estimate 4-5 million type 2 patients out of control in the US alone, failing orals, probably badly enough that DPP-4 inhibitors won't be potent enough – and there are fewer than 500,000 patients on Byetta today, so that's quite a market[1].) At the analyst meeting, Lilly announced that it plans to submit its inhaled

[1] To be sure, we see a very sizable market for DPP-4 inhibitors as well, especially as glycemic targets are reduced and as physicians learn how easy it is to put patients on therapy – this assumes no long-term safety problems, of course, with this new class. From our talks with doctors, we see patients appropriate for DPP-4 inhibitors as more the early patients with A1cs of 6.5-7.5 striving to get to a normal A1c, whereas those appropriate for Byetta seem to tend to be those who have already failed other orals and likely have a higher A1c where the potency of a drug like Byetta is needed, and where weight loss could also be a major help.

insulin product, in development with Alkermes, for FDA approval in 2009. As we've previously noted, approval of Arxxant (ruboxistaurin) for retinopathy has been delayed with an approvable letter – we are impressed that Lilly is appealing to the FDA, and we certainly hope the FDA will think more about "doing no harm" than about making it so difficult for manufacturers to get drugs approved for complications that they just quit investing in them. The FDA wants an additional trial supporting efficacy and safety, a request that Lilly has appealed, for it may push back approval up to five years. Five years! We need some patient advocacy on this one…

- **Transition Therapeutics—Two early stage drugs:** Transition Therapeutics has two diabetes drugs in the pipeline as noted in its annual meeting on Dec 11: GLP1- I.N.T. and E1- I.N.T. Of interest, Dr. Dan Drucker of the University of Toronto, Dr. Gordon Weir of the Joslin, and Dr. Jay Skyler of the University of Miami are on the company's advisory board. Transition recently completed a $25 million private placement funded by Great Point Partners. E1- I.N.T is Transition's first generation product, partnered with Novo Nordisk, which just completed exploratory phase 2 trials. Interim data show that the first four type 1 patients who used E1- I.N.T for four weeks reduced their insulin use, with peak reduction at eight to 12 weeks, suggesting a possibly regenerative response though this is obviously very early-stage research. Novo Nordisk has provided $48 million upfront in R&D milestones as well as commercial milestones and (low-escalating, double-digit) royalties. It will make a decision at the end of phase 2 whether to assume development costs based on the data – we imagine by March or April. GLP1- I.N.T is Transition's second generation (and we would say higher interest) product, currently funded by the JDRF, which just contributed $4 million to take GLP1-I.N.T. to the end of phase 2. Still preclinical, management says GLP1-I.N.T. should enter phase 1 studies by early 2007. Management noted during the meeting that GLP-1 analogs are said to potentially promote new islets and gastrin has been shown to enhance this effect (from the research of Dr. Rabinovitch of the University of Alberta). Management said gastrin enhances GLP-1's effect seven or eight-fold. In animals, there is islet regeneration observed with this treatment, and glycemia remains normal for at least 10 to 12 weeks post-treatment. The strategy is to find a commercial partner to take the product forward well into phase 2. Phase 1 is to begin in early 2007 (followed by "the initiation" of phase 2). We imagine the partnership talks must be very interesting given the huge interest in GLP-1.

- **Avanir—Zenvia for diabetic neuropathy? Sounds like a long way off…:** Avanir Pharmaceuticals held its F4Q06 earnings call on December 11, 2006. The company's lead development product is Zenvia, a combination of the glutamate inhibitor dextromethorphan and the enzyme inhibitor quinidine, which increases the bioavailability of dextromethorphan. Zenvia was submitted to the FDA in January 2006 for the treatment of involuntary emotional expressiveness disorder (IEED) and is currently also under phase 3 studies for the treatment of painful diabetic neuropathy (DPN) – results are expected mid-2007. We thought the call was fairly negative in terms of this drug actually being approved for DPN, and the circumstances again remind us of the difficulty of developing drugs for this complication – particularly troubling given the limited arsenal for neuropathy drugs (and more broadly, drugs for microvascular diabetes complications). Management said it is meeting with the FDA in February 2007 to discuss what is needed for a new NDA. That seems like a long wait to us, but they called it a good opportunity to prepare and plan after an investor expressed a similar sentiment during Q&A. Mmm. Avanir hopes to eventually partner Zenvia for DPN, but the development program will depend heavily on whether the drug is approved for IEED first. One investor pointed out that the FDA has higher safety thresholds for DPN drugs than IEED drugs, and management admitted as well that the FDA may be more accustomed to that because of the polypharmacy usage of most diabetes patients and because these patients are not as compromised as IEED patients. The situation does not look very encouraging to us – it sounds like while Zenvia did demonstrate efficacy in the phase 2 trial for DPN, it may be hampered by intrinsic safety issues that will make an FDA approval for this indication – and possibly any indication – difficult to achieve.

- **Sanofi-Aventis—Rimonabant date set for April, SERENADE positive but CNS side effects still troubling**: Sanofi announced December 8 that the FDA set a six-month review for the October 26 resubmission of rimonabant's NDA, and the goal date for action is April 26, 2007. We note that this will be right around the pre-diabetes conference in Barcelona (2nd International Congress on Pre-Diabetes and the Metabolic Syndrome, April 25-28, 2007), where we imagine Sanofi will be a sponsor. From a safety perspective on the CNS front, the SERENADE data weren't reassuring, although we would assume the drug will ultimately get approval and will have a black box label on the CNS front (depression, anxiety, etc). We think the FDA is under pressure to show some progress on obesity and that that is positive for Sanofi. Sanofi's head of pharmaceutical operations Hanspeter Spek reiterated in an October 31 conference call that Sanofi will not speculate on the FDA's plans or timeline for the drug. We think this is smart, because in retrospect, there was probably too much speculation last year. See NAASO conference notes this issue for more perspectives on likely rimonabant approval. Regarding SERENADE, this 278-person, 56-center trial showed slightly better glycemic data in our view than did RIO-Diabetes. Similar to all the RIO trials, cardiovascular risk factors were improved in patients given rimonabant. Drug naïve patients receiving rimonabant fell from a 7.9% baseline A1c to 7.1% after six months, compared to 7.6% in placebo, suggesting a "real" reduction of 0.5% from a fairly low baseline. Half (51%) of rimonabant-treated patients achieved A1c <7%, compared to 35% of those on placebo. Weight loss was 6.7 kg for the treated group compared to 2.8 kg for placebo, from a baseline of just below 100 kg. While this phase 3 trial probably isn't enough to submit for a diabetes indication, the data are promising and support Sanofi's positioning of rimonabant as a drug for cardiometabolic risk reduction, not just weight loss. SERENADE represents the first major non-obesity trial for rimonabant, with 5% of the participants neither overweight nor obese. Yet we note that while the efficacy data were better than expected, the safety data were arguably worse. The discontinuation rate due to adverse events was 9.4% in the treatment group compared with 2.1% in placebo patients, and the rate of "serious adverse events" ran to 6.5% and 3.6% for the two groups respectively. Rates of "depressed mood" were markedly higher for rimonabant patients vs. placebo-takers – 5.8% vs. 0.7%. There were four drop outs for psychiatric reasons.

- **Novartis—Hoping for Galvus in February 2007, submitting metformin combo:** Novartis continues to build up the clinical evidence behind Galvus (vildagliptin) as the FDA considers the additional safety and efficacy data the company submitted in November. At IDF, Dr. Vivian Fonseca of Tulane University presented new sub-group analyses of data from phase 3 vildagliptin trials that support the drug's efficacy in three subsets of more difficult-to-treat patients: poorly controlled (high A1c), elderly (hypoglycemia-prone), and obese patients. He showed that the drug lowers A1c more in high baseline A1c patients – which we certainly think is positive, but is not particularly distinctive from every other antihyperglycemic. He pointed out that hypoglycemia is a bigger problem among the elderly, as had other experts at IDF (see GSK). However, when given in combination with insulin, vildagliptin actually decreased the incidence of hypoglycemia while improving glycemic control – all without any changes in overall insulin requirement. It is very unusual, he said, for a drug to reduce A1c without increasing hypoglycemia in combination with insulin, and Novartis has "vigorous efforts" underway to study this further. We can imagine! This is a very intriguing result. We note that an indication with insulin would be very good for the DPP-4 inhibitor class. For obese patients, Dr. Fonseca emphasized the advantages conferred by the weight neutrality of this drug. Earlier, the company also indicated on November 28 that it intends to seek approval for a Galvus/metformin combination in Q107 – we note that Merck has already submitted for this combination with Januvia.

- **Compellis Pharmaceuticals—Newly patented nasal spray for obesity**: Compellis won a patent on December 6 for CP404, a nasal spray intended to treat obesity by blocking the senses of smell and taste, thereby reducing patients' food intake. We spoke to CEO Chris Adams about the product, which he said would enter the market in 2010 if clinical trials go well. The drug would cost about

$500 to $1,000 a year, which sounded low to us. Adams told us that the plan is to begin phase 1 human trials with about 50 healthy overweight volunteers in mid-2007. The potential market for the drug is anywhere from 50-100 million patients. He said that its leading competitor is Sanofi's rimonabant, but the advantage of Compellis's product is that it would only be locally delivered, on an as-needed basis, and have fewer systemic effects. CP404 works by reducing patients' sense of taste and smell. He added that it could also be taken in combination with other compounds – certainly, we've heard leading doctors say at many conferences that the future of obesity therapy, like diabetes therapy, is polypharmacy. We were a little put off to hear that CP404's effects will likely last four to six hours after administration – when we asked if patients might balk at a drug that reduces their senses for so long, Mr. Adams pointed out that "if it helps your weight problem," patients will likely take it. He noted that Compellis has already received many emails from people asking if they can get the drug now. We asked if Compellis was looking to partner the product in the future, and Adams said that they are actively looking for partners for both development and marketing.

- **Nastech—Dose ranging studies of insulin and PYY_{3-36} nasal spray positive:** On December 21, Nastech announced positive results from a study of PYY_{3-36} nasal spray designed to evaluate pharmacokinetic parameters, dosage safety, appetite, and food intake in obese subjects. The double-blind cross-over trial tested several doses of PYY_{3-36} nasal spray against placebo and intravenous PYY_{3-36} in 24 obese subjects with BMI between 30 and 40 kg/m^2. The Nastech press release indicated that results from the trial will be used to establish dosing information for a phase 2 program and are sufficiently positive to "advance [Nastech's] obesity clinical program in 2007." The phase 1 study established that PYY nasal spray was well-tolerated and produced dose-dependent treatment effects – though numbers were not given. Nastech also announced positive results on December 6 from a placebo-controlled, dose-escalation phase 1 study comparing the company's insulin nasal spray to Exubera and Novolog insulin. Nastech's nasal insulin spray acted more quickly (between 16 to 19 min to maximum) than Novolog and Exubera, though Novolog achieved higher plasma insulin levels. Nastech pointed out that speed of onset is important, especially for type 2 diabetics who have enough insulin but do not have sufficiently fast postprandial insulin response to cover meals. The focus on speed rather than efficacy seems to us like a bit of a concession that noninvasive delivery may not be as efficient as injected insulin. Interesting… The trial included 12 participants and compared three doses of nasal insulin with one of Exubera, one of Novolog, and one nasal spray placebo. No clinically significant hypoglycemia was observed for nasal or inhaled insulin. CEO Dr. Steven Quay said that the study achieved both of Nastech's goals for nasal insulin: faster onset of action than injected insulin analogues and greater concentration of insulin than existing inhaled insulin. He said that the company would continue to work on increasing bioavailability and duration of effect as they work on expanding formulations

- **Innodia—Phase 2 trials initiated for novel obesity compound Adyvia:** Innodia announced December 5 the initiation of phase 2a clinical studies to assess the safety and efficacy of Adyvia, an oral drug candidate for the treatment of obesity. The 12-week trial will enroll 100 patients in all, with results expected at the end of 2007. Adyvia passed phase 1 studies in healthy adults with dose-proportional pharmacokinetics and good safety and tolerability. In animals, the drug has produced gradual and steady weight loss, in particular decreasing visceral fat, by an undisclosed "novel and previously undefined" mechanism of action. Innodia is currently conducting preclinical studies to look for more potential obesity and diabetes compounds that target the same mechanism. It also has a preclinical program looking at compounds that prevent islet amyloid polypeptide deposition, a contributor to beta cell decline.

- **GlaxoSmithKline—Highlighting Avandia at IDF with ADOPT and DREAM washout**: Both ADOPT and the DREAM washout results presentations at IDF were very well-attended, and overall both were positive for rosiglitazone. ADOPT showed that monotherapy with rosiglitazone keeps type

2 patients at goal longer than either metformin or sulfonylureas (see lit review in this issue of the *NEJM* results and editorial) while the DREAM washout showed that rosiglitazone does delay progression to diabetes in prediabetes patients – while patients are taking the drug. We spoke to Dr. Anne Phillips at GSK about the results of both trials, about Avandamet, and about a potential combination use with Byetta. Dr. Phillips stressed that the UKPDS showed that diabetes is a relentlessly progressive disease, but we wondered if ADOPT has changed anyone's thinking on that point. We were curious for data on compliance or "adherence" rates for TZDs, but this information was not available. The results of the trial were clearly beyond Dr. Phillips' initial expectations - one could hear this from the tone of her voice. When we asked her about her initial reaction, she promptly said that she had been stunned when she saw the first results. "I first saw the efficacy graphs... The durability was simply stunning to see. It is very clear that Avandia could be used as initial therapy and that it can be a cornerstone of treatment." She discussed how doctors are using more combination therapy, which we have written about widely this year. Even though combination therapy wasn't studied as part of ADOPT, we see that as a major high point of the trial results - monotherapy, in our view, may as well be dead, except for the earliest presenters. Said Dr. Phillips, more diplomatically, "Combination therapy is a complex decision, and use varies from place to place, depending on standards and guidelines, which vary widely. We have the indication for Avandia to be used as monotherapy; it is up to doctors to understand new data and decide how relevant it is to their practice. I think that the numbers for Avandia in terms of the risk of monotherapy failure are striking, given the 32% and 64% risk reductions for Avandia compared to metformin and glyburide." We questioned Dr. Phillips about the relative lack of efficacy with SFUs and whether they should still have a place in diabetes therapy. She responded that there will be a place for SFUs but pointed out that doctors are very concerned about use in the elderly, due to hypoglycemia risk in particular. "Doctors need choices," she emphasized, "and patients need choices, so it is important that SFUs are available. That said, it's very clear - it doesn't matter if you look at fasting or postprandial blood glucose or an A1c - the results here were consistently in favor of Avandia, then with Metformin." There are, of course, many aspects to consider with drugs - durability, tolerability, adverse events, cost (both direct and indirect, as well as the cost of not treating aggressively); indeed, this is a complex series of components. We also asked Dr. Phillips about GSK's plans for use of Avandia in pre-diabetes. She stressed, as expected, that it is important to realize there is not an indication for pre-diabetes in the US. DREAM looked at pre-diabetes and showed some very impressive results in reducing the progression to diabetes, she said, and the washout results were also interesting, though they covered just a short period of time and made her want to do more studies, so she is excited about DREAM ON, the follow-on trial. The DREAM washout data showed that once someone goes off Avandia, they will develop diabetes at the same rate as those on placebo. When we asked Dr. Phillips about potential for beta cell regeneration or preservation, she said that they saw the possibility of some disease modification and that when you stop the drug you stop the influence - but that more work needs to be done on this front. When asked about combination use of Avandia and Byetta, she said that was a very interesting idea because combination use takes into consideration different mechanisms; we also asked if lower doses of each drug might mitigate the adverse events of both drugs, and she said that was certainly possible. Finally we asked Dr. Phillips whether she would assume rosiglitazone's results with monotherapy failure and progression to diabetes are a class effect, and she said that until more studies could be done, she would be very hesitant to say they are. GSK estimates that as of July 2006, about 900,000 people were on Avandia and more than 55,000 were on Avandamet. Since the launch of each drug, over 4 million have taken Avandia and over 1 million have taken Avandamet.

- **Novo Nordisk—Strong presence at IDF, adding to US sales force, funding European research:** We note that Novo had the strongest exhibits at IDF this year, with billboards in the airport and all around the convention center, a very well-attended pre-conference symposium, and well-trafficked booths. The company also reported positive new results on December 5 from a sub-group analysis of

PREDICTIVE, the company's ongoing multinational observational study of Levemir (detemir) long-acting insulin. The new results come from a 14-week analysis of a European subgroup of 2,377 type 2 patients who had newly switched from oral to insulin therapy. After 14 weeks, the patients lost a mean weight of 0.7 kg, with greater weight loss in higher-weight patients (to be fair, many might just term this weight neutrality, but that's better than weight gain!) Mean A1c dropped from 8.9% to 7.6% and, surprisingly, the incidence of hypoglycemic episodes also dropped. Favorable results, though we caution that this was not a randomized trial. Most likely the patients were taking weight-gain promoting oral agents before the switch, such as sulfonylureas and thiazolidinediones. While the results don't suggest that detemir causes weight loss, detemir does seem more weight neutral than some oral agents. The decrease in hypoglycemic episodes is likely also an artifact of taking patients off oral secretagogues, but the data are certainly good arguments against the fear of hypoglycemia that prevents some patients from switching to insulin. Overall, this study is quite positive – we note that Novo continues to gain market share in the long- and short-acting analog market. To further expand this trend, Novo announced December 1 that it will increase its US sales force to 1,900 from 1,200 in 1H07 to further promote its insulin analogs and to prepare for liraglutide's expected 2009 release. AERx, its inhaled insulin, should also hit markets in 2009. Both products will have stiff competition, which we imagine is at least some of the motivation behind this move. On the European side, the company announced on December 12 that it will be collaborating with the EASD and JDRF on two new initiatives to promote diabetes research in Europe. The first, in partnership with both foundations, will focus on type 1 diabetes and the second, in partnership with the EASD, will focus on type 2 diabetes. Together, the two initiatives will fund approximately 3.6 m euros ($4.5 m) of research over the next three years.

- **Pfizer—Exubera adoption continues slowly; new obesity compounds**: Pfizer announced at its November 30 analyst meeting that two of its obesity compounds have shown efficacy comparable to Sanofi's rimonabant in early clinical trials. The first, CP-945,598, is an antagonist of the cannabinoid receptor 1, the same receptor that rimonabant blocks. Patients taking CP-945,598 have lost 4% to 5% of their body weight in phase 2 trials and the drug is now in phase 3 studies. The second compound works through MTP inhibition and has thus far produced weight loss around 6%. We're not surprised that the world's biggest pharmaceutical company is moving into obesity, given the huge potential market for efficacious obesity drugs, but the me-too strategy is unlikely to produce something disruptive anytime soon. We'll be very interested to hear more about the MTP drug, going forward. In the meantime, Exubera continues to underwhelm as endos and diabetologists (the focus of Pfizer's controlled 2006 launch) fail to embrace the product. Pfizer is now scheduled to launch Exubera to general practitioners in January, who we think will likely be slightly more interested in the product compared to specialists, though because the dosing etc will still not be as simple as other products, the teaching time involved for insulin –naïve patients may be a serious disincentive. How Exubera ultimately does will depend on how enthusiastic PCPs are and how quickly the product catches on – by 2010, the next three inhaled insulin products could be on the market: Novo and Aradigm's AERx-iDMS, Lilly and Alkermes's AIR insulin, and Mannkind's Technosphere insulin. The latter is the most anticipated because of its especially rapid action and because it may well be far easier to dose than traditional insulin. Pfizer announced plans on November 28 to cut its US sales force by 20% in what has been widely termed as an acknowledgement that its current model for marketing drugs to doctors is too expensive. We hope this isn't an indication that the company will be cutting back on educational efforts accompanying Exubera's launch.

- **Bayer 3Q06—Weaker sales compared to first nine months:** Bayer reported November 27 that net sales for the Diabetes Care segment were $244 m in the September quarter, down 1.1% from last year's $247 million. Sales in the first nine months were $778 million, up 12.8% from last year's $690 million. When asked about weak third quarter growth compared to the nine month figure, management said that the results in Q3 were a function of destocking in the US. Management said

that while the diabetes business was relatively weaker in Q3 compared to prior quarters, sales in October and November were very strong. Bayer expanded its diabetes product range with its July acquisition of Metrika, a manufacturer of A1C monitoring devices. The diagnostics business has now been divested. Bayer will hold an R&D meeting sometime in 1H07 and will provide pipeline updates at that time. However, management said the first-pass review is complete, and the company is clear about where it will head with key assets.

- **Johnson & Johnson—Topiramate for possible use in diabetes and obesity:** Johnson & Johnson was involved with a study appearing in January's issue of the *International Journal of Obesity* on "Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes." The first author was Professor Hermann Toplak from the Institute for Diabetes and Metabolism in Graz, Austria. Topiramate (Topamax) is an Ortho-McNeil drug approved for migraine and epilepsy – it had been studied in Phase 3 trials for obeisty, but was summarily dropped after trouble CNS-related side effects. We are interested to see its use in combination therapy with lower doses. This study published was a randomized, double-blind, placebo-controlled study investigating topiramate in obese type 2 individuals being treated with metformin. Weight loss was 1.7%, 4.5%, and 6.5% in the placebo, 96 mg/day, and 192 mg/day groups respectively. A1c reductions were 0.1%, 0.4%, and 0.6% - it was unclear the extent to which the A1c reductions were direct or not. The authors call for further study in obese people with diabetes, and there is currently an ongoing phase 3 trial investigating topiramate for weight loss in subjects with metabolic syndrome, sponsored by Northeastern Ohio Universities College of Medicine. We'll be watching this closely.

- **Veraxa Health—Joslin spin-off to market Joslin Vision Network for retinopathy**: Veraxa is the Joslin Diabetes Center's first for-profit spin-off, launched November 15 as an independent company focused on marketing the Joslin Vision Network (JVN), a diagnostic retinal evaluation service for diabetic retinopathy. JVN includes a camera workstation made by Topcon Medical Systems and Joslin software that allows healthcare professionals to image patients' retinas without dilated eye exams and send the images to diabetes eye-care clinicians at Joslin, who evaluate them for diabetic retinopathy and other ocular disorders. Results and care recommendations are sent back within two business days. Undiagnosed retinopathy remains a problem in diabetes care. JVN is already used in federal healthcare systems, so we hope Veraxa will be able to bring the service into more private practices.

—by Kelly Close, Daniel Belkin, Cindy Glass, and Jenny Jin

2. FDA approves label expansion for Byetta as an add-on therapy to TZDs

We were expecting to see this label expansion approved this year and from a patient perspective were very happy to see this come in as we think the timing is excellent for Amylin, as well as GlaxoSmithKline and Takeda. The combination should be very complementary (even synergistic) because it will work on both defects in type 2 diabetes - insulin resistance and insulin secretion. TZDs confer insulin sensitivity, vascular protection, and other fairly impressive metabolic benefits while Byetta improves insulin secretion, reduces hepatic glucose output, and slows gastric emptying.

Dr. Bernie Zinman presented the clinical trial evidence on this combination at ADA back in June (Abstract #117-OR; see DCU #59 for our take). Briefly, this was a 233-subject trial of type 2 diabetes patients not at goal on a TZD with or without metformin. After 16 weeks, 62% of patients who added Byetta achieved A1c < 7% compared to 16% of placebo patients. Patients on Byetta lost 3.3 lb compared to a 0.4 lb loss on placebo. Only 20% were on a TZD alone – the rest were on both a TZD and metformin – but the slight weight loss in placebo was a little surprising to us. This seems very counterintuitive unless there was a heavy lifestyle element, in which case the weight loss with Byetta add-on also should be adjusted. Nonetheless, we do think that one of the best aspects of a Byetta and TZD combination is the likelihood that Byetta mitigates or even cancels the weight gain usually experienced on TZDs. Another

very real element to watch is potential beta cell regeneration or prevention – the jury will remain out on this until the appropriate studies are done, but we are getting optimistic about this in spite of ourselves – what a time for patients if one of the major findings of UKPDS could be reversed – that diabetes will always be a progressive disease.

There's been some speculation that the TZD class – which sold over $4 billion in 2006 - will be heavily hurt by DPP-4 inhibitors because of the latter's weight neutrality, so we think this combination is very positive for TZDs, especially Avandia, after all the data presented at this year's IDF. We aren't actually sure if this will be *more* positive for Byetta or TZDs, but certainly both will benefit. However, this combination will be more expensive than the other two (TZDs with metformin or a sulfonylurea) so it will be interesting to see how payors react.

We caught Dr. Steve Edelman of the VA San Diego Healthcare Center and asked for his overall reaction on the news - Dr. Edelman is founder and Director of the superb patient-education program Taking Control Of Your Diabetes (TCOYD), and we know he is very patient-oriented and patient-focused. He said that the newly approved combo of TZD/Byetta represents an "excellent combination" of "two powerful drugs that attack some of the main defects of type 2 diabetes." TZDs, he said, have clearly been shown to preserve beta cell function via their effects on reducing insulin resistance and have a clear advantage in terms of prevention of CVD (he cited PROactive) and type 2 diabetes (he cited DREAM) and have a lower secondary failure rate (he cited ADOPT). Continued Dr. Edelman, "Byetta works synergistically on glucose-dependent insulin secretion and glucagon suppression as well as improved beta cell health. The combination is safe and effective without hypoglycemia or weight gain. Many caregivers have been using the two together off label and for the cautious prescribers this opens the door for using both of these effective therapies together." When asked about cost concerns, Dr. Edelman replied, "The cost of not doing something is far greater."

We also wanted to take a chance to speak to the doctors who work with Byetta at Amylin so we rang up San Diego and found Dr. Orville Kolterman, Amylin Senior Vice President of Clinical and Regulatory Affairs, who was, as would be expected, extremely positive as well. When we asked him how DPP-4 inhibitor combos will compare to Byetta/TZD (or other) combos, he said, "Pick your combo of choice, Byetta and the combo will beat the DPP-4 inhibitor and the combo any day," underscoring that Byetta potency is extremely impressive in both absolute and relative terms, especially over time. He said the combo will provide patients and caregivers with another approved tool to use in the management of their diabetes. When we asked how this will expand the market for Byetta, he emphasized that the inclusion of 'use with TZDs' in the label allows all patients treated with TZDs to use Byetta as a labeled indication. "Thus," he remarked, "another barrier to coverage by third party payors has been removed." Certainly, we think some healthcare providers may have wanted to use this combination before but could not get it reimbursed. We know this will help open the door for the needed reimbursement as well. Dr. Kolterman was optimistic about a synergistic effect between the two drugs, noting that, "Since the study was done adding Byetta on top of a TZD, the resulting ~1.0% reduction in A1c was achieved on top of whatever the TZD was already doing to lower A1c. And….the patients lost weight!" Weight loss is the most notable aspect about the combination, he believes. "Byetta, when used in conjunction with a TZD, appears to have the ability to 'contain' the weight gain driven by TZD use alone." Very powerful, as nearly 500,000 patients have seen to date.

—by Jenny Jin and Kelly Close

3. UN Resolution a Victory for People with Diabetes – and an Oregon Family

The global threat of diabetes has now been officially recognized – and one family's battle to bring the disease "out of the shadows" has been rewarded.

On Wednesday, December 20, the United Nations General Assembly passed a resolution that recognizes

diabetes as a worldwide threat, marking the first time the UN has made such a designation for a non-infectious disease. The resolution calls for governments worldwide to develop national policies to improve diabetes care and prevention.

Exactly how governments are to do this, and with what funds, is unclear, and skeptics might dismiss the resolution as having no more meaning than a UN call for world peace. But there is significance in calling attention to a malady that has long been known as a "silent killer" or a "silent disease" – a condition that many patients themselves are reluctant to discuss.

"Diabetes has been a very hidden disease, and it's often hidden in the statistics," said Charlotte Ersboll in an interview with us this morning – Ersboll is vice president of corporate branding for Novo Nordisk, which was one of the campaign's sponsors. "Every country should at least have a national health plan that addresses diabetes – it should be addressed as a human rights issue, that every person has access to good care."

Among other things, the resolution now means that on World Diabetes Day, November 14, diabetes advocates can make presentations at the UN, creating ample media opportunities as well. It will be interesting to see the response to the Resolution next November in New York City.
Interestingly, no reference to a cure is made in the resolution.

Its origins appeared to have occurred five years ago at the kitchen table of Kari Rosenfeld and her daughter, Clare, in Eugene, OR. Clare, diagnosed with type 1 diabetes at age 7, was 15 years old at the time and already heavily involved in youth advocacy programs. She wondered how else youngsters could have a voice.

"What about the UN," she asked.

"I really don't know anything about the UN," her mother said.

They began doing research, and in 2003, Clare gave a speech in Paris at the International Diabetes Federation Congress – by now, she was traveling to many countries as a teen advocate – and she approached IDF Vice-President Martin Silink with the idea that his organization should pursue such a resolution.

"He was somewhat shell-shocked, but he invited us to breakfast the next morning," Kari says.
The effort picked up steam last year, and Kari became the project manager for the resolution. The IDF formally launched the campaign – "Unite for Diabetes" – at the 2006 ADA meeting in New York. Both the ADA and the JDRF participated in the effort, and industry played a central role. In addition to Novo Nordisk, corporate sponsors included GSK, J&J, Lilly, Merck, and Pfizer (platinum) as well as Bayer, Novartis, and Sanofi-Aventis (gold) and Abbott Diabetes Care (silver).

Ultimately, the People's Republic of Bangladesh sponsored the resolution until it was accepted by the G77 (a coalition of 133 developing and transitional countries led by the Republic of South Africa).
The effort, Clare hopes, will do what the grim tally of the epidemic has not done. "Statistics have been unmotivating and haven't changed people's minds," she says. "But the resolution brings diabetes out of the shadows and represents a legitimizing force" for advocates, who will now have greater credibility when they press for improved care or greater resources for patients.

Ultimately, Silink is also given great credit for his work on getting the resolution passed - he was recently named President of IDF, and we believe the passing of the resolution represents an extremely promising way to start his role.

Clare is now a 20-year-old student at Lewis and Clark College in Portland, studying both chemistry and international relations; she wants to go into pediatric endocrinology. She is impressed by how rapidly the resolution came about, once everyone came together. "It was an idea that started out at our kitchen table, but it was desired around the world for quite awhile."

—by James S. Hirsch and Kelly L. Close

4. A Conversation with Dr. F. Xavier Pi-Sunyer

Dr. Xavier Pi-Sunyer, the Chief of the Division of Endocrinology, Diabetes, and Nutrition at St. Luke's - Roosevelt Hospital in New York, is perhaps the foremost authority on obesity in the United States. It would take more than one article to do justice to a career that began over 40 years ago and has included the Presidencies of the American Diabetes Association, the American Society for Clinical Nutrition, and the North American Association for the Study of Obesity, 120 journal articles, academic appointments at Columbia University and Rockefeller University, panel positions at NIH and the FDA, and continuing work in virtually every area of obesity treatment.

It seems that at any given moment he is always involved with the leading developments in obesity research. This year is no different. Dr. Pi-Sunyer was a lead investigator in Sanofi's clinical trials for rimonabant, the latest pharmaceutical drug targeted for obesity. He is on the Obesity Advisory Board for Amylin, which last month began a combination therapy (pramlintide plus leptin) clinical trial.

Dr. Pi-Sunyer is also the co-chair of the executive committee for the Look AHEAD study, a multi-center randomized clinical trial designed to examine the effects of lifestyle intervention on achieving and maintaining weight loss over the long term through decreased caloric intake and exercise. Look AHEAD is focusing on the disease most affected by overweight and obesity, type 2 diabetes, and on the outcome that causes the greatest morbidity and mortality, cardiovascular disease.

We interviewed Dr. Pi-Sunyer in late November at his office at St. Luke's in New York. What struck us as most noteworthy is his optimism about the future for obesity, despite having seen the problem grow to epidemic scale during his professional lifetime. Here are excerpts from our conversation:

On the currently approved drugs: I think there's a bit of nihilism from the point of view of both the patient and the doctor, saying that there really isn't very much to help me. And certainly the two drugs that are available, even though they have an effect, it's a modest effect. And most people don't get reimbursed for it…So, there isn't a very good pharmaceutical basis for treating [obesity]. . . If you don't have a pharmaceutical base and you're uncomfortable with a behavior base, then you're going to ignore the problem. I think that's what's happening.

On the need for outcomes data: The other problem is with the use of pharmaceuticals. This was the attitude of Medicare – show us they're really effective. And the cost benefit ratio -- for what we're paying, what are we getting out of it, in terms of decreased mortality, decreased morbidity? And there aren't really sustained, long-term trials of how these drugs affect cardiovascular events, type 2 diabetes complications, etcetera…I think because obesity is a long-term risk, not a short-term risk, you can't get that information with a six-month trial. You'd need a ten-year trial or a twelve-year trial, like we're doing with Look AHEAD[2] now, and with DPPOS[3] for prevention. You need long-term trials. The drug companies aren't

[3] DPP, the Diabetes Prevention Program, is now known as DPPOS – the Diabetes Prevention Program Outcomes Study. According to the Biostatistics Center at the George Washington University, the DPP Collaborative Group was funded to do

going to do those trials. They don't have the money or they don't want to spend that kind of time. So, they don't get done, and the data aren't there.

…So I think there are a lot of ways that one can modify the DPP to make it cheaper and much more translatable. You can certainly go to group therapy, which is the way the Look AHEAD trial is now being done. We treat patients here all the time. We very seldom treat people individually [as they were in DPP]. We treat them in groups, because we particularly are interested in behavior change. So, we don't use a medical model, whereas around the country, what is used most often is a medical model where a patient goes to a doctor and the doctor provides the service, and there's no ancillary help for the doctor, and he's only got 12 minutes, and he's got other things to talk to the patient about, and he doesn't get to it. I think you need to set up a whole different mechanism of how to treat these patients. . . But it can be done. I don't think you look to the DPP as a model for how to translate this to a larger group of people. You look to the DPP to give you the rationale for saying we need to have these people lose weight.

On the Look AHEAD trial: Look AHEAD[4] is a trial that is also NIDDK-funded. It's not a prevention trial for diabetes, it's a prevention trial for cardiovascular disease in patients who have diabetes. And so, the question we are asking, does weight loss and increased physical activity in diabetic patients prevent cardiovascular disease . . . So, again, it's a behavior change trial. But, what it's measuring is cardiovascular events in patients who have type 2 diabetes, who are much more prone to these events. … And I am optimistic. I think the trial is going very well. It's a long trial, 11, 12 years, 4,000 people. So, it's an expensive trial. I think it's more translatable in a way than the DPP, because we're doing all the behavior change by groups rather than by individuals. And it's an important trial, because it will show whether there's a rationale for asking diabetic patients to lose weight. Right now, we're telling them to do that, but we don't have really good evidence that it's going to improve their prospects for preventing complications.

On genes and neurophysiology: Nowadays we know that there are many genes that affect food intake behavior and food intake regulation. We know that a lot of neural transmitters are involved. We don't know enough, but we've learned much more. And gradually, but rather quickly, we're learning more about these networks and how they interact. The more we know about these mechanisms, the more likely we are going to be to target particular molecules that would be helpful in inhibiting food intake and preventing weight gain.

On the likelihood of developing better and safer drugs: I think as we learn more, we'll be able to design molecules that would target specific receptors or block specific receptors that would affect behavior. I mean, that's been the whole breakthrough in psychiatry in the last 25 years, the change from the idea that you're going to analyze a patient to the idea that you're going to get drugs that are biologically active that will change behavior and improve the way people's minds and brains work. And I think much as we're getting anti-psychotic drugs, and anti-manic-depressive drugs, and anti-depressants, we're going to get better drugs that hit other parts of the brain.

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continued follow-up of the DPP cohort for an extra five years to evaluate the effects of the interventions on further development of diabetes and diabetes complications, including retinopathy, microangiopathy, and cardiovascular disease.

[4] In 1997, a workshop was convened by the NIH and CDC and a conclusion was that only an RCT (randomized controlled trial) of intentional weight loss could provide needed guidance on the risks and benefits of weight loss to inform rational clinical and public health policy. It was suggested that such a study should focus on obese individuals who already had a co-morbid medical illness, both because of the clear public health recommendation of weight loss for such individuals and because of their increased risk of adverse health-related outcomes. Look AHEAD (Action For Health in Diabetes) is a multi-center randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise.

On combination therapy: I think that the future of pharmacotherapy for obesity is going to be a combination of medications, such as has been the case with diabetes and with hypertension. You don't really get a full effect with one drug, you've got to go to multiple drugs. I think there's no reason to think that obesity is going to be different…I think Amylin is pretty smart, in thinking about the possibility of a combination of pramlintide with other drugs. And of course, they bought the rights to leptin from Amgen, and I think they're thinking about trying a combination of leptin and pramlintide…They're also thinking about a combination of PYY, which is a gut hormone, with pramlintide, and combining those two, or combining all three. So, they're looking at biologicals that are already being produced in the body, but may be produced in a deficient fashion, that they could put together and that would help individuals regulate their food intake better. I think it's a smart way to go to try to put together drugs that might be synergistic on food intake regulation. These drugs have peripheral effects and they have central effects. They obviously work on food intake, on gastric emptying, and they keep the stomach full longer, or they slow down the G.I. tract motility. On the other hand, they also seem to have central effects that directly inhibit hunger. So, it's smart to see if they can try to put them together in a non-toxic way.

On the importance of environment: …I'm not one to say that we're going to solve this problem only by giving people more drugs. Eventually, when so many people are affected, you have to really look at the environment, and see how the environment affects them, and how you can change it for the better. It's clear that there is an enormous propensity to gain weight by the human species if the environment is conducive to it. We wouldn't have 60% of people overweight unless there was a really high propensity to do this. It makes some sense biologically that the body really defends against underweight but doesn't defend much against overweight, since the survival problem in the past eons has been famine, not over-eating. So, we've built up some very good defenses against famine, but not very good defenses against overweight.

On what to do next: I think I can understand why doctors are somewhat pessimistic about their ability to impact weight loss, but doctors are influential figures and they should really get involved with *preventing* weight gain. The real way to solve this problem is not to treat fat people but to prevent people from getting fat and that means beginning when their children, adolescents, and young adults. People gain a lot of weight in the US between age 15 and age 40 and that's what you want to prevent. You want to sensitize all of your patients the same way as you tell them not to smoke. You tell them not to gain weight and as soon as somebody begins to gain weight, you need to talk about why this is not a good thing for them. That's done very little. The preventive side is a problem for doctors because they are used to treating conditions. They're not so attuned to prevent. They're not trained to do it. This happens in schools of public health, but it doesn't happen much in medical school. It's a real problem. I see it in our residents. What kind of education do they get when they are residents? All treatment-oriented. They don't get any education on prevention. All their education is geared to treatment of conditions, and so they get used to writing prescriptions for treatment and that' the medical model and the model that we're using now for obesity. It's not a model that is working very well.

On what Dr. Pi-Sunyer is eager to follow in the field: I'm eager about the one we're doing, the Look AHEAD trial. I'm eager about anything that would be acceptable as a new agent that could help people who are trying to lose weight but these are few and far between. I think any that's gone to a Phase 3 trial I'm interested in as a potential drug that might be helpful, and I'm interested in anything that is being done in terms of environmental change (although, as you know, this is expensive and hard to do).

—by Kelly Close

5. More on ADOPT – An Interview with Dr. Barry Goldstein

Shortly after the ADOPT results were presented at the IDF meeting in Cape Town, we spoke with Dr. Barry Goldstein about the trial. Dr. Goldstein is the Director of the Division of Endocrinology, Diabetes and Metabolic Diseases, at Jefferson Medical College of Thomas Jefferson University in Philadelphia. The ADOPT trial evaluated the efficacy of rosiglitazone, metformin, and glyburide as initial treatment for type 2 diabetes, including duration of effect in monotherapy. Rosiglitazone kept patients at goal the longest, followed closely by metformin, and trailed at a distance by glyburide, a sulfonylurea. The cumulative incidence of monotherapy failure at five years, by the Kaplan-Meier test, was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. Risk of failure was reduced by 32% with rosiglitazone compared to metformin and by 63% with rosiglitazone compared to glyburide.

Asked whether the results of ADOPT conformed to his expectations, Dr. Goldstein said that they did. He said that a lot of data over the years, from open label studies to the RESULT trial, have supported the durability of treatment with rosiglitazone. In the RESULT trial, rosiglitazone produced a fairly consistent response when added to sulfonylureas.

Dr. Goldstein said that the long-awaited ADOPT data have a lot of credibility because, like DREAM, this was a very large, multi-center study. He said DREAM was scientifically well done and supported what he and other doctors anticipated: that rosiglitazone could prevent diabetes. Regarding ADOPT, Dr. Goldstein believes that rosiglitazone's maintenance of glucose control is an important result. He also thinks that the safety data are important. In ADOPT, there was little heart failure, despite the relatively high rates of congestive heart failure (CHF) seen in DREAM. In this way, he said, the ADOPT results are more consistent with other data. We point out that other long-term trials such as PROactive have prompted questions about safety and the ADOPT safety profile was cleaner than most experts anticipated.

We asked Dr. Goldstein if the ADOPT results would change the way he prescribes TZDs, metformin, and SFUs. He said he did not think they would; in fact, the results support his current paradigm. He uses metformin as initial therapy for most patients; he said he would be hard pressed not to use metformin as initial treatment when it is in all the international guidelines. However, he adds rosiglitazone early on when necessary. Dr. Goldstein said that as far as he knows, in the rest of the world many still use SFUs as second-line therapy but ADOPT reinforces staying away from them. We certainly agree – the ADOPT results call into question for us whether SFUs have any place in clinical therapy, given the short efficacy period and the challenging side effects, especially weight gain and hypoglycemia (which spawns fear of hypoglycemia). ADOPT and prior studies show that glyburide does not confer as many benefits as rosiglitazone, but also causes weight gain and hypoglycemia. Dr. Goldstein said the ADOPT data showed how dramatic the loss of glycemic control is with glyburide. According to the results, rosiglitazone had 63% monotherapy failure risk reduction compared with glyburide. By the four-year mark, only 26% of patients in the glyburide were at target, compared with 36% and 40% on metformin and rosiglitazone respectively. ADOPT itself actually shows stable weight in the glyburide group (compared with some gain in the rosiglitazone and metformin group), but glyburide caused significantly more hypoglycemia, with eight serious events compared to only one in the metformin and rosiglitazone groups.

We asked how relevant it was that rosiglitazone modestly outperformed metformin during ADOPT. Dr. Goldstein said this was a difficult question and, ultimately, people should not argue over which drug is better. When the study was developed, the authors were taking monotherapy very seriously, he said, but we are no longer treating diabetes that way – or at least, he implied, we no longer should be. ADOPT showed metformin performs very well. If we were looking for a single agent that would be adequate, there might be an argument for using rosiglitazone before metformin, but it is now understood that patients will need combination therapy to maintain glycemic control over time. Dr. Goldstein added that

though he consistently uses metformin over rosiglitazone for initial therapy, he has no great argument for doing so. Metformin is not really an insulin sensitizer. However, he also mentioned metformin's successful track record and the absence of weight gain and fluid retention on this drug.

Though it measured efficacy in monotherapy, Dr. Goldstein thought ADOPT provided support for combination therapy- This make sense to us because, indeed, all the monotherapy data were poor relative to more recent combination data. Dr. Goldstein said, bottom line, the two winners in this study were rosiglitazone and metformin, and that it looks like this combination has considerable durability, efficacy, and safety. Everyone knows, he said, that monotherapy will not work in the long term to get people to less than 6.5% A1c, which is his goal. Also, with submaximal doses of both drugs in combination, there are fewer side effects and less concern about hypoglycemia. At submaximal doses of rosiglitazone, Dr. Goldstein pointed out, you see less fluid retention and weight gain, but you still get significant glycemic response and vascular protection. At submaximal doses of metformin, you see fewer gastrointestinal problems. ADOPT suggests that a metformin-TZD combo may work well, as clinically we know it does, he said.

When we asked how Dr. Goldstein viewed the weight gain associated with rosiglitazone, he again emphasized the benefit of submaximal doses. If you push rosiglitazone up to 8 mg, he said, people are going to gain weight, which of course no one wants. Metformin in combination would mitigate the weight gain associated with rosiglitazone. Dr. Goldstein noted that high doses are necessary in studies for more pronounced results, but this also means more side effects. Asked if he would use Byetta to mitigate weight gain, Dr. Goldstein said that clinical trials have shown that TZDs and Byetta in combination work fine. He did mention other inconveniences of Byetta like the necessity of injecting it.

Dr. Goldstein thought it may be impossible to say if ADOPT has any implications for DPP-4s. There are no data from ADOPT that pertain to them. With data in the future, Dr. Goldstein said, there may be good rationale for using DPP-4s early in treatment. If it turns out that they protect beta cell mass in humans, we may see them as having a similar role to TZDs. Positive for diabetes, he noted, is the arsenal of drugs being built that normalize glycemia without hypoglycemia, including both DPP-4s and rosiglitazone.

We asked what Dr. Goldstein thought about the evidence for improved beta cell function with rosiglitazone. Dr. Goldstein said that the durability of effect of rosiglitazone was probably due both to improved beta cell function and improved insulin sensitivity. There was continued improvement of insulin sensitivity, but not really of beta cell function. Both effects were likely present because rosiglitazone's regulation of fasting glucose was significantly better than metformin's even though metformin is thought of as controlling hepatic glucose and fasting glucose.

Regarding safety, Dr. Goldstein thought that the lower rate of CHF in ADOPT was more consistent with the larger body of evidence. The higher rate of CHF in DREAM may have been an aberration, he said. There were cases of heart failure even in the ramipril arm of DREAM, which seems strange. What we know about TZDs is that they do not appear to damage the heart and he thinks what happened in DREAM does not make sense in the larger body of clinical trial evidence. He noted that the high rate of CHF was likely related to fluid overload rather than heart damage. In the RESULT trial, Dr. Goldstein recalled, most of the patients were elderly, and there were very few, if any, cases of CHF. He mentioned that more detailed cardiovascular data from DREAM will be coming out in the future.

Finally, we asked whether the results from ADOPT concerning rosiglitazone could be generalized to TZDs as a class. Dr. Goldstein said he expects that pioglitazone and rosiglitazone would work in a similar way and have a similar effect. He thinks of them as being much more similar than different. Though he would anticipate similar effects with pioglitazone, he noted that scientifically, it would be

inaccurate to say that rosiglitazone's behavior in this study is representative of the class.

—by Daniel Belkin, Rashad Jaeger, and Kelly Close

6. The UK Addresses Childhood Obesity Problem in Aggressive, though Controversial, Way

The British newspaper *The Observer* published a story recently on the soon-to-be-published childhood obesity recommendations by the body that makes clinical guidelines for England's National Health Service (NHS). The guidelines include bariatric surgery for severely obese children – a measure that critics claim is too extreme and too risky for the problem.

The National Institute for Health and Clinical Excellence (or the dreaded NICE, as some know it, evaluates medical outcomes and cost-effectiveness data to standardize treatment plans for different diseases. Like many worldwide, the British are recognizing obesity as a public health crisis. The article suggests that about 1,000 children now have type 2 diabetes in the U.K., 20% of children are overweight, and between 2% and 3% of children are obese. What's more, 10% of children in the U.K. are expected to be obese by the year 2010. To curb the crisis, NICE recommends bariatric surgery in severely obese children, a decision that has faced some controversy.

The guidelines also suggest that NHS offer bariatric surgery to obese teenagers for whom other treatments have failed, to prevent diabetes, cancer, and certain heart conditions. The guidelines, which have taken a whopping two years to create (which is nothing compared to how long it's been since the US has had new obesity guidelines), also include a number of less controversial recommendations. These guidelines urge general practitioners to give clear advice to obese adults; encourage workplaces to provide fitness programs and exercise-friendly facilities (like showers); and suggest that employers provide healthy foods for employees. Apparently, obesity experts have advised NICE that bariatric surgery is both medically effective and cost-effective in the long run. According to the article, the surgery in those for whom drug treatments have failed reduces mortality by up to 30%. Though little long-term data exist for children under 16, NICE was convinced that the benefits in adults would also appear in children. Also, the recommendation for bariatric surgery applies only to children with a BMI over 40, which means the children will likely not be younger than 15 or 16 years old.

Interestingly, appearing in the January issue of *International Journal of Obesity* is an article called "Bariatric surgery for pediatric extreme obesity: now or later?" by authors at the Cincinnati Children's Hospital Medical Center. This is a review by Drs. Inge, Xanthakos, and Zeller, supporting earlier use of bariatric surgery in treating extreme obesity. The evidence shows that bariatric surgery in adolescents does provide significant improvements in both obesity and its co-morbidities and also suggests that the long-term health and psychosocial benefits of the surgery may be greater in younger patients. The authors conclude as well that resources need to be in place to ensure both medical and psychological support for adolescents going through this type of surgery. The authors call for further studies on the safety and efficacy of weight loss interventions and applaud the beginning of the U.S. federally funded LABS, or Longitudinal Assessment of Bariatric Surgery, and Teen-LABS, which will follow adolescents who have undergone this surgery.

Despite the seemingly strong evidence for NICE's recommendation, according to the *Observer*, it has met with resistance due to the price of this surgery, among other issues. In England, bariatric surgery procedures cost about £8,000 (~$15,800). NHS, the country's public healthcare system, is already facing an £800 million deficit (~ $1.6 billion). Apparently, NHS is already cutting jobs and restricting patient access in certain areas. At this point, most primary care trusts will not pay for the surgery, so though many more teenagers would be eligible, only 50 to 200 could get the treatment each year. Other experts decry NICE's recommendation, because they feel it misinterprets the problem. They say that bariatric surgery is a "purely medical approach" to a problem that has to do with environment and behavior.

—by Daniel Belkin

7. Diabetes Study by BMJ Publishing, United Health Foundation Distributed to 500,000 Doctors
On December 12, BMJ Publishing, which publishes the renowned *British Medical Journal*, released a comprehensive review of clinical evidence related to diabetes. The author, Dr. Sheila Feit, told us in an interview that while she assessed the world's literature on the subject, she would still like to see more information on how best to deliver care and what doctors can do to help people comply. She also emphasized how *very* challenging it is to research patient adherence, "whereas it is much easier to study outcomes based on A1c's," even though A1c's don't give the entire picture.

Both Dr. Feit and Dr. Beth Nash from the BMJ Publishing Group were quite adamant that A1c's should not be our sole measure of diabetic care – a view that we strongly endorse. Drs. Nash and Feit emphasized that optimal diabetes care requires a "whole person" approach, which we infer to mean emotional and psychological dimensions as well. Indeed, a major conclusion of the study is that the highest quality of care must recognize the patient's perspective. Drs. Nash and Feit also stressed the overlooked benefits of group education, and they urged that everyone should be on a statin. We feel there is extensive research already on statins, but it's a point worth repeating.

The United Health Foundation (part of the UnitedHealth Group) commissioned BMJ to write the review, which is titled "Putting Evidence into Practice: Outpatient management of type 2 diabetes mellitus." The goal is to help close the gap between available scientific evidence and actual care. The article was sent to 500,000 American physicians.

Dr. Fiona Godlee, editor of the BMJ, called the review "exhaustive" – which we thought was true pharmacologically but not in terms of medical devices. Still, it's hard to argue that 252 references is anything but impressive. For the treatment of type 2, it discusses all the available oral agents including DPP-4 inhibitors ("on the horizon") and injected agents including insulin, exenatide, and pramlintide, as well as combination and comparison of oral therapies, diet and exercise, drugs to control blood pressure, and drugs to control lipids. We applaud the review for including the category of "parenteral" agents – injectable drugs – rather than just ignoring them while more data are amassed, as other recent reviews have done. The BMJ review also includes discussion on non-pharmacological treatment strategies, including education, some surgical procedures, and a discussion on compliance. This excellent review concludes with a call for more research in certain areas including prevention, treating the elderly, the effect of treatments on quality of life, and how to optimize compliance/adherence.

United Health Foundation also commissioned BMJ Publishing to do a piece on obesity. This report as well as the diabetes report can be found at http://unitedhealthfoundation.org. There are also several commentaries available at the website, including one by Dr. Richard Kahn of the ADA called "Making a Difference in Diabetes Care." In this commentary, Dr. Kahn points out that there are two main strategies we need to adopt to deal with the growing prevalence of diabetes. The first is to reduce the prevalence of pre-diabetes and to delay progression to diabetes in those who have pre-diabetes – he notes that both lifestyle modifications and pharmacotherapy have been proven effective in delaying progression, though both approaches "are difficult to maintain and their cost-effectiveness may be challenging." The second strategy is to prevent complications in patients with diabetes, which includes regular screening for CVD risk and prescription of low-dose aspirin, blood pressure control, and maintenance of LDL cholesterol < 100 mg/dl. He emphasizes that doctors should treat all the risk factors of CVD individually and aggressively. Lastly, he highlights the ADA/EASD consensus guidelines on type 2 diabetes management published in *Diabetes Care* this August, which encouraged initial metformin and lifestyle therapy for new type 2 patients followed quickly by insulin, a sulfonylurea, or a thiazolidinedione if patients are not at goal. As we've mentioned before, we applaud the ADA/EASD's emphasis on aggressive glycemic control and early insulin therapy, but question their choice not to include any of the newer therapies in the consensus guidelines.

The United Health Foundation's report on obesity was also commissioned by BMJ Publishing. It is entitled "What Works for Obesity?" and, like the diabetes report, is a summary of research related to the treatment of obesity. It is as long as the diabetes report, but with only about 60 references, partially due to insufficient research in the area. It was published in April 2004, so its possible pharmacological interventions do not mention incretins or the endocannabinoid pathway. Metformin is of questionable efficacy for adult obesity, but it was the most promising drug in the report of the very few studied for childhood obesity. The report also concluded that from the limited evidence, bariatric surgery is more effective than conventional management strategies in those who are morbidly obese. Surgery patients maintain weight loss for up to eight years and have reduced risk for diabetes and hypertension. Studies that evaluate surgery in adolescents are not available. From how much the pharma landscape has changed in the last two years, we think United Health is ready for another report!

—by Kelly Close, Daniel Belkin, and Jenny Jin

8. Conference Reports

- **IDF, December 3-7, 2006, Cape Town, South Africa**

  We learned a great deal at the 19th World Diabetes Congress in Cape Town this year. As expected, incretins and neuropeptides were a big theme, but so were the thiazolidinediones, thanks to interest in adiponectin as well as the presentation of the ADOPT and DREAM washout results, and rimonabant, as obesity has become an increasingly important topic in any discussion about diabetes. The conference closed with the important message that diabetes is fast becoming the epidemic of the 21st century – it will be imperative as we move forward to develop better strategies for treating obesity and preventing and treating diabetes, but also for us to look toward and help developing countries that continue to struggle with just the basics of diabetes care. Our top takeaways from IDF are listed below.

  There is a sobering contrast between diabetes care in developed and developing countries. The conference was almost split between presentations on the new therapeutics like incretins and weight-loss drugs available in developed countries and much more sobering presentations on the lack of medical supplies and access to basic care in poorer countries. In Mozambique, as we wrote from our blog from Cape Town, diabetes is a death sentence within a year of diagnosis because insulin availability is so uncertain. We certainly help the UN Resolution on Diabetes can provide some help on this front.

  Incretin buzz was apparent throughout the conference. There was a great deal of discussion about incretins and the important role of gut hormones, as well as GLP-1 receptor agonists and DPP-4 inhibitors as therapeutic agents. Doctors are clearly excited about these drugs and their potential for beta cell preservation and regeneration – though Dr. Daniel Drucker reminded us that this remains to be proven. Interestingly, while cost of devices compared to cost of care in Cape Town seemed to represent one major reason for less interest in continuous monitoring, for example, we still saw significant interest in pricier new classes of diabetes drugs.

  Compared to US meetings, insulin and insulin analogs generated much more interest. Insulin is old news for US practitioners but the analogs in particular are seen as clinical advances in countries where even regular insulin supplies may be low. We thought Novo had the strongest presence throughout the conference – it had the most advertising presence, one of the biggest exhibits, and the most well-attended pre-conference symposia.

  Obesity was seen as a cause of metabolic syndrome, but so too were other problems that contribute to diabetes and CVD risk. Central obesity and visceral adiposity were widely mentioned as important contributors to macrovascular risk, but many other factors were cited as contributors to

the rising prevalence of metabolic syndrome: family history (both genetic and environmental), the stress of modern lifestyles, and fast changes in society in developing countries all lead to detrimental inflammatory responses, immune system changes, and insulin resistance.

TZDs came out with a net positive from our view and we continue to believe this class will grow despite discussion about them disappearing from the market due to the introduction of DPP-4 inhibitors, which we find absurd. On the trials, as detailed elsewhere in this report, ADOPT and the DREAM washout results showed that rosiglitazone both prevents diabetes and prevents progression of diabetes more effectively than other oral drugs – metformin and especially SFUs. We believe that particularly in areas where patients are less able to afford branded drugs, clinicians will be much more eager to prescribe TZDs for both prediabetes and diabetes once the drugs go off-patent – it will obviously be very key to watch how difficult it will be to develop an official indication for pre-diabetes – we think very. Several doctors who presented were very favorable about this class because the drugs benefit multiple metabolic parameters, not just glycemic control. Still, concerns about weight gain and edema linger – though we note that ADOPT actually didn't show increased congestive heart failure for rosiglitazone, which from our perspective was perhaps the biggest positive of the trial for GSK.

On the metabolic syndrome debate, most doctors come down in favor of the concept. We attended a debate on the validity of the syndrome between Dr. Michael Stern (against) and Dr. Paul Zimmet (for) in which the former argued that a continuous risk score would be better and the latter argued that metabolic syndrome is clinically convenient and significant. Audience members voted in favor of the concept at the end – at least 2/3 in favor.

Rimonabant chatter remains mixed, but SERENADE results reasonably favorable. We heard a lot about the need for drugs that address multiple aspects of the metabolic syndrome, which rimonabant certainly does, but at the same time we felt there wasn't as much interest and excitement about this drug overall as we expected. This probably partly reflects the limited availability of the drug – April 26 will be the new FDA decision date – and in fact we feel TZDs got more buzz as antihyperglycemics that address other aspects of the metabolic syndrome. Safety of rimonabant continues to be a major concern so even though weight loss and A1c drop were good, it's hard to pound the table about the need for the drug – we do note that drop outs were much lower in this trial, only about 15%, which was s positive sign.

The obesity and diabetes epidemic is hitting children hard. We heard some surprising statistics from Dr. Sonia Caprio suggesting that as many as one-third of obese children with impaired glucose tolerance will progress to type 2 diabetes within 21 months – strikingly faster than the progression of disease in adults. Progression was strongly correlated with weight gain, another reminder of the importance of stemming childhood obesity. Dr. Francine Kaufman and Dr. Henk-Jan Aanstoot gave very interesting talks on the IDF theme for 2007: diabetes in children. We're excited for more on this front, especially with the passing of the UN Resolution for Diabetes, and in light of significant media attention coming.

The etiology and pathophysiology of diabetes differs between ethnicities. Notably, Asians have higher body fat and especially visceral fat than Caucasians, Africans, and Hispanics of the same BMI, leading to a much higher risk for diabetes at every weight. Importantly, the IDF guidelines for metabolic syndrome account for racial differences in their diagnostic criteria. Beta cell failure also seems to be a bigger contributor than insulin resistance to diabetes in Asian populations. Interestingly, we heard one doctor remark that this could mean DPP-4 inhibitors would be especially suited to treat Asian diabetes patients.

There was very little interest in devices. Barring an excellent symposia sponsored by Roche on the first day of the conference and a few other talks throughout, devices were hardly mentioned. Insulin and oral drugs were the topics of the day. The lack of interest in CGM was notable – the technology is simply too expensive for most countries. We believe if randomized, controlled trials show striking results, this could begin to change. A presentation on non-invasive glucose monitoring also confirmed how far this technology remains from clinical use.

The evidence for intensive insulin use in the hospital continues to accrue, though it is mixed. We attended an excellent symposium that reaffirmed the beneficial effects of intensive insulin therapy in critical care. Although large studies to date (i.e. DIGAMI 2) have not proven that insulin infusion is always favorable, the study design of this study in particular has also viewed as imperfect.

- **NAASO, October 20-24, 2006, Boston, Massachusetts**
  Below we present our highlights and detailed notes from NAASO, the 2006 meeting of the Obesity Society. We note that this meeting was attended more by basic scientists than doctors. Certainly not all of the enthusiasm expressed about the research could be attributed to its clinical potential. A great deal of the research was in animal models or even in vitro, and many attendees were simply interested in being updated in the basic science of other researchers in the adipokine / obesity field. Still, at least a couple hundred clinicians did attend, all of whom seemed to enjoy the clinical symposia and pre-conference symposia on pharmacotherapies for obesity; at these we saw more enthusiasm for upcoming drugs than existing therapies.

  Clinically, there was a great deal of dissatisfaction with current drugs. Clinicians seemed frustrated by a lack of unbiased (non-company-sponsored) research in the literature on what exactly works; they are frustrated from seeing patients they cannot treat. The relatively low efficacy of orlistat and sibutramine was discussed relentlessly.

  During Q&A at one session, the question of rimonabant availability arose, as did the question of whether the drug would be a significant advance. The response was strikingly negative for an official meeting. Dr. David Arterburn, of the Center for Health Studies at Group Health Cooperative in Seattle, said, "My interpretation is that there are significant barriers to it becoming available. The FDA is revising their criteria for weight management drugs coming into marketplace; it has to do with the efficacy criteria of >5% weight loss at one year. And the drugs have to demonstrate that the incidence of significant adverse effects is not greater than 1/1000. I think we're in a holding phase on rimonabant unless there's more that I don't know. Can I ask the audience to raise their hands if they think it will be a significant advance?" About a dozen out of 200 raised their hands.

  Regardless of rimonabant's metabolic effects, efficacy is still the main thing doctors are looking for, and the weight loss efficacy is not that much better than orlistat and sibutramine. We don't have a good sense for how important tolerability is perceived to be. We do think if the drug is approved, it will be for weight management; although we know Sanofi is interested in a diabetes label, it is tough to say whether there is a significant impact on glycemic control that is not an indirect effect of weight (rather than something prompting a direct effect). While the SERENADE results at IDF were positive, we don't think they will suffice on their own for a diabetes label.

  Safety remains a huge concern in pharmacotherapy for obesity. Questions about safety were at the forefront of every drug discussion, from sibutramine to rimonabant. At the same time, we sensed some frustration that obesity drugs seem to be held to a higher standard than, for example, diabetes drugs to receive approval. In general, though, clinicians seemed very cautious about safety, in particular with drugs that target the central nervous system.

There was a great deal of interest in adipokines. Certainly, it seemed to us that the sessions on adipokines were the most well attended. Understanding of adipocyte regulation and secretion is continuing to grow – our favorite talk in this area was by Dr. Susan Fried, delivered to a packed room of several hundred. There, she summarized her research on the cellular regulation of adipokine signaling from adipocytes, both pre- and post-translational.

Dr. Louis Aronne of Weill-Cornell Medical College (and former President of NAASO) talked about historical problems with obesity pharmacotherapy safety and discussed his view that our current paradigm is to over-treat patients with one medication, increasing the dose until they reach side effects. He believes lower doses of multiple drugs are better – further reinforcing the strong trend toward combination therapy. He also talked about the importance of pharmacovigilance as we move forward with more new drugs for obesity and the need for a better post-approval system for scientific evaluation of adverse events of drugs.

Talks on CNS neuroendocrines that regulate the brain's appetite control centers were well-received, though incretins were not mentioned as much as we would have expected. However, in some ways this focus makes sense, because the basic scientists at this conference would be more interested in hormones such as ghrelin, orexin, etc., which are not yet well understood, than they would be in pramlintide or exenatide.

Society makes both weight loss and weight maintenance extremely difficult. Dr. Kelly Brownell gave a compelling public policy talk about the need to change our current "obesogenic" societal environment, and Dr. James Hill and Dr. Michael Rosenbaum gave excellent lectures on the physiological mechanisms that prevent weight loss maintenance and the lengths to which individuals have to go in order to be successful (long-term) weight losers.

Bariatric surgery is effective, but may not be as cost-effective as often argued. Economist Eric Finkelstein presented data suggesting that it may take as many as 18 years before the overall cost-benefit ratio for bariatric surgery to pay off, even for the average patient. Overall there may be no cost savings at all for the procedure because of hospital admissions costs for patients who experience complications from the surgery.

- **Amylin Annual R&D Day, October 24, 2006, New York City**
  Below we review highlights of Amylin's first annual R&D day and take a closer look at its research and development work. By day's end, we felt even more strongly that Amylin is the best play around for a long-term investment in diabetes and obesity.

  What are the main takeaways?
- **Amylin is poised to be a significant player in obesity therapies with its physiologic approach. Byetta's success has been so dramatic that we think the potential of this obesity platform gets lost when considering Amylin's long-term strengths as a biotech company. True to the meeting's billing, the focus was on Amylin's pipeline projects – and the story was mainly about obesity, with some important diabetes grace notes. We believe Amylin's approach to therapy – synergistic combinations of peptide hormones that mimic the body's natural path – reflects a trend toward more physiologic therapies that has already begun to play well in diabetes, and we believe will also take hold in obesity therapy. Amylin's considerable experience with these peptides is a competitive advantage that we expect will make it hard for competitors to follow.**
  - **Amylin's therapies mimic the body's own hormones – which we believe speaks to better safety profiles both in perception as well as in reality.** While the most impressive aspect of Amylin's obesity pipeline was the efficacy of the combinations, the safety profile was also featured, which we point to as an important differentiator. For example, Amylin mentioned the

experience of Symlin (we believe there must be hundreds of patients who have used it upwards of a decade) and alluded several times to the extensive non-clinical toxicology program completed and the absence of neuro-psychiatric or idiosyncratic adverse events. We see this as a positive; with increased rates of depression observed in the rimonabant trials, the absence of a corresponding effect in a potentially competitive drug is encouraging. (That said, if rimonabant is approved in 2007, we assume it will have at least a couple of years "jump" and can use the time to prove safe use in a broad population if possible; the five-year CRESCENDO trial is enrolling 17,000 patients, a trial strategy that seems designed to prove more extensive safety and efficacy.)

- **Although most of the excitement of the day involved obesity, a couple of elements of its diabetes presentations reinforced the extent to which Amylin can wildly expand the market for diabetes drugs.** For example, Amylin is targeting its diabetes therapies to shoot right past a "good enough" 7.0% A1c and target "normal" A1c levels of 6.0% and lower. The drive to "normalcy" is a very attractive one and has been seen in other therapeutic areas – for example, as President and COO Dan Bradbury noted recently, today, if a patient has blood pressure checked and it is even a small measure above normal, the patient is put on an ACE inhibitor or an ARB. With two-thirds of diabetes patients out of glycemic control, the same rigor isn't true for diabetes, but we believe Amylin's drugs will contribute toward patients going on earlier, more aggressive therapy – and the pipeline seems to reinforce that as a goal.
- **The power of leptin continues to impress – selectivity is becoming a major iteration in speaking about weight loss potential.** We heard much of Amylin's leptin story at ADA, where we were impressed by its potential. Unlike any other therapy we've seen – including surgery – leptin influences the kind of weight that is lost – namely, early studies show the loss of fat mass and preservation of lean mass. We see this selectivity as a meaningful advance in thinking about how to safely help people lose weight
- **Amylin's science muscle seems well defined.** The company spent a considerable amount of effort educating us all on why its "fast to man" approach can shave years off drug development times. Amylin credits Polypeptide Hormone Library (PHORMOL) as the major contributor to its ability to move quickly, efficiently, and effectively. We can't really say that we have the ability to define the nuances between Amylin's approach and that of other sophisticated biotech companies, like Genentech. What we can say is that at present, most of Amylin's competition in the metabolic arena appear to be focused on developing small molecules, which involves a very different process that is unlikely to create a drug that can rival the physiologic properties of one that is injected. Further, we believe that Amylin's focus on developing an endocrinology peptide library confers a competitive advantage.
- **Amylin continues to build expertise in creating treatments for metabolic diseases.** In the concluding presentations, Amylin described its acquisitions of early-stage technology (e.g., Gryphon) to enhance its R&D capabilities as "risk advantaged." While we don't have extensive information on this or other technologies, we do certainly believe it is building an intellectual fortress that will be difficult for others to replicate.

What new things did we learn about Symlin? We found the mentions of Symlin in the meeting very exciting. We heard that progress on the 2nd generation, more concentrated formulation continues – we would see full-blown development as conferring potential major advantages in terms of delivery. That is, we believe continuous infusion of Symlin might well work even better than the two to three shots daily taken by those on insulin – and the other positive side effects of the drug might well be accentuated as well (weight loss, "happy drug" effects, etc.). Also, we were excited by the hint that a long-acting formulation along the lines of LAR might be possible. As for the current Symlin product, Amylin anticipates receiving approval for a Symlin pen in mid 2007 that will ultimately support the pramlintide-obesity programs as well. We think the pen significantly improves the hassle factor and will meet with patient enthusiasm.

We were also intrigued by Amylin's response to a question on whether the pen would accommodate the largest dose under study, 360 mcg. The answer was "no." Because this larger dose would be the most appropriate for treating obese patients, we think a separate pen for larger doses would give Amylin some pricing and marketing flexibility as it expands Symlin's indications.

What new things did we learn about Byetta and LAR? On the positive front, we heard additional confirmation that Byetta's application for use in combination with TZDs will likely be approved later this year based on a Q106 filing and estimated 10-month review. On the-less-than-positive front, we heard that Amylin's application for Byetta as monotherapy is taking longer than we had expected – no data until late 2007 and no filing until 2008! Initially, we weren't sure why this study should take so long and were a bit disappointed in the timeline, although it may be that enrolling people failing diet and exercise (with A1c's of 7-10%) takes longer than we would imagine, because while plenty of type 2 patients are not at goal, only about 15% are taking no drugs, whereas over 50% are on some sort of oral agent. As for LAR, no new data, same timeline: data in the second half of 2007 and commercial scale-up finalized in the second half of 2008. Amylin continues to be extremely enthusiastic about this compound, and we continue to look forward. That said, we also think a disproportionate degree of AMLN's valuation is currently locked up in LAR. Should problems emerge with LAR, from a clinical standpoint, Byetta is a fine substitute. However, we would expect Wall Street to punish the stock in the short term. We also believe that Amylin is building a strong, durable franchise in therapies for metabolic diseases that will prove much bigger than either Byetta or LAR.

What is Amylin doing in obesity? In general, we are very enthusiastic about the potential of Amylin's "molecular franchises" for treating obesity. We once again saw animal data supporting the concept of synergistic weight loss as leptin is added to pramlintide, and PYY_{3-36} is added to the leptin/pramlintide combination. Particularly compelling is the specificity of weight loss to fat mass while preserving lean mass. To illustrate, animals in Amylin's studies showed a plateau in their weight loss not because the drug stopped working, but because they didn't have any more fat mass to lose. While it's true that a big bet is being made on animal models being highly predictive for both efficacy and toxicity, the early work in animals is certainly promising; and given the programs in humans we learned about, we assume management has become more confident over time. The programs in obesity underway are the following:

- **Pramlintide** for obesity is in phase 2b and Amylin is developing its phase 3 program; no timeline offered.
- **Four new studies in Q406** include:
  (1) 2nd generation pramlintide phase 1 single-dose study to gather safety, tolerability, and pharmacokinetic data
  (2) Pramlintide and leptin proof-of-concept study initiated in 24-week, 180 patient study
  (3) Pramlintide and PYY_{3-36} safety and tolerability study initiated
  (4) Pramlintide and oral agents – this was particularly interesting to us as an obesity program
- **The proof-of-concept work on triple therapy with pramlintide, PYY_{3-36}, and leptin starts in 2007.** Early work shows weight loss of up to 20-25% with this combination – potentially profound in our view.

Not many promises were made with respect to dates on these programs. We will be eager to watch progress closely.

What is Amylin doing with GIP, the plainer sibling of GLP-1? We were a bit surprised to hear discussions about work on GIP, which even Amylin referred to as the "second incretin." Amylin is working on a 2nd generation GIP in combination with GLP-1. Granted this work is early, but we were struck by animal data for this combo that showed glucose lowering from about 160 mg/dL to 100

mg/dL – which can translate to an almost 2 point drop in A1c. We can't imagine any company with more knowledge on this front – we hadn't really thought about GLP-1 and GIP being actually additive or even synergistic, and believe this program will be an exciting one to watch.

What were our impressions of the meeting overall? Amylin is on a roll, and although most of the investor excitement about the company centers on LAR, after this meeting we certainly see that's not the half of it! Or quarter. Or tenth. Amylin clearly has developed a program that looks geared to deliver sustainable revenue and earnings growth into the foreseeable future. We see lots of good companies doing lots of good things for patients. But what we don't see very often are companies like Amylin that manage to pull together hard-to-achieve things all at the same time: extraordinarily strong management and scientific and sales teams, an outstanding scientific platform focused on an important therapeutic area with little competition, a solid intellectual property portfolio, a wildly successful launch of a novel therapeutic, a sleeper drug already on the market, and to top it off, a huge pipeline that isn't all pre-clinical. And, did we forget to mention that these therapies aren't just novel, but are leading the way for clinicians to completely change their approach to treating disease? We don't think it's a happy accident that Byetta's launch coincides with more and more buzz among doctors about the importance of respecting the body's physiology when approaching metabolic diseases.

—by Cindy Glass, Jenny Jin, and Kelly Close

9. Reviewing the Diabetes Literature – Highlight on *Nature* and ADOPT

Below is our list of 25 of the most important articles on diabetes published since our last DCU. Our team is always looking for the most relevant articles on new diabetes research, and this month we've compiled papers from journals such as the Diabetes Care*,* Diabetes*,* Endocrine Reviews*,* NEJM *and more.*

Our favorite literature this month came from two special journal issues by the Nature Publishing Group: the December 14 issue of *Nature* and the December issue of *Nature Clinical Practice: Endocrinology & Metabolism*. The former featured an Insight supplement on diabetes and obesity, sponsored by the Nestle Research Center, which included seven excellent review articles on – well – diabetes and obesity. We highlight all of them in our column below. The latter included articles on some of the most important clinical trials and developments in diabetes management from 2006 – we highlight two of them.

- *Brit J Pharm - The MC4 receptor and control of appetite - Adan et al:* The human melanocortin (MC)4 receptor is involved in regulating appetite, insulin sensitivity, and energy expenditure; MC4 receptor agonists decrease food intake, though clinical trials were discontinued after the discovery that agonists also cause unwanted penile erection. This basic science-focused review looks at the physiologic role of melanocortins in weight control. We're not sure that MC4 will ever become clinically useful, but we found this review to be a very comprehensive look at an important biological system.
- [***] *Diab Obes & Meta - Inhaled insulin delivery – where are we now? - Muchmore, Gates:* This review by scientists from Eli Lilly provides a good historical background of this technology and a useful compilation of the inhaled insulin devices currently under development. The authors are in favor of inhaled insulin and express optimism that only long-term studies will be needed to resolve doubts about safety and efficacy compared to injected insulin. We're not convinced that inhaled insulin will ever be as good as injected, but this was a good review.
- [***] *Diabetes - Feasibility of Automating Insulin Delivery for the Treatment of Type 1 Diabetes - Steil et al:* This study showed the feasibility of Medtronic's closed-loop system. Despite the imperfect

[***] We thought this review was especially noteworthy. Space does not permit us to go into more details here, but if you would like our full-length review of this piece, please write litreviews@closeconcerns.com.

accuracy of continuous sensors, the patients in this study were able to achieve good control under closed-loop therapy. However, we note that the study was conducted under relatively artificial, inpatient conditions – much more work needs to be done to make the system practical in day-to-day life.

- ***Diabetes - Leptin Regulation of the Anorexic Response to GLP-1 Receptor Stimulation - Williams et al:* This animal study showed that leptin pretreatment enhances weight loss induced by GLP-1 or exenatide in rats. Fasting usually reduces the anorexic response to GLP-1 or exenatide via a leptin-dependent mechanism, but the authors were able to reverse this effect by exogenously replacing leptin. We thought this study was intriguing with regards to the possible synergistic effects of leptin and exenatide for weight loss in humans – of course, Amylin is currently pursuing pramlintide / leptin for obesity, but the potential for an exenatide combination remains.
- *Diabetes Care - Patient Interpretation of Neuropathy (PIN) Questionnaire - Vileikyte et al:* This study reports the development of a 39-item questionnaire that reliably assesses the aspects of patients' cognitive and emotional attitudes toward neuropathy that affect their foot self-care. We're encouraged to see something that could help clinicians help patients become better self-managers of this complication.
- *Diabetes Care - Long-Term Effect of the Internet-Based Glucose Monitoring System on HbA1c Reduction and Glucose Stability - Cho et al:* This Korean study showed that in a 30-month follow-up study of diabetes management, patients who used an internet-based glucose monitoring system in addition to attending their three-month conventional clinic visits did better than those who attended clinic visits only. We think this is encouraging evidence in favor of a relatively inexpensive tool for better diabetes management.
- ***Diabetes Care - Effect of the DPP-4 Inhibitor Sitagliptin as Monotherapy - Aschner et al:* This study showed that in 741 drug-naïve type 2 diabetes patients who had a mean baseline A1c of 8.0%, 100 mg and 200 mg of sitagliptin once daily reduced A1c by a placebo-subtracted value of 0.79% and 0.94%, respectively, after 24 weeks of treatment. The publication of two sitagliptin studies in this issue of *Diabetes Care* is a boon to Merck, which continues to lag behind Novartis in the number of papers it has published on its DPP-4 inhibitor.
- ***Diabetes Care - Efficacy and Safety of the DPP-4 Inhibitor Sitagliptin Added to Ongoing Metformin Therapy - Charbonnel et al:* This study showed that in 701 type 2 diabetes patients inadequately controlled on metformin monotherapy, treatment with 100 mg sitagliptin once daily reduced A1c by a placebo-subtracted 0.65% from a baseline of 8.0% after 24 weeks. This study is in support of Merck's sitagliptin/metformin combination (coined Janumet), which the company has already submitted to the FDA.
- ***Diabetes Care - Relationship of Fasting and Hourly Blood Glucose Levels to HbA1c Values: 7-day continuous glucose sensor - Garg, Jovanovic et al:* This study reports the results of a clinical trial testing the safety and efficacy of DexCom's 7-day continuous sensor in 86 insulin-using diabetes patients. In the unblinded phase, use of the CGM devices resulted in improvements in target-range glycemia across all A1c values.
- ***Diabetes Care - Hyperglycemic Crises in Adult Patients With Diabetes: A consensus statement from the ADA:* This consensus statement deals with diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS), two serious complications of hyperglycemic crises. The authors discuss the pathophysiology, precipitating causes, diagnosis, and recommended treatment for these conditions as well as how to treat their complications and to prevent them in the first place.
- *Diabetes Care - Weight Control in Individuals With Diabetes - Bloomgarden:* This is the third in a continuing series of articles reporting presentations from the 2006 ADA meeting. This one discusses presentations on bariatric surgery, rimonabant, dietary treatment, and exercise. How appropriate that this article came out in the December issue, in the middle of what we've found to be a very obesity-centric month in diabetes news.
- *Diabetes Care - CGMS With an Alarm: A tool to reduce hypoglycemic episodes in pregnancy with diabetes - Worm et al:* This short report describes a case study of a 32-year-old woman with a history

of diabetes for 21 years who was able to drastically improve her glycemic control during pregnancy after she began using Medtronic's Guardian RT continuous glucose monitoring system. We note that Medtronic also published the results of the GuardControl study in this issue of *Diabetes Care*, but as it is already described in the Company Watch section we did not include that article in this column.

- ***Endo Rev - Emerging Therapeutic Strategies for Obesity - Foster-Schubert, Cummings:* This comprehensive review paper looks at the body's natural neuroendocrine regulation of body weight and discusses two therapeutic strategies for reducing weight: drugs that stimulate catabolic pathways and those that inhibit anabolic neuropeptides. The authors also touch on gut peptides that regulate food intake and finish with a look at cannabinoid-1 receptor antagonism. We think this is a very, very good review of the field and the emerging, promising research in obesity treatment.
- *Pediatric Diabetes - ISPAD Clinical Practice Consensus Guidelines for 2006-7 - ISPAD:* We'd like to highlight that the International Society for Pediatric and Adolescent Diabetes (ISPAD) will be publishing their new consensus guidelines on clinical diagnosis and treatment of pediatric diabetes in the next few issue of *Pediatric Diabetes*, beginning with the December 2006 issue.
- ***Nature - Mechanisms linking obesity to insulin resistance and type 2 diabetes - Kahn, Hull, Utzschneider:* The authors of this review describe a theoretical model of disease in which beta cell dysfunction is the underlying mechanism that links obesity, insulin resistance, and type 2 diabetes. We found it a fascinating model, though as with any theory, by itself it does not explain the epidemic rise in diabetes. It does, however, do an excellent job of describing the mechanisms in which obesity, insulin resistance, and type 2 diabetes feed into each other.
- ***Nature - Adipocytes as regulators of energy balance and glucose homeostasis - Rosen, Spiegelman:* These authors review our current knowledge of adipocyte biology and describe the many important hormones secreted by adipocytes (leptin, adiponectin, visfatin, omentin, tumor necrosis factor-alpha, resistin, and retinol-binding protein 4) and how our understanding of these hormones may lead to therapeutics for obesity. We enjoyed reading the comprehensive description of leptin's physiologic roles in this review and agree with the authors that adipocyte-targeting drugs are an important area of future research.
- ***Nature - Gut hormones and the regulation of energy homeostasis - Murphy, Bloom:* These authors review the known human gut hormones and discuss their roles in energy balance, with an emphasis on how they can be used to treat obesity. Hormones discussed include: ghrelin, peptide YY (PYY), cholecystokinin, pancreatic polypeptide, amylin, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), and oxyntomodulin. Pramlintide is mentioned only briefly but the authors devote a few paragraphs to exendin-4.
- ***Nature - Inflammation and metabolic disorders - Hotamisligil:* This review takes a more public health perspective on metabolic disease; the author writes that the evolutionary conservation of our metabolic and immune systems has over time produced an extensive interface between the two systems that is itself a central homeostatic mechanism; dysfunction of this mechanism leads to the cluster of chronic metabolic disorders that now threatens our global health.
- ***Nature - Sirtuins as potential targets for metabolic syndrome - Guarente:* The author of this review points out that since metabolic syndrome and caloric restriction (CR) represent opposite ends of the metabolic spectrum (as characterized by food excess and restriction), then the pathways that mediate CR – controlled by SIR2-related proteins, or sirtuins – may be useful as targets for treating metabolic syndrome.
- ***Nature - Mechanisms linking obesity with cardiovascular disease -Van Gaal, Mertens, De Block:* These authors discuss how various risk factors influence or mediate the increased risk for cardiovascular disease associated with obesity. Smoking, physical activity, and dyslipidemia seem to have effects on cardiovascular risk independent of obesity, but other risk factors like insulin resistance and adipokine secretion are more adiposity-dependent, which we interpret to mean they should ideally be treated through weight reduction – yet another reminder of the need for better anti-obesity drugs.

- ***Nature - Abdominal obesity and metabolic syndrome - Després, Lemieux:* These authors discuss the roles of abdominal obesity and metabolic syndrome in clinical diagnosis, touching on the metabolic syndrome controversy and concluding that better risk assessment algorithms for diabetes and cardiovascular disease are needed. Overall, this article is in favor of metabolic syndrome as a useful clinical tool – we thought it was one of the more logical pieces on the syndrome that we have read.
- ***Nature - An obesity-associated gut microbiome with increased capacity for energy harvest – Turnbaugh et al:* These authors report that the proportion between two types of gut bacteria differs in lean and obese people. They put 12 obese people on diets and monitored their gut bacteria for a year and found that dieting changed the balance towards what is observed in lean people. We think this is a tantalizing first report of the relationship between obesity and gut flora, and we hope to see more research in the future clarifying whether manipulation of intestinal bacteria can help treat obesity.
- ***Nat Clin Prac Endo Met - How prevalent are diabetes-related complications in patients with youth-onset type 2 diabetes mellitus? - Miller, Silverstein:* Adolescents with type 2 have a higher prevalence of microalbuminuria and hypertension than those with type 1 diabetes. The authors suggest that this may be because hypertension, microalbuminuria, and diabetes are all manifestations of the metabolic syndrome that occur with hyperglycemia rather than because of it. We would tend to agree that the syndrome probably indicates the presence of underlying metabolic abnormalities that go beyond hyperglycemia. This paper has important implications for clinical screening of adolescents with type 2 diabetes.
- ***Nat Clin Prac Endo Met - Mechanisms of Disease: endothelial dysfunction in insulin resistance and diabetes - Rask-Madsen, King:* This comprehensive review looks at all how various biochemical changes that occur in patients with type 2 diabetes and insulin resistance cause endothelial dysfunction. We found this to be an excellent, strongly science-based look at the etiology of endothelial dysfunction. The paper also includes a very interesting table on some of the evidence available on possible mechanisms and treatment of endothelial dysfunction. The focus on reducing complications is very important, we think.

Below we present a summary of our reviews on the ADOPT trial results and editorial by Dr. David Nathan, which were published in NEJM on December 4 concurrently with the presentation of the trial results at IDF.

Main takeaways: 1) **ADOPT was positive for combination therapy even though combination therapy wasn't tested.** The results support both metformin and rosiglitazone as good initial treatments, but also show durability issues with each as well as significant side effects at maximal doses. Using them together, at submaximal doses, as first-line treatment may be the way to go. At this point, it's generally agreed that monotherapy does not work. 2) **Sulfonylureas (SUs) were the major losers of the study.** Glyburide monotherapy was the first of the three to fail both glycemic standards (180 mg/dL and 140 mg/dL) and also put the fewest people at target A1c and kept them there the shortest amount of time. This inferiority may be one of the stronger conclusions to be drawn from this study. 3) **Metformin is still likely the drug of choice for first-line therapy.** It is hard to argue with cheap and no weight gain, though we think these results will speak strongly for TZDs as the next first-line therapy of choice for patients who have intolerable GI side effects on metformin – assuming they can afford it. 4) **The weight gain, though expected, was still very unpleasant to see** and is particularly problematic because the study showed that TZDs help the most obese patients the most, but these are also the patients who doctors are most reluctant to put on anything that causes weight gain. 5) **Still, in general, we would guess that more drs/nurses will consider using TZDs sooner after seeing these results**.

Kahn S, Haffner S, Heise M, Herman W, Holman R, Jones N, Kravitz B, Lachin J, O'Neill C, Zinman B, and Viberti G, for the ADOPT Study Group. "Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy." N Engl J Med 4 Dec 2006. Published online ahead of print.

In this original research paper, Kahn and colleagues report the results of the ADOPT trial, a large-scale randomized controlled trial evaluating rosiglitazone for initial treatment in type 2 diabetes compared with metformin or a sulfonylurea. A Diabetes Outcome Progression Trial or ADOPT was multicenter and double-blinded. It evaluated the difference in efficacy of a thiazolidinedione (TZD), a biguanide, and a sulfonylurea (SU) in patients receiving monotherapy, including how long patients could stay at goal on monotherapy.

Thiazolidinediones reduce insulin resistance and delay progression to type 2 diabetes in people with impaired glucose tolerance, as determined by DREAM. The DREAM trial, presented at EASD 2006, supported the potential preventive capacity of TZDs in type 2 diabetes. However, negatives for the class were the side effects of weight gain and congestive heart failure (CHF).

ADOPT included 4,360 subjects randomized to three treatment groups: rosiglitazone (a TZD), metformin (a biguanide), and glyburide (a sulfonylurea). Inclusion criteria were: age between 30 and 75 years and a fasting plasma glucose range from 126 to 180 mg/dL. Patients were recently diagnosed with type 2 diabetes (within three years) and had not received any previous pharmacological treatment. The exclusion criteria were: uncontrolled hypertension, congestive heart failure, unstable or severe angina, renal impairment, hepatic disease, and a history of lactic acidosis. At screening, patients were predominantly middle-aged, white, and obese. The median duration of treatment for rosiglitazone and metformin was four years and for glyburide three. Sixty-three percent completed the study in the rosiglitazone group, 62% in the metformin group, and 56% in the glyburide group. Dropouts were due primarily to adverse events: 12% of patients in the rosiglitazone and metformin groups and 15% in the glyburide group.

Participants were randomized to 4 mg rosiglitazone (n=1,456), 500 mg metformin (n=1,454), or 2.5 mg of glyburide (n=1,441) daily. Doses were increased at each visit where the patient's fasting plasma glucose level was 140 mg/dL or more, up to maximum daily effective doses. They were lowered in the case of adverse events. FPG and A1c were measured every two months in the first year and every three months afterward. At least annually, liver function, blood count, C peptide, and lipids were measured. An examination and electrocardiograph was performed annually as well as at baseline.

The primary endpoint was time to monotherapy failure based on fasting plasma glucose; the results show that rosiglitazone was associated with the longest time to monotherapy failure. Monotherapy failure was defined as having fasting plasma glucose levels of more than 180 mg/dL consecutively after at least six weeks of treatment at the maximum-tolerated or maximum-allowed dose. The authors note that at the initiation of this trial, consensus guidelines focused on FPG levels, which explains this choice for primary outcome rather than A1c. However, we note that several doctors say the choice of using FPG rather than A1C is strange, and guidelines at the time of initiation did support use of A1C as a measure of glycemic control. In any case cumulative incidence of monotherapy failure at five years, by the Kaplan-Meier test, was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. Risk of failure was reduced by 32% with rosiglitazone compared to metformin and by 63% with rosiglitazone compared to glyburide. We found the relative magnitude of this effect impressive. At time of failure, about 99% of patients were receiving the maximum dose of their treatment drug.

Rosiglitazone excelled in many of the secondary outcomes including time to a lower-threshold failure (an FPG of 140 mg/dL or greater), A1c, insulin sensitivity, and beta cell function. With a

lower threshold for monotherapy failure, rosiglitazone still produced a 34% risk reduction compared to metformin and a 62% risk reduction compared to glyburide. A reanalysis with a lower threshold is due to the change in guidelines over the course of the trial. When the trial began, guidelines recommended an FPG of under 180 mg/dL, whereas they now recommend an FPG of under 140 mg/dL. While early on, rosiglitazone had the lowest rate of A1c improvement, by the four-year evaluation, it was shown to be the most effective, with 40% in the rosiglitazone group having an A1c of less than 7%, compared to 36% of patients in the metformin group and 26% of patients in the glyburide group. A1c below 7% was also maintained longest in the rosiglitazone group, for 60 months, compared to 45 months in the metformin group and 33 months with glyburide. In the first six months, insulin sensitivity (as determined by HOMA) increased more in the rosiglitazone group than the metformin group, and though the rates evened out thereafter, there was a significant difference at four years (insulin sensitivity changed little with glyburide). As far as beta cell function, rosiglitazone had the lowest rate of decline (after six months, as determined by HOMA), followed by metformin and then glyburide.

On the other hand rosiglitazone group had significantly more weight gain, edema, LDL, and fractures. Weight increased an average of 4.8 kg from baseline over five years, while it decreased in the metformin group by 2.9 kg, and remained relatively constant in the glyburide with an increase of 1.6 kg. Like in DREAM, waist-to-hip ratio saw no net change. However, weight gain, though expected, is a clear negative for rosiglitazone. Rosiglitazone was also associated with more frequent edema and higher levels of LDL than the other two drugs. One other side effect with rosiglitazone was more bone fractures in women. This side effect was very surprising and somewhat worrying. Rosiglitazone was associated with fewer gastrointestinal side effects than metformin, which was very high at about 40%, and less hypoglycemia than glyburide.

Though the study was not designed to evaluate cardiovascular disease outcomes, congestive heart failure was specifically examined, since TZDs have been associated with an increased risk. Cases of CHF were determined by a blinded panel of three cardiologists. The rate of CHF in the rosiglitazone was not much different from the metformin group, though it was greater in both than in the glyburide group. That the rate of CHF was the same in rosiglitazone as metformin was a surprise but very positive for rosiglitazone. In the rosiglitazone group, 1.5% of subjects had CHF events compared to 1.3% in the metformin group and .6% in the glyburide group.

Issues with this study, acknowledged by the authors, included the high rate of withdrawal from the study, as well as doubt over the relevance of the primary endpoint. Many of the withdrawals were due to side effects, all of which were expected from these drugs. The groups did not differ much in how many subjects withdrew or why. Only about 60% of participants completed the trial. However, the authors write that analyses accounting for potential bias due to withdrawal yield results consistent to the study's findings. As far as the primary endpoint, it is unclear how clinically important the time to an FPG of 180 mg/dL is. A1c correlates better with complications, so an endpoint based on FPG was a curious choice to begin with. Given an endpoint based on FPG, the lower threshold is more relevant since guidelines changed. Though this was a secondary endpoint and was consistent with the results, but it was a reanalysis and the study was not expressly designed to measure it.

Nathan, DM. "Thiazolidinediones for Initial Treatment of Type 2 Diabetes?" N Engl J Med 4 Dec 2006. Published online ahead of print.

In this editorial, Dr. Nathan looks evenhandedly at the conclusions that can be drawn from ADOPT: though the study was positive for rosiglitazone use, metformin is still going to be the logical choice for initiating treatment. Dr. Nathan writes that earlier studies on TZDs showed no greater efficacy than other anti-diabetes drugs. He writes that this fact, as well as the side effects (of weight gain, edema, and congestive heart failure), contributed to the decision not to include TZDs in the guidelines as

possible first-line treatment for diabetes. ADOPT showed, however, that rosiglitazone did extend the time to failure, compared to both glyburide and metformin. The benefits of rosiglitazone over glyburide are more convincing, Dr. Nathan writes, than the benefits of rosiglitazone over metformin.

An A1c endpoint would have produced a comparison between rosiglitazone and metformin that was more clinically significant than the FPG-based monotherapy failure endpoint. Dr. Nathan writes that the choice to base monotherapy failure on FPG "seems anachronistic." A1c was the primary target at the time the study began and correlates best, among measures of glycemia, with the risk of complications. A1c results, however, are less impressive than FPG results in ADOPT. The mean A1c at four years in the rosiglitazone group was .13% less than in the metformin group, and .42% less than the glyburide group. We note that a .5% change in A1c does seem to be the unofficial standard for clinical significance. The percent of patients at target was 40% in the rosiglitazone group and 36% in the metformin group, which Dr. Nathan notes is only a 4% difference.

The high withdrawal rate was indeed a loss. Dr. Nathan writes that the high withdrawal does weaken the results of the study. He suggests that it was due not only to side effects but to other factors as well, possibly including the very small number of patients followed at some of the clinical sites (almost 500 sites in all). This added weakness casts doubt on rosiglitazone's already modest advantage over metformin in terms of durability.

That TZDs may protect beta cell dysfunction and therefore alter the underlying physiology of type 2 patients is supported only weakly. Dr. Nathan notes that the difference between insulin secretion in the rosiglitazone group and metformin group was, though significant, small, and that initial improvement with rosiglitazone drops off after a year.

Dr. Nathan concludes that metformin is still the logical choice for initial therapy, due to the only modest glycemic benefit of rosiglitazone and its higher cost. We would agree that metformin is going to remain the first choice for first-line. For us, the real issue is the weight gain on TZDs. The ADOPT study, though it highlighted the side effects of the other two drugs, also highlighted the weight gain on rosiglitazone. Even if the weight gain comes with a redistribution of fat, it is scary, especially in those who are already obese. ADOPT was positive for rosiglitazone, but we think ultimately that it needs to be used in combination or at submaximal doses, so second-line will be its best option for right now.

—by Kelly Close, Daniel Belkin, and Jenny Jin

10. Upcoming Conference Preview

- **ADA 54th Annual Advanced Postgraduate Course, Feb 23-25, New York City, www.diabetes.org/pg/**

  The ADA Postgraduate meeting is a quick three-day gathering to give health care professionals the latest clinical research in diabetes and, importantly, information on how to translate these results into clinical practice. The meeting alternates between New York and San Francisco, and this year it will take place in the Big Apple – note also that it's a bit later than usual. We organized talks and workshops somewhat chronologically into areas of interest and have recommended the ones we think look most promising. Workshops are limited, so register early to get your top choices.

  Prevention

  On Friday afternoon, the conference begins with a general session called Diabesity. We'd recommend arriving at 1 pm, in time for the first talk, which is on *IFG and IGT: How should we treat these states of hyperglycemia?* Dr. Ronald Goldberg from the University of Miami will likely discuss preventive strategies. The next talk we'd highlight won't be until Saturday morning, when the meeting splits into two tracks, one on Education and Self-Management and the other on Hot Topics. For those interested in type 1, the Hot Topics track has an *Update on Type 1 Prevention Trials*. We haven't seen much on

type 1 prevention lately, and Dr. Carla Greenbaum, from the Benaroya Research Institute in Seattle, should be worth listening to.

Education

At 8 am Saturday morning, we'd recommend *Best practices in diabetes education recognized programs*. Gayle Lorenzi, a CDE from the University of California-San Diego, who was the AADE Diabetes Educator of the Year in 2001, will be giving this talk. Stay in the Education and Self-Management track for Linda Siminerio, a noted CDE (and PhD) from the University of Pittsburgh, who will speak on *Diabetes Self-Management Training Outcomes Study Results*. Her data will bolster (or undermine?) experiential findings about the best strategies for diabetes education.

Patients and Patient Care

Also on Saturday morning, 10:00-10:50 am in the Hot Topics track, catch Dr. Edwin Gale from the University of Bristol in the U.K. speaking on *Multiple Types of Diabetes: Type 1, 2, 1.5, 3 (1+2)*. The etiology of diabetes is likely more complex than we knew, and this should be interesting. Next, Dr. Arthur Agatston, from the Agatston Research Foundation, will discuss *Screening for Cardiovascular Disease*, an area of growing interest. Finally, on Saturday afternoon, we're looking forward to attending a workshop led by Dr. Irl Hirsch, from the University of Washington, on *Managing the "Brittle" Patient*. This workshop has limited space (though it will occur twice).

Drugs and Devices

Dr. Satish Garg, from the Barbara Davis Center for Childhood Diabetes, is leading a workshop on Saturday afternoon (also given twice) on *Glucose Sensing and Monitoring: A potential tool for changing patient behavior*. We're eager to see how this will be characterized to the many doctors and CDEs who may have limited experience with it. Sunday morning features the last session of the meeting, on Medications. Dr. Robert Ratner, from the Medstar Research Institute, is discussing *The Practical Use of Incretin Mimetics and Enhancers*. A full house is expected. After the coffee break, Dr. William Cefalu, from the Pennington Biomedical Research Center in Baton Rouge, LA, will speak on *The Realities of Inhaled Insulin*. We wonder if he will share our skepticism. Finally, in a very surprise appearance, Dr. Sidney Wolfe, from the Public Citizen's Health Research Group, will discuss the *Adverse Effects of Diabetes Therapies*. He's been trying to get Meridia (Abbott's sibutramine) off the market for years – we expect this to be a hostile talk (Dr. Wolfe is usually very anti-industry). We're eager to hear his thoughts on Merck's Januvia, which has been shown in trials to be much more tolerable.

—by Kelly Close and Daniel Belkin