# DIABETES CLOSE UP

**Diabetes Close Up**
**October 2006, No. 62**
**Januvia and DREAM and more…**

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

*From the Editor:*

*Close to home, James S. Hirsch, a principal here at Close Concerns, has written a compelling new book – "Cheating Destiny: Living with Diabetes, America's Biggest Epidemic" – to be published by Houghton Mifflin this month. A blend of historical research, contemporary journalism, and personal memoir, "Cheating Destiny" is a must-read for diabetes insiders. In our view, the book captures the "human drama" of the disease like no other – the blame, frustration, and guilt – as well as the courage, perseverance, and triumph – ever-present in the field. In addition to being a former reporter for The New York Times and The Wall Street Journal, Jim knows this subject intimately: he has type 1 diabetes himself, and he diagnosed his young son, Garrett, while he was researching the book; his older brother, leading endocrinologist Dr. Irl Hirsch, also has type 1. Jim communicated with nearly 1,000 patients, doctors, researchers, and nurses to learn about their experiences, and his unique perspective will help you better understand customers, patients, and family members (and yourself, for any PWD). We also recommend Jim's outstanding article, drawn from his book, in Parade Magazine on November 5. To learn more about the book and to read an excerpt, visit www.cheatingdestiny.com and pre-order on Amazon (www.amazon.com). The first twenty readers to ask will also receive a free copy – write me at kelly.close@closeconcerns.com.*

*The days are rolling and our field remains as dynamic as ever ~ this issue is once again full of company news. The big highlights of the moment are that Merck announced the approval of DPP-4 inhibitor Januvia yesterday (Oct. 17) and that Novartis marked the start of the DPP4-TZD war last week with an announcement of a new head-to-head trial between Galvus and TZDs. See inside for some quick expert responses to this new drug. Also in the news recently was BD exiting the blood glucose monitoring market to pursue greener pastures in diabetes, Roche returning to the insulin pump market, and Lilly giving up on dual PPARs. Major news from EASD, stemming from DREAM, was that prevention of diabetes could one day be a mainstay – this notion seems suddenly squarely in the mainstream and our hearts are lighter, even if we ultimately think, perhaps, right idea, wrong drug.*

*Earnings season is again upon us, starting with Roche and J&J this week! And back on the road - this year, autumn is even busier than usual, with an astonishing number of new and familiar meetings. In the next few weeks we'll be in Toronto (Canadian Diabetes Meeting), Tucson (the Robert W. Johnson Diabetes Initiative Capstone), Boston (the Cardiometabolic Health Congress and NAASO), Atlanta (Diabetes Technology), Berlin (the World Congress on Controversies in Obesity, Diabetes and Hypertension), and Washington, DC (the Insulin Congress). We've just returned from a new obesity meeting at the Cleveland Clinic – more inside on the rapid-fire growing interest in the area and this excellent gathering. We also recently attended one of Dr. Steve Edelman's excellent patient conferences last week: the Taking Control of Your Diabetes meeting in Silicon Valley. Dr. Edelman is inspiring and inspired, and we too were gratified, watching 1,100 patients traipse around the Santa Clara conference center. Too, check out Dr. Edelman's new show, TCOYD TV – a fantastic new channel for getting information out to patients. If you're Out West, don't miss the Twelfth Annual TCOYD, November 18 in San Diego. Til then…*

*—Kelly L. Close*

**In this issue:**

**Quotable Quotes from October's DCU:**

Dr. Mark McClellan, the administrator for the Centers for Medicare and Medicaid Services (CMS):

- *"We pay more when we get worse care. We ought to pay more for what we want."*

Barbara Dominguez, a nurse practitioner:

- *"When I'm with a patient, time stops..."*

Carolyn Pare, CEO of Buyers Health Care Action Group:

- *"Even once you have a provable intervention, it takes 10 years to get reimbursed. It's all about the money."*

Dr. Anne Peters:

- *"I try never to judge and to always make people know that you believe in them. So often people feel like a failure, and once you feel like a failure, then it builds. They say, 'I disappointed you. I failed you.' I say, 'You're not allowed to use those words.'"*

***And see inside for a number of expert words on DPP4s from Drs. Zach Bloomgarden, Irl Hirsch, Paul Jellinger, and Bill Polonsky***

**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.**

- **October 17: NYT Kolata on moving straight to drugs**
- **October 11: Trend Toward Healthful Snacks Continues in Schools**
- **October 10: Raising risk awareness... how effective is it?**
- **October 10: NYC considers ban on trans fats**
- **September 25: Diabetes means cancer too? Maybe...**
- **September 25: More sad statistics on obesity**
- **September 21: Dietary interventions for obese children... who needs those?**
- **September 15: EASD Part 2! Ten things about DREAMing on ...**
- **September 14: India and Diabetes: N.R. "Sonny" Kleinfeld's Bleak Take**
- **September 14: EASD Part 1**

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

1. **DCU Company Watch**

- **Merck:** Januvia was approved this morning (Oct. 17) – please see our in-depth piece below.
- **J&J announced its third quarter earnings on October 17, with LifeScan sales of $505 million up 9% both in the US and internationally (from $462 million a year ago).** For J&J, the call is usually relatively light on in–depth news on diabetes and obesity (there are 230 operating companies, after all). Still, there were some interesting aspects. Lifescan revenues of $505 matched the 1Q06 result exactly and was down slightly from last quarter's $522 million. While they are on track for over $2 billion this year, on this trendline, they won't exceed it by much. U.S. sales for the corresponding periods were $278 million, up 9%, versus $255 million while sales outside the U.S. were $227 million, up 9%, versus $207 million. Management attributed most of the 9% growth to Animas. As for blood glucose monitors, the OneTouch Ultra contributed to growth outside the US. J&J launched the Mini in the US during the quarter as well as the UltraEasy in Europe - this is their low-cost meter that is $19.99 in the US. Currency impact outside the use was 1%. This quarter was the second full quarter of Animas sales. We've anticipated a $100 million year for Animas, which suggests about $25 million in sales this quarter - commentary makes it sound like they did a bit better than that, but it's hard to say since they don't report separately. We're surprised a bit if Animas is outperforming, but we have heard the new Medtronic pump is viewed as "a lot of hardware" and Animas has a great salesforce that has probably been bolstered at least a bit with J&J (no doubt some have also left for Dex Com and other places). With overall Lifescan revenues up $43 million year over year (and down $17 million sequentially), if we pull out our Animas estimate, we believe the base business grew very little, perhaps around 2-4%. The blood glucose monitoring industry right now is challenging (pricing pressure from managed care, more low-cost competitive pressure, concerns about competitive bidding, expected competition from continuous with the most profitable users - though this will probably take less time than thought, Byetta users testing less, etc.) and we see any growth in this environment as a positive. Within the Ethicon Endo-Surgery review, growth for the EndoCutter, described as a key product for bariatric surgery, was a robust 20%. The EndoCutter was a strong growth contributor last quarter as well with 18% growth in Q206. We didn't heard specifics on Bariatric Edge or US trials for JNJ's gastric band (the old Obtech bariatric business that was purchased in 2002). We were surprised that there was no mention of Metabolex, the company with which J&J is working to develop metaglidasen and MBX-2044, two insulin sensitizer drugs.
- **J&J LifeScan postscript**: Camps for diabetic children have a long and rich tradition, but it's not just the children who benefit. The staff do as well. We'd like to share this story by Geoff Drake, the U.S. Web Manager for LifeScan, Inc., who wrote about his experiences as a counselor. Even if you think you know what having diabetes is like, we urge you to read the piece – so vivid, so much resonance. This was first published for *Children with Diabetes* – many thanks to Jeff Hitchcock for allowing the reprint. www.childrenwithdiabetes.com/camps/GeoffDrake2006.htm
- **Roche reported September quarter earnings on October 16th.** Roche Diabetes Care's sales rose 5% in 3Q, low growth for this market. Accu-Chek Aviva generated high sales volumes in the major EMEA markets and in the US and Canada, as did Accu-Chek Active in Latin America and Asia-Pacific – good news for the franchise. Outside the US, Roche's pump business posted a very healthy 15% growth. Diabetes related drug news: 1) Roche has exercised its option to license Ipsen's GLP-1 analog for type 2 diabetes. A phase 2 efficacy and safety study in a sustained release formulation is scheduled to start early in 2007. This was expected but still is a positive for Ipsen. 2) Roche dropped its DPP4 inhibitor R1438 because it "did not show enough clinical differentiation and, therefore, had been replaced by a back-up compound which indicated the profile as requested." On the call, management declined to say whether it was safety or efficacy related – it just implied it was too far behind Merck and Novartis to invest in a non-differentiated compound so it said no to Phase 3. It is not too surprising that this was dropped - we believe more and more DPP4s in development will be dropped because for any it is tough to show differentiation and it's hard to make the argument to

invest when there are compounds that will be on the market shortly. An exception might be compounds that are more selective, which might translate to safety. Overall, Roche's recent pharma activity shows us how important it is for Big Pharma to be in the incretin game and also how difficult and costly it is.

- **Novartis**: **Trial program initiated in anticipation of battle with TZDs – can't wait for Nov 28!**: Novartis announced October 11 the start of GALIANT, a 7,500 patient clinical trial that will compare the company's DPP-4 inhibitor Galvus (vildagliptin), as an add-on therapy to metformin, in a head-to-head battle against TZDs. Yesterday (Oct 17), we had a chance to discuss the trial with Dr. Marjorie Gatlin, Vice President of US Clinical Development for Cardiovascular and Metabolic Diseases at Novartis. So it sounds like the three-month multi-center trial at 800 (800!) research centers throughout the U.S will mostly be conducted by primary care physicians in what Novartis is calling "real-world" conditions. We note that previous trials have already shown that Galvus is comparable to Avandia (rosiglitazone) in monotherapy so we suspect the point is really to show the side effect profiles of the two classes, side by side, and also, importantly, how much weight is gained or lost with each drug. Patients with A1cs of 7.0 – 10.5 on metformin monotherapy are eligible for enrollment (why there would be any patients on metformin monotherapy with A1cs above, say, 8, is a reasonable question, but we know there are many) and we suspect the trial will be powered for lots of interesting sub-group analysis since Novartis seeks to enroll patients of diverse ages, ethnic backgrounds, etc. The primary outcome will be non-inferiority to TZDs, but we suspect Galvus may well do better than TZDs in terms of A1c – we also wonder if the three month time frame may be a little short to adequately assess the impact of TZDs. TZDs can take longer to have "peak impact" in the system; Gatlin did allow, however, that PCPs would generally make some assessment after three months so this will be interesting to watch. We also wondered in terms of weight whether all the patients would have a rigorous "diet and lifestyle" element so that Januvia might even show weight loss, but Gatlin said the diet and exercise counseling will be limited to "whatever the PCP would ordinarily do." We're staying tuned and hope that results might be available at EASD next year – enrollment will be six months and then three months for the trial, so results likely won't be available for ADA (that, and publishing, may be another reason for the short time frame). To us, the trial seems like a fantastic way to introduce Galvus to scores of primary care doctors, who will likely be the main prescribers for the new DPP4 inhibitor class and who should have some robust data to assess. This is also a way for Novartis to get its drug into primary care a little early. Novartis CEO Daniel Vasella told Reuters it would be "a big surprise" if GALIANT did not show that Galvus is superior. In case there was any question … the battle with TZDs is on! The battle with Januvia is also on, we note – this also gives Novartis an opportunity to introduce the drug. Ultimately, one of the only differences between the two drugs may be that PCPs should test renal function with Januvia; Galvus does not accumulate in patients with renal insufficiency, so it isn't expected renal function would need monitoring. While this may be small, it may also be perceived as hassle factor as it adds another step – we'll also be interested to see the "real world" response on this front.
- **More on Novartis, from UBS**: Several weeks ago in a presentation at the UBS Global Life Sciences Conference, Novartis Chief Marketing Officer Kurt Graves emphasized that based on data shown at the summer meetings that Galvus is every bit as effective as TZDs; he even took a poke at TZDs as a class by reminding investors that PROactive (with pioglitazone) failed in its primary endpoint last year and DREAM (with rosiglitazone) did not demonstrate improved CVD outcomes. For our part, we don't find it particularly surprising that CVD outcomes were not improved in only three years in DREAM, but it is certainly true that DPP-4 inhibitors don't produce the kind of weight-gain / fluid-retention effects (we're ignoring associated congestive heart failure for the moment) seen with TZDs. Graves certainly stressed Galvus' superior efficacy, simplicity (once-a-day dosing regimen), safety, and tolerability compared to TZDs. He also noted Novartis' commitment to the GLORIOUS megatrial program, promising more data on GLORIOUS would be shared at the R&D day on Nov 28 in London. No mention was made of Merck's DPP-4 Januvia, but Graves implied that Novartis has more clinical data than Merck. (Merck did not present at the UBS conference.) Specifically, Graves

said that Galvus will have one of the largest NDAs ever submitted to the FDA for an oral anti-diabetic product. Novartis has extensively profiled this drug in monotherapy, combination therapy, and as an add-on to additional therapies (metformin, TZDs, sulfonylureas, insulin – Merck did not have data with the latter two although the FDA has requested it); certainly, based on its very strong showing at EASD, we were also very impressed with Novartis, and we believe the DPP-4 inhibitor class will do well commercially because it'll expand the number of patients receiving diabetes treatments – not so much because it's stealing share, though we expect gliptins to steal some share from SFUs and TZD and those who have been prescribed metformin but just put it on the shelf due to tolerability issues. We do believe Novartis is strongly positioning Galvus for monotherapy, and though we predict initial resistance to broad reimbursement for monotherapy, longer term we believe it could be successful because patient compliance could well be far better than with sulfonylureas or metformin or TZDs or insulin, all drugs that have major tolerability problems. Too, as noted earlier, DPP-4 inhibitors will likely be easier/less hassle for primary care physicians to prescribe. Although the potency in monotherapy is sub-optimal compared to monotherapy, the monotherapy data for Novartis may be slightly better – but it's really tough to compare because even though we now have real baseline data with the Januvia label (not just placebo subtracted) the baselines for the two are different – 8.0 for Januvia and 8.2-8.6 for Galvus – so it's tough to assess the 0.6 and 0.9 Januvia and Galvus A1c drops. At any rate, although the 0.6 drop doesn't blow one away, for newly diagnosed patients who don't need a *major* drop in A1c, this might well be the ticket for earlier, intensive therapy, even if monotherapy, especially if metformin can't be tolerated. We've been hearing and reporting that phrase for years – earlier, more aggressive therapy - and we're finally convinced it'll start to happen on a much broader basis – and to boot, that we'll really start to see earlier, more aggressive combination therapy, in a range of permutations. Merck and Novartis seem committed to getting these drugs on formularies – that's the other big question. It does seem DPP4 inhibitors can help patients in monotherapy if they are starting at 7.0 - 7.5 A1cs, but above that, they'll need *more* help. Here, here, to patients being urged toward normal glucose levels and toward combinations – we'll hope that long-term safety data is strong (that's an area where much more data is needed) and that the gliptins will serve as good starting points.

- **Roche: Accu-Chek Spirit available in the US**: More than three years after the FDA banned sales of Disetronic pumps in the US (July 2003), the agency announced on October 8 that it has lifted the ban. This was following an inspection of the Disetronic site in 2005. The decision has cleared the path for an imminent launch of the Accu-Chek Spirit pump in the US. The Spirit pump has been FDA approved for some time, and marketing has begun, though we also assume Roche still needs to ramp up its sales staff. Roche says it will begin shipping out Spirit on October 30. Roche's announcement for their US launch estimated that insulin infusion products have a global market of $787 million (which sounds low to us) and a growth rate of 11-12% (which seems right). US sales currently account for about 70% of this market. Though we believe the re-entry will help drive some industry expansion, the pump market is already very competitive and differentiation may prove quite difficult. However, Roche is pursuing a "simple and easy" strategy, which make senses directionally, since doctors/nurses currently need to spend too much time with the average pumper and thus some have a disincentive to encourage pump therapy, even if it is more physiologic than all other forms of insulin delivery.
- **Novo Nordisk: Annual Capital Markets Day reinforces strength moving into autumn. Novo had an excellent analyst day October 6, highlighting the strength of its entire diabetes portfolio from insulin analogs to new portfolio drugs.** The biggest news of the meeting, in our view, was that Novo is working on a 550-person, 20-week phase 2 liraglutide weight-loss study, investigating optimal dosing in obese patients (BMI between 30 and 40); this is scheduled to start in the first quarter of next year. Novo implied that it expects to see more weight loss in non-diabetics than diabetics, and it appears to be going for an (easier) weight management indication, rather than cardiovascular management. This is interesting, as GLP-1 competitor Amylin has said that it doesn't intend at this time to develop exenatide specifically for non-diabetics (the company does, of course,

have pramlintide (Symlin) for non-diabetics, which we assume is nearing phase 3). Novo has already enrolled three of five of the excellently-named LEAD (Liraglutide Effect and Action in Diabetes) trials, and it emphasized its goal to get all the indications at once - monotherapy, add-on to metformin, add-on to sulfonylureas, and add-on to dual-agent combos. Ambitious! Management said a 2008 liraglutide filing was realistic and implied that results would show progress in beta cell protection and regeneration though the company has not provided significant data at this stage. Novo emphasized that one of liraglutide's benefits is that patients will require fewer fingerstick tests – we were surprised to see an insulin company come right out and articulate this so plainly though we aren't surprised at all. One session chart implied that the company is working on a longer-acting liraglutide, but Novo didn't say much about it. In reviewing its diabetes pipeline, Novo also highlighted NN9101, an early-stage glucokinase activator (a class that stimulates glucose-dependent insulin secretion), which has demonstrated good glucose regulation, no weight gain, and increased insulin content in the pancreas in preclinical trials. In early human trials (phase 1), NN9101 reduced both fasting and post-prandial glucose. As for PPAR delta products, management noted that Novo continues to be interested despite the problems to date. The ongoing IMPROVE trial was mentioned as well. This is a 40,000-patient global observation study looking at Novomix (a lot of investment in pre-mixes and a lot of controversy). While there was not much focus at this meeting on devices, during the Q&A Novo management was asked about acquiring a pump company. Management responded that Novo's interest is not in traditional pumps, but perhaps in disposable pumps. It will be interesting to watch whether the company pursues a buy or build strategy – the former might be easier given all the locked-up intellectual property.

- **Lilly: FDA wants phase 3 trial on ruboxistaurin; positive European opinion on exenatide:** In a blow to Lilly (as well as to patients), the FDA in August sent an approvable letter to Lilly for ruboxistaurin, meaning the drug is not approvable at this time but may become approved with more data. The FDA clarified on September 29 that it would require *another* three-year efficacy trial for further clinical evidence. The ruboxistaurin submission was originally risky because Lilly only submitted one "real" phase 3 trial; it seems that will not be enough so it's likely we can bid farewell to the chances for this drug to survive. Pity! Critics say that Lilly rushed the trial and didn't plan a proper submission. It is hard to argue with that. The question is whether Lilly will stick with the product – we think it is quite likely that the company will walk away because another multi-year wait would limit patent life, though we estimate the company would have patent protection until 2017. Basically, anyone smart about Lilly shakes their head in disgust when you even begin to ask the question. "*Ruboxistaurin? Forget it! That's dead*!" We are disappointed that it looks like this drug won't be added to the armamentarium to treat patients. While it may not have seemed a major blockbuster-in-the-making, it did look like it had real potential to help patients prevent or treat microvascular risk – a serious need. Analyst estimates had been about $500 mm for this indication, but we had thought that sounded low, long term. We had also thought Lilly would do more trials showing it could prevent/treat other microvascular complications and that it would be used for this off label, anyway. The FDA's action is a dismal signal to other companies about how hard it is to get drugs approved for complications – and also a critical signal about the importance of investing in and getting buy in on very solid trial design very early.
- **On a much more positive note, Lilly announced September 21 that it received a positive opinion recommending** approval of exenatide from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Evaluation Agency (EMEA). Marketing authorization by the European Commission is expected to follow later this year. The positive opinion is no surprise – Byetta is highly anticipated in Europe. The only question now is how quickly the final approval will come. We anticipate strong demand … a side note from EASD was that seemingly in every oral presentation on every drug, the question at hand was what happened with weight. Said one presenter, "I'm tired of hearing about weight! It is glucose that matters!" But there was resistance to this, as many said the two were inextricably linked, and that weight loss could be very important to patient motivation in European countries just as it was proving to be in the US. Very satisfying for the

Lilly/Amylin Byetta franchise to hear this out of Europe…

- **Even more on Lilly! Eli Lilly honors healthcare blogger extraordinaire Amy Tenderich**: Lilly also recently awarded five LillyforLife Achievement Awards, one of which went to healthcare blogger Amy Tenderich for her extraordinary blog DiabetesMine.com, founded in 2005, which features interviews, news, personal accounts, and product reviews. This is an excellent resource for patients, but *also* for those who work in diabetes or are involved with patients in any way. She is also the co-author, with Dr. Samuel Jackson at Joslin, of the forthcoming "Know Your Numbers, Outlive Your Diabetes: Five Essential Health Factors You Can Master to Enjoy a Long and Healthy Life," a highly-awaited tome that cuts through the clutter for patients, giving them the final low-down on what numbers they need to know and why. What are the five? You'll be tested at the end! A1c, blood pressure, lipids (HDL, LDL, triglycerides, microalbumin, and a yearly eye exam). Kudos to Amy for her amazing work – and check out her blog, diabetesmine.com, etc, right now – there's an interview by her hot off the press by a patient that has taken and loves Exubera!
- **BD—Exiting the BGM market:** CEO and president of BD, Ed Ludwig, chaired a conference call on September 28 to discuss the company's plans to close its blood glucose monitoring business. As one of the most hallowed names in the diabetes industry, BD's decision underscores how difficult it is for a company to move across product lines in diabetes. There are a number of current challenges in the glucose-monitoring market, including managed care power, tough competition (including both entrenched deep-pocketed competitors as well as nimble low-cost competitors), increasingly expensive customer acquisition costs, and new drugs that may be changing the testing paradigm (e.g., GLP-1 and DPP-4 inhibitors). That said, even if pricing trends and other industry challenges were less pronounced, product-related problems are always difficult to overcome for smaller franchises. Most of the industry has experienced product problems over the past year, but others have more of a cushion to absorb them – that is less so for BD. On the conference call, Ludwig offered a brief opening statement, noting that the decision was "difficult but necessary," and that BD will continue to invest in diabetes products. The estimate for the charge to earnings was $50 - $70 million. Ludwig said that diabetes care is an important BD franchise and that BD would look broadly at diabetes care, including insulin delivery and other areas (molecular, cellular, diagnostic), where the company thinks it could add real value – we could see the company just investing in GLP-1 studies, as Byetta has certainly contributed to BD's very strong year to date in pen needles! Ludwig said the company is working on an ongoing basis with Medtronic to ensure that customers using BD/Medtronic products will continue to receive supply until alternatives are available – sounds like until the end of 2007. Regarding the supply agreement, he said this would devolve over the short term. Ludwig said that work in CGM would continue, but on a reduced basis. He said that he thought BD had some unique capabilities in this area that he wanted to confirm through clinical evaluation – this will be very interesting to see. Of course, BD had very interesting data at the ADA about a potential product that could speed the rate at which insulin enters the system – we look very forward to hearing more on that front. The day after BD's decision was announced, Abbott Diabetes Care announced that it would give all BD users an Abbott meter and "starter strips" at no charge. Bayer, HDI, LifeScan, and Roche all followed, unsurprisingly – the BD users were likely frequent testers, and since all the companies have meter "upgrade" programs anyway, this is a cheap way to win profitable new users. That surely was the old TheraSense reflected in the early Abbott action – great to see!
- **Valeritas—Gearing up for h-Patch launch in 2H07:** Valeritas, the "old" Biovalve, will be publicly traded early next year, and we will be watching this company closely. Kind of similar to our thoughts on DPP-4 inhibitors, depending on the product, we believe Valertias would expand the insulin pump pie rather than slicing up the pie. At the UBS Global Life Sciences Conference, CEO Robert Gonnelli reviewed plans for the h-Patch insulin delivery system, a disposable pump for type 2's, which recently received 510k approval and will launch in 2H07. He billed it as a way to achieve more physiologic control. We agree that delivering insulin by any kind of pump is more physiologic than using syringes or pens, and we believe the trend is 'with' Valeritas on that front… we look forward to seeing more clinical data supporting this device. Valeritas plans to market first to type 2 patients

taking pre-mixed insulin 1-2 times per day or those on multiple daily injections (MDI) - about 1.6-1.8 million patients in the US. The company hopes patients will prefer the convenience of a pump to a pen or vial, but based on experience to date, we aren't confident that type 2 patients will switch to a pump easily – although we do acknowledge the potential is big depending on form factor, reimbursement, clinical advocates, etc. Some data will be available upon launch but likely not enough for CDEs – typically an instrumental group in "selling" products to patients. Gonnelli noted he expects growth to eventually come from the 3.8 million patients on oral agents and basal insulin that fail to achieve control. In fact, we believe this is an underestimate – according to our research there are five million alone on oral meds who are not at target. As for the trend toward earlier, more aggressive therapy – the impact of insulin isn't as clear these days, since some going on GLP-1, for example, have backed off insulin, and some taking oral meds earlier may delay the move to insulin because their control improves early on. To boot, we don't know enough clinically to anticipate rapid adoption; a phase 4 program, which will address dosing issues, is slated to begin this December. On the plus side, the device is simple and discreet, which is important: it has a start button and a bolus button – no external catheters or electronics – and is changed every 24 hours. We assume most type 1 patients wouldn't want to use it due to dosing issues, but these haven't yet been clarified. Clearly, more type 2 patients should go on insulin – if this is a mechanism, we'll soon find out….

- **DexCom: Billing STS as a "first generation" device with improvements in store:** DexCom CEO Andy Rasdal, at the UBS Global Life Sciences Conference, gave more information on hospital and pediatric products, where the company is clearly making investments. We are more positive about the latter than the former. DexCom was doing end-of-quarter promotions last week, and we wouldn't be surprised to see the company miss numbers, though of course estimates did come down after last quarter's revenue disappointment. We heard throughout his talk, for the first time, many references to STS as a "first-generation device" – making some concessions that it isn't a perfect product, but emphasizing that DexCom is moving in the right direction to get to a better product. DexCom is now talking more and more about rapid product iterations and calling the first generation an "early mover platform" – we think this is smart. The 2nd generation is at FDA, 3rd generation is in human trials and 4th generation is in animals. However, not much was said about the later generations except for a focus on how small they are. On the inpatient front, DexCom is currently developing two in-hospital product platforms for critical care and non-critical care use. On pediatrics, Rasdal said DexCom's pediatric product will be different from its regular STS and that the company is currently conducting pediatric feasibility trials with STS "optimized for pediatric usage." DexCom intends to submit IDE prior to initiating pediatric approval; beyond that, Rasdal was close-lipped but mentioned he had a "very productive pre-IDE meeting with the FDA in September on pediatric approval requirements."
- **Medtronic: Efforts to expand the pump market and lead the way to the artificial pancreas**: CEO Arthur Collins's remarks on Medtronic's diabetes business at the UBS Global Life Sciences Conference focused on the potential for increasing the pump market and Medtronic's commitment to the artificial pancreas (AP). We're always glad to hear about AP progress, but we didn't agree with some of his views on pump market size. Specifically, he said 35% of type 1 patients in US have received a pump, then corrected himself and said it was more like 25%. We believe the percentage of type 1s in the US who actively use pumps (as opposed to historic pump purchasers) actually hovers closer to 20% at the high end – probably somewhere between 225,000 and 250,000 of the 1.2-1.3 million type 1 patients total. The percent of type 2 patients wearing pumps is likely very low. Collins did point out that of endos and diabetologists who are diabetic, 70% are pumpers. This is an old, often-quoted stat but does reinforce the point that a high portion of patients probably should be pumpers. Collins also mentioned the STAR trials but gave no new details in the presentation; we note that the trial timing continues to change and that the first results, seen at EASD, although promising for patients, didn't represent data that we think would convince payors. At any rate, Collins highlighted Medtronic's pump market leadership and said there was a lot of work to do on developing both US and international markets. The latter is very true, but we note that reimbursement pressures outside the US represent a major barrier. As for the AP, Collins said Medtronic would have the first

sensor augmented pump, which will eventually lead to the artificial pancreas. We agree and look forward to this but also believe that the market underestimates the length of time that a "high hassle factor" (stemming from user and provider acceptance issues as well as reimbursement problems) will be present.

- **Metabasis: Continuing work with diabetes/dyslipidemia candidates in the pipeline**: CEO Paul Laikind updated investors on Metabasis' pipeline at the UBS global conference. Of note: CS-917, a novel oral drug for type 2 diabetes, is currently in phase 2b. Metabasis is developing it in collaboration with Daiichi-Sankyo. Proof of concept studies, including 14-day and 28-day studies, have met primary efficacy endpoints and showed statistically and clinically significant reductions in fasting plasma glucose compared to placebo. Sankyo is enrolling subjects at 90 centers and expects to complete the study by the end of this year or early next year and have top line data in the first half of next year in preparation for a phase 3 trial in late 2007. MB7803, a second-generation compound that acts through the same mechanism as CS917, is in its second phase 1 study. Metabasis expects to do a proof of concept phase 2 study early next year with data available mid next year. The company owns all of the rights to this drug – Sankyo had an option at one time but did not exercise it; and for now, Metabasis is moving forward on its own. The company also has a novel product for hyperlipidemia, which uses an as-yet-undisclosed mechanism and is ready to go into the clinic. It has shown efficacy in six species. Laikind said it was as effective as Lipitor in a monkey model. Lastly, Metabasis has an early stage project with Merck on a drug targeting AMP-activated protein kinase, which will be used for diabetes and possibly hyperlipidemia and obesity as well.
- **Nastech: Clinical trials to begin of rapid-acting-insulin nasal spray**: Nastech announced September 19 that it would begin phase 1 trials on its rapid-acting-nasal insulin spray. The trial will evaluate the product's safety, bioavailability (pharmacokinetic and pharmacodynamic), and subjects' glucose response. The study will compare Nastech's product with Exubera; Nastech is positioning its nasal absorption technology as potentially safer than the deep lung absorption that Exubera requires, but we think that data validating this remain to be seen. Nasal tissue, as a drug absorption site, has its own complications and sensitivities. CFO Phil Ranker did say at the UBS Life Science conference that the Nastech device would be much smaller than the Exubera inhaler – he likened it to a pack of gum. This would be a plus for patient convenience, but we're skeptical on this application overall.
- **Diamyd: Potentially promising type 1 drug finishes phase 2 in Europe**: Swedish company Diamyd presented the results of a phase 2 trial of its anti-autoimmunity drug at EASD. The drug is based on GAD, a protein target for autoimmune attacks in type 1 diabetes. In an initial phase 2 clinical trial published earlier this year, the drug helped slow islet cell deterioration in LADA (latent autoimmune diabetes in adults) patients. As a reminder, these are patients who have both type 2 diabetes and islet cells antibodies associated with type 1 diabetes; over time they lose islet function like type 1 patients on top of their type 2 insulin resistance. Diamyd presented a second, more recent phase 2 study at EASD that included 70 type 1 patients aged 10-18 yrs who had been diagnosed with type 1 diabetes within the past 18 months. The patients were randomized to receive two injections of the drug or placebo four weeks apart. At 15 months follow-up, treatment patients required less insulin than placebo patients. No numbers were given, but from press release charts it looks like the treatment patients had a 31% increase in insulin requirement at 15 months compared to a 51% increase in placebo patients. Thus, while the drug seems to mitigate the loss of islet function over time, it did not stop beta cell deterioration. However, company CEO Anders Essen-Möller pointed out that the trial patients who were treated particularly early in their disease (within three months of diagnosis) actually showed an improvement in insulin production at 15 months. The decline in C-peptide levels in the overall treatment group was half as much as in the placebo group, but for patients treated within three months of diagnosis there was no loss of C-peptide levels at all. A caveat to this finding is that these patients comprised only 4 of the 30 patients in the treatment group, so the data are preliminary at best. Nonetheless, these results suggest that Diamyd's product could be promising. Essen-Möller noted that phase 3 trials both in the US and Europe are in planning; he hopes to begin these next year. FDA submission could be as early as 2008 if all goes well. He also expressed hopes

that the drug would eventually be developed into a vaccine, though no clinical trials for this indication have been done yet. As a reminder, competitors in the field of autoimmunity treatment include TolerRx's anti-CD3 TRX4, Genetech's anti-CD20 Rituxan, Roche's CellCept and Zenapax, and Macrogenics' CD3 Mab.

- **Roche: Still catching up on incretins, but ahead in developing GKA class**: Eduard Holdener, Roche's global head of product development, gave a presentation on the company's drug pipeline at the UBS conference on September 25. Ipsen's GLP-1 product is now in phase 2, and the company appears to believe it is quite promising. Ipsen has already published some "interesting" data, said Holdener. He referred to results published at ADA of a trial that looked at an immediate release formulation of the drug over 28 days of continuous subcutaneous infusion, which showed a linear response, good A1c control or even a decrease in that value, good tolerability, and a trend for weight loss. Work on the sustained release formulation has started and will be very important for the competitive position of the product, Holdener said. We note that Ipsen implied that the needle would be "very thin" – we don't know if this reflects the drug's duration (1x daily) or the formulation (something concentrated that lasts for days) or neither. Roche is also working on several products in the DPP-4 inhibitor class. Holdener admitted that it was clear that Roche was not the leader in this area. He focused on the fact that Roche will make a decision about whether to move ahead next year – we thought that the fact that he made this point underscored meaningful uncertainty in this compound. The company will likely also want to watch market development for Merck's Januvia and Novartis' Galvus (see related stories). In other news, glucokinase activators (GKA) are a new class in which Roche considers itself "actually" in the lead followed closely by one or two other companies (among them Novo). Roche's GKA is currently in phase 2, and the phase 3 decision will come up next year. "If it works the way we hope it will," Holdener said, "we should be able to file in 2009." Finally, a Japan Tobacco cholesterol ester transfer protein (CETP) inhibition drug is in phase 2a. In monotherapy, there a significant CETP reduction was observed[1]. Roche and Japan Tobacco signed the agreement in October 2004, and Roche has exclusive worldwide rights, excluding Japan and Korea. The ultimate decision about whether to enter phase 3 and the start of phase 3 are now scheduled for 2007.
- **ConjuChem Q3FY06: Continuing development of once weekly GLP-1**: ConjuChem CFO Lennie Ryer gave an as-usual upbeat report on the results of a phase 1/2 study on PC-DAC, its exendin-4 compound, during the company's 3QFY06 call on September 14. Ryer said the study "confirmed the compound's excellent safety and tolerability profile and reaffirmed our belief in its potential as a once-per-week treatment for type 2 diabetes." The company said it will release results of an ongoing randomized, double-blind, single-dose, 3-week inpatient trial in the fourth quarter. Those results will yield more safety and efficacy data. ConjuChem also announced October 10 that it began a 60-person multi-dose phase 1/2 trial that will test three dosages of the once-weekly drug for one month; results will be available in January. The company reported a net loss of $10.5 million in the third fiscal quarter, which ended July 31, compared to $7.4 million in the previous quarter; management attributed the greater loss to R&D expenses related to clinical trials for PC-DAC and DAC:GRF (the company's HIV lipodystrophy drug). We learned at EASD that GLP-1 agonists tend to differ more than DPP-4 inhibitors, suggesting that it is easier to differentiate various compounds in the GLP-1 class than DPP-4 inhibitors. In particular, there appears to be meaningful variation with the GLP-1 class in terms of weight loss, 24-hour glucose coverage, etc – for now, we would say that the weight-loss advantage with some GLP-1 compounds promises to render those without the benefit at a meaningful disadvantage. In contrast, the sentiment about DPP-4 inhibitors is that "they're all the same," as we heard more than once at EASD, suggesting that companies with greater sales and marketing resources and skills should benefit the most.
- **OrSense: Accurate Non-Invasive CGM?:** OrSense, an Israeli company that is developing a non-invasive CGM system based on occlusion spectroscopy technology, showed results at EASD September 14 on the accuracy of its device. This technology measures blood constituents through an optical beam shot across the finger, "which overcomes the key technological barrier related to the

very low signal to noise ratio and non-specificity inherent in competing approaches." The trials compared OrSense's finger cuff to conventional subcutaneous CGM systems. The mean relative absolute difference has ranged from 15% to about 20%, depending on the application, and was 19.5% in the EASD results. Clarke error grid analysis showed that ~95% of measurements fall within zones A and B. Though these studies were done with the NBM-100G model, the first model expected to be launched is actually the NBM-200G, which is about a quarter of the size – potentially exciting. There is no word yet on the likely launch date. OrSense is preparing FDA trials now, and these trials will focus on type 1 and insulin-dependent type 2 diabetes patients who make decisions with frequent testing. However, "there is no limitation to who are the right patients," suggested CEO Lior Ma'yaan, and the system can be used for spot measurement as well as continuous monitoring and can be used in the ICU as well as at home. Reimbursement is a concern. However, "the cost of this device will be lower than what we're used to with subcutaneous devices," said Ma'ayan. The device has two parts, the sensor and the receiver; the sensor is disposable or semi-disposable because accuracy deteriorates overtime, but duration studies have not been done yet to determine how long it would be indicated to last.

- **Mannkind: Technosphere efficacy results are good, safety study ongoing**: Mannkind announced September 14 at EASD that it has completed the enrollment for its open-label randomized phase 3 study to evaluate the long-term pulmonary safety of Technosphere insulin. Included in the trial are about 1,800 type 1 and type 2 patients as well as a small group with no diabetes. This is the first pivotal study to complete enrollment. Mannkind's CFO Dr. Peter Richardson emphasized that the product reduces post-prandial glucose excursions and causes no weight gain. The results of Mannkind's phase 3 efficacy study were also presented at EASD on September 16; this study compared Technosphere with NovoLog on top of basal glargine in 308 type 2 patients. It's not clear what the baseline A1c was, but after 24 weeks the Technosphere group had a drop of 1.05% compared to 1.30% in the NovoLog group. No differences in pulmonary function were detected, but a mild cough was experienced by some Technosphere patients. Significantly fewer patients experienced hypoglycemia in the Technosphere group than in the injection group. Interestingly, there was a weight loss of 0.76 kg in the Technosphere group compared to a weight gain of 0.23 kg in the injection group. CEO Al Mann was probably referring to this when he remarked at the UBS Life Science conference on September 27 that longer-term studies with Technosphere are starting to show weight loss. We would have guessed Technosphere might have been weight neutral at best, since there is no theoretical reason why insulin would cause weight loss on its own without lifestyle changes.
- **Amylin: Byetta measures up to premixed**: Amylin announced strong results at EASD from a 52-week open-label non-inferiority trial comparing exenatide to biphasic insulin aspart (NovoMix 30/70) in 501 patients. Originally, we weren't sure why the comparison was to pre-mixed, but we believe it is because premixed is two shots a day, so it is similar to Byetta in that respect. Baseline A1c was 8.6% in both groups. The A1c drop was slightly better with exenatide (1.04% vs. 0.89%), though not significantly; however, exenatide patients finished with much flatter postprandial profiles, which of course is good in the glycemic variability department – we believe there is increasing emphasis on this measure. Weight profile was better for exenatide as well (down 2.5 kg vs. up 2.9 kg), and, as expected, there was considerably more nausea (33.2% vs. 0.4%) than with insulin. Four percent of exenatide patients discontinued because of nausea. Hypoglycemia was not severe and was the same in both groups. Thirty-two percent of the exenatide patients achieved A1c <7% whereas only 24% of the insulin patients did. Eighteen percent of exenatide patients achieved A1c <6.5% compared to 9% of insulin patients. We look very forward to label expansion going forward so that exenatide can be combined with drugs that will enable a higher percentage of patients to achieve glycemic targets.
- **Merck: Substantial A1c lowering with Januvia presented at EASD**: Merck announced the results of a phase 3 trial for Januvia (sitagliptin) at EASD on September 14th. This was a 24-week double-blind study of 1,056 untreated patients who were randomized to 100 mg sitagliptin once daily (n=175), 500 mg metformin twice daily (n=178), 1,000 mg metformin twice daily (n=177), 50 mg

sitagliptin twice daily plus 500 mg metformin twice daily (n=183), 50 mg sitagliptin twice daily plus 1,000 mg metformin twice daily (n=178), or placebo (n=165). Unsurprisingly, the best reduction was seen in the group that received 50 mg sitagliptin twice daily plus 1,000 mg metformin twice daily; the patients in this group dropped 2.1% in A1c from their mean baseline of 8.8%. As expected, side effects were mild, and sitagliptin doesn't appear to cause additional problems on top of the usual GI problems seen with metformin. As noted, we think the minimal side effects of DPP-4s will resonate well with PCPs. In this trial, we would have liked to have also seen a monotherapy arm of 50 mg twice-daily sitagliptin in order to do a more comprehensive comparison. (See our longer story on the Januvia approval below.)

- **Arena: Lorcaserin for obesity enters Phase 3**: Arena announced the initiation of the phase 3 program for lorcaserin, its 5-HT2c agonist for obesity, on September 12. As we reported in DCU #60, Arena said in its 2Q06 earnings call that it would initiate this trial program (called BLOOM) in September/October of this year – which it has certainly done – and at the UBS Life Sciences conference on September 26, the company said it expects to enroll all 3,000 patients before the end of the year. Wow! The first data assessment of trial results will come in mid-2007.
- **Neurocrine Biosciences: Altered peptide ligand NBI-6024 for type 1 discontinued**: On September 12, Neurocrine announced that it was discontinuing development of NBI-6024 after the drug missed its primary endpoint of preserving C-peptide levels in a phase 2b trial that included 188 type 1 patients. NBI-6024 was an altered form of a dominant pancreatic antigen engineered so that it would not be recognized by the autoimmune cells that destroy beta cells in type 1 diabetes. The hope was that the altered peptide would generate production of regulatory cells that would in turn down-regulate the autoimmune response against the body's islet cells. We see this as a reminder of how complicated preventing type 1 is.
- **Merck: Impressive new VP for diabetes and obesity**: Merck continues to move forward on the diabetes front. On August 16, it announced the appointment of Dr. Luciano Rossetti to the new position of senior vice president and franchise head of diabetes and obesity. Dr. Rossetti was previously a professor at the Albert Einstein College of Medicine of Yeshiva University and serves as Director of the Einstein Diabetes Research Center. He will have scientific direction of the diabetes and obesity drug discovery and development process for Merck – a very big job for a renowned doctor. We look forward to seeing Dr. Rossetti's influence – a real win for Merck.
- **Sanofi-Aventis: Rimonabant debate in JAMA**: As we wait and wait to see what happens with rimonabant, we noticed recently quite an interesting pair of letters in the August 9th issue of *JAMA* regarding psychiatric adverse events associated with rimonabant, a cannabinoid CBI receptor antagonist for weight loss. In a letter titled, "Effect of Rimonabant on Weight and Cardiometabolic Risk Factors," Dr. Kishore Gadde of Duke University pointed out data from the RIO-North America trial, which showed that patients who received 20 mg of rimonabant daily had 2.7 times the rate of psychiatric disorders leading to early study withdrawal or removal compared to patients receiving placebo. He wondered if the rate would be even higher in 'real life' obesity patients, who tend to be more prone to depression than normal-weight patients; he implied that the RIO trials sought to include only patients with minimal or no depressive symptoms. Dr. Gadde also pointed to studies by Hill and Gorzalka showing that CBI knockout mice are particularly prone to melancholic depression. He suggested that inhibition of the CBI receptor in humans may cause depression. In reply, the first author of the RIO-North America study, Dr. F. Xavier Pi-Sunyer, explained that patients were not excluded from the RIO trials based on their baseline Hospital Anxiety and Depression score. Regarding the Hill and Gorzalka data, he pointed out that early developmental adaptations in CBI knockout mice may produce different reactions than treatment with a CB1 antagonist in patients with functioning endocannabinoid systems. Rimonabant has actually shown antidepressant-like effects in animal models of depressive disorders. Dr. Pi-Sunyer also gave a breakdown of depression subscores for the patients given placebo, 5 mg rimonabant, and 20 mg rimonabant in the RIO trials from baseline to follow-up; changes in these subscores over the course of these trials were statistically indistinguishable between the three groups. We found his arguments fairly convincing. It's an

ongoing topic of broad speculation when this drug will be approved – it's sounding more and more like 2007.

- **SemBioSys: Insulin from safflower plants?** SemBioSys Genetics released news on July 18 that it has engineered safflower seeds that yield human insulin protein levels as high as 1.2% of total seed protein. Company CEO Andrew Baum says this will have clinical and commercial implications on the future of insulin production within the next few years. His calculations? Based on the company's current methods, it should be able to extract one kilogram of insulin from every acre of safflower growth (or about a ton of seed), which would be enough to treat 2,500 diabetes patients for a year. This means the company would require only a few thousand acres of farms to supply the total current worldwide market for insulin (about 4,000-5,000 kg annually). Management cited capital cost reductions of 70% and actual product cost reductions of 40% compared to conventional insulin manufacturing methods. We're skeptical about the likelihood of this technology actually taking off, but it's certainly a novel idea for cost reduction.
- **Macrogenics: Financing CD3 antibody for type 1**: We missed this one in the summer! Macrogenics completed a Series C financing round that raised $45 million for its monoclonal antibody programs. Macrogenics' lead product is a CD3 monoclonal antibody (CD3 Mab) with a modified Fc component called hOKT3 (ala-ala), which targets the CD3 receptor on autoreactive T cells; the antibody is in phase 2 testing for slowing the progression of new-onset type 1 diabetes. Macrogenics believes CD3 Mab may also be effective against systemic lupus, multiple sclerosis, arthritis, psoriatic arthritis, ulcerative colitis and psoriasis; in a previous phase 2 trial the antibody reduced joint inflammation and pain in patients with advanced psoriatic arthritis. The funds raised will go toward international phase 2/3 trials for the type 1 diabetes indication. Ventures West was the lead investor in this round of financing. New investors included Caisse de dépôt et placement du Québec, RiverVest Venture Partners, and Biogen Idec New Ventures. Existing investors that participated include a blue-chip group: Texas Pacific Group (TPG) Ventures, Alta Partners, InterWest Partners, MPM Capital, Mithra Ventures, OrbiMed Advisors, and Red Abbey Venture Partners.
- **Media Postscript!** In yet another sign that diabetes is increasingly becoming a topic of mainstream discussion, diabetes played a prominent role in ABC's new Sunday night drama, *Brothers & Sisters*. In this episode, Paige, the pre-teen daughter of one of the five siblings featured in the series, was diagnosed with diabetes (presumably type 1, though it was not specified.) While the episode presented a fairly accurate portrayal of the disease – Paige was diagnosed after weeks of excessive thirst and fatigue - other details were less realistic, such as the fact that her blood glucose was reduced to 170 almost as soon as she was admitted to the hospital (though they did not mention what her glucose was to start). Aside from briefly mentioning in-patient diabetes education about insulin needles, there were very few other technical details mentioned. However, the show did go out of its way to emphasize that patients with diabetes can lead "full" lives (we'd say, at least!). In fact, the episode ended with a shot of Paige happily running in the yard. Interestingly, there was not a lot of focus on the emotional issues that arise in a family when a child is diagnosed with diabetes, aside from a brief comment by Paige's mother that she would need her family's help and support with all of the future doctor appointments. We are interested to see how this plot line plays out in future episodes, if at all. Stay tuned!

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

## 2. Januvia approved! Get ready for earlier, earlier therapy…

And, they're off! Yesterday morning (Oct. 17) that Merck received FDA approval to market Januvia -- the first of the DPP-4 inhibitor class of anti-diabetes drugs, for type 2 patients, to enter the market. We expect the sales launch to commence as soon as Merck can stock pharmacy shelves, with primary care physicians as the initial target market. The next DPP-4 expected for approval is Galvus by Novartis (also featured in a separate company news piece, above, in this issue of DCU), which should come in the next two months.

**Why is this news exciting?** The FDA approved Januvia for improving glycemic control for type 2 diabetics, either as monotherapy or in conjunction with metformin or a TZD. With an estimated 64% of the over 15 million patients with diabetes in the US, almost 10 million patients are not at goal. This number excludes the 5 million-plus undiagnosed and the 50-odd million with pre-diabetes. In other words, many people need help. We believe Januvia could be an important tool for helping primary care doctors address glycemic control when numbers first start wandering out of a normal range – in other words, we think one of the most important uses of the drugs will be for patients who are just hitting above 7.0 % A1c – or for that matter, just above 6.5% A1c.

**Why aren't these patients getting help?** Currently, physicians, specifically those in primary care settings have the following pharmaceutical choices as the first line of attack:

- sulfonyureas, which cause hypoglycemia, weight gain, and GI distress
- metformin, which causes GI distress
- TZDs, which cause weight gain, edema, and sometimes CHF
- insulin, which causes weight gain and hypoglycemia

For both patients and physicians, all of these options require a balancing act between treating the diabetes and incurring uncomfortable (GI problems, weight gain, edema), sometimes dangerous (hypoglycemia, CHF), side effects. Given these options, it's no surprise that primary care doctors focus more on statins and blood pressure treatments, which have few side effects. As a result, many patients don't get treatment when their A1c levels first stray above 7, to 7.5, or 8 or even higher. But many believe we are beginning a new era. Today's mantra is treat earlier and more aggressively, and the focus has finally shifted to getting people to normal glucose levels.

**The DPP-4s can't do everything, but they can do something important.** As a reminder, DPP-4s have a distinct mechanism of action. They work by inhibiting the breakdown of incretins (such as GLP-1), thereby stabilizing incretins in the body. Incretins help regulate blood glucose in two ways: (1) they trigger the pancreas to increase insulin secretion, and (2) they signal the liver to reduce glucose production. In clinical trials, Januvia has been shown to significantly reduce both fasting and post-prandial glucose levels when used as monotherapy or as an add-on to metformin or pioglitazone. In monotherapy studies, Januvia also produced significant improvements in beta cell function, as measured by HOMA-beta and the fasting proinsulin/insulin ratio.

With an average A1c drop of -0.6 from an average baseline of 8.0 observed in the 24-week monotherapy trial, the DPP-4s probably won't do much for A1c levels that are 8.0 or higher. They just aren't that efficacious. Emphasized Dr. Irl Hirsch, professor of medicine at the University of Washington, "The problem is in the typical patient with the very high A1c, the hypoglycemia benefit may not be all that important and, like the TZDs, these may be used as yet another procrastinator for those who need insulin." Most physicians with whom we spoke seemed to think that the DPP-4s would initially be used as second- or third-line drugs. Dr. Paul Jellinger, professor of medicine at the University of Miami, thinks DPP-4s will be "mainly [used] with metformin and TZDs initially." Others have a slightly more optimistic view. Dr. Zachary Bloomgarden, Clinical Professor of Medicine at Mount Sinai, thinks that "DPP4-s will be perfectly suitable for 1st, 2nd, and 3rd [line therapy], and if physicians take the 6.5-7% A1c goal seriously, most type 2 patients will need multiple agents to achieve it." How wonderful to think about more patients diagnosed at A1cs of 7.0 – 7.5 and being able to put on monotherapy with relatively lower potency but that are easier to take, to get them used to treating their diabetes. From our perspective, even though the DPP-4 inhibitors are much more costly then generics, if the generics aren't taken, who loses? The patients, and ultimately the taxpayers who ultimately pay for so many of the longer term diabetes complications that arise.

Undoubtedly, the major advantage of the DPP-4s is their tolerability, which is so "clean" that they pretty much run circles around the other options: no weight gain, no hypoglycemia, no GI impact, no CHF, and no edema. And the dosing is easy. DPP-4s are taken orally once a day, which is very convenient for patients. We spoke to Dr. Bill Polonsky, the behavioral expert, who stressed that from a behavioral perspective, " … the role of side effects is critically important in terms of medication compliance, especially when the subjective efficacy (i.e., can I really feel that this is working?) is low or absent (like with most blood pressure drugs and most oral hypoglycemics). So one might expect that better tolerability should be very important." He also emphasized the power of positive side effects: "However, when competing against exenatide, where the subjective efficacy is likely to be high in the majority of cases (i.e., I'm losing weight!), [the role of] perceived side effects many not be as important."

The DPP-4s' easy dosing and tolerability should also make them attractive to PCPs. As Dr. Hirsch explained, "For the PCP who has 11 minutes per patient…, writing a 'script and pushing the patient out the door is unfortunately how primary care has evolved, making DPP-4s more in-line with our dysfunctional health care system." Dr. Jellinger agreed. "Endos will probably continue to gravitate to Byetta [for] weight loss and use DPP-4s in those intolerant to Byetta," he said. "Those who simply won't take an injection and some non-overweight and non-obese type 2's." Thus, despite their modest efficacy, we believe the DPP-4s could do a lot for patients caught early in the treatment cycle – most likely by their primary care doctor.

**Some details from the approval.** As expected, Januvia was approved as an adjunct to diet and exercise for improving glycemic control in type 2 patients and in combo with metformin and TZD where the single agent and diet and exercise aren't working well. There are no contraindications and it seems generally a win for Merck as far as label. The patient Q&A implies it is a pretty easy drug to take (relatively few side effects, stored at room temp, etc). Merck also indicated that it expects a decision on the Januvia/Metformin combo in late March. Dosing is once daily, with or without food. And, pricing is $4.86 per tablet. The release describes availability as in the "near future."

The main questions from our end are still about long-term safety since the drug hasn't been studied long-term in many patients – only about 1,100 patients have been treated for more than a year. As for additional trials, 43 studies are completed or underway and four more studies will begin this year but we don't have details on these new studies. Roughly 6,700 patients are included in the studies, with 4,700 treated with Januvia.

Selected detail from the news release and label insert:

- *Action is glycemic dependent.* One of the highlights of the press release is Merck's description of the glycemic dependency of Januvia. If we understand this correctly, like with Byetta, Januvia basically "stops" working when the patient's blood glucose is normal.
- *Side effects.* The overall incidence of side effects is comparable to placebo with the most common side effect stuffy or runny nose and sore throat, upper respiratory infection, and headache.
- *A1c reduction.* Merck described the A1c reduction as "powerful" in the news release. In the label, A1c reduction as monotherapy at 18 weeks and 24 weeks is -0.5 and -0.6 compared to an average baseline of 8.0; the difference from placebo is -0.6 and -0.8 (which was all we previously had as comparison), respectively. We thought it unusual that Merck described an A1c of <8 as "mildly elevated" and 8-9% as "moderately elevated". The average reductions in these categories are 0.6 and 0.7, and 1.4 for those with A1cs over 9.0, respectively (18 week average)
- *Renal insufficiency requires different dosing.* The label recommends a dosage adjustment for people with moderate or severe renal insufficiency, or with ESRD requiring dialysis. A fair amount of detail is included on this topic as expected. The label also states that patients should be tested for renal insufficiency before going on Januvia, and should receive "periodic" testing while on the drug. This

may well turn out to be viewed as a hassle, especially if other DPP4 inhibitors become available where this testing isn't required.

- *Who shouldn't take Januvia.* The label states specifically that Januvia should not be used for type 1s or as a treatment for ketoacidosis.
- *Januvia in combination with metformin or TZDs.* Merck highlighted Januvia as more powerful when added to metformin or TZD. Merck is clearly focused on alpha and beta cell dysfunction and note that Januvia in combination with metformin or TZDs addresses the three key type 2 defects: insulin resistance, beta cell dysfunction (decreased insulin release), and alpha cell dysfunction (unsuppressed hepatic glucose production). In combo trials, Januvia showed a 0.7 A1c difference from placebo for both the metformin add on study and the Actos add on study from baselines of 8% and 8.1%. Merck states that twice as many people got to A1cs below 7% with Januvia. (This information wasn't shared for the monotherapy trial). In combination, the percentage getting under 7% was 47% with Januvia plus metformin versus 18% on metformin alone, and 45% with Januvia plus Actos versus 23% on Actos alone. Merck states that Januvia provides powerful A1c reductions through combined lowering of both post-prandial and fasting glucose throughout the day: the PPG reduction was 51 mg/dL and the FPG drop was a 25 mg/dl reduction compared metformin alone.

We believe Merck did well with this label – nothing out of the blue to give us pause except perhaps the periodic renal function monitoring suggested and the lower A1c reduction from baseline after the placebo increase was removed. Our surprise is the price. We believe Merck priced Januvia (relatively) low (compared to higher priced non-generics) and expect that the goal was some managed care advantage.

**Some potential limitations.** The DPP4s are an exciting new class, and Januvia is first. But they aren't perfect - far from it.

- *Long-term safety is unknown.* We still don't know a lot about this new class of drugs. They affect a lot of different receptors in the body and nobody really knows yet if they impact any other system(s) in an unacceptable way. So far so good, but we've heard repeatedly that we won't really know about safety until the drugs have been used in thousands upon thousands of patients. We also don't know much about durability either. Diabetes is a progressive disease. How long can the DPP4s hold the A1c drop before patients start to creep back up and need more aggressive therapy? Many of the currently available agents don't last long at all – many, less than a year, depending on state of disease progression – although TZDs and Byetta both have far better durability, so it will be interesting to compare and contrast. As noted, we aren't aware of any open label trials, but we will be looking to find out more on this front. To be taken seriously, we'd like to see the DPP4s hold their effect at least a couple of years – this will be interesting because perhaps taking them earlier in disease therapy – versus, before, taking nothing – will help stave off advancing the disease and the ugliest microvascular and macrovascular complications. What a positive that would be and we hope from a patient perspective first and foremost that that is what is seen.
- *Likely that tests for renal insufficiency will be required.* We weren't surprised to see recommendations for different dosing in the case of renal insufficiency. We do wonder however if the need to first test patients for renal insufficiency and then to conduct periodic tests going forward won't add some hassle factor. While we don't think this requirement is a deal breaker for primary care doctors, we do believe it will confer some advantage to Novartis once Galvus is on the market (another reason for Merck to seek formulary wins early, which we're sure it is doing).
- *Reimbursement is complicated.* Speaking of, Merck and Novartis have some reimbursement hills to climb. We are intrigued by Merck's decision to price below $5 a day and assume Novartis will follow. This price point seems designed to attract managed care support even though it is still pricier than generics. Regardless, we expect these companies to hit the ground running on the payor front as both Merck and Novartis have leverage with other drugs to wield.. However, we ultimately note that epidemic or not, reimbursement is getting harder for diabetes, not easier.

- *We'll be looking for more peer reviewed, published data, in addition to all the abstracts.* It may be just a matter of time, but peer-reviewed papers in important journals should go a long way toward addressing economic benefit and likely reimbursement.

**Market impact.** What do we think the DPP-4s will do to TZDs, GLP-1s, etc., in the marketplace? Not much. In our view, this story isn't as much about stealing market share, though there will be some of that; it's about growing the pharma pie for patients who didn't have adequate treatment options. Of note on that front, Merck has also submitted an NDA for MK-0431A, a combination of Januvia with metformin, and expects FDA action by the end of March 2007. As Dr. Jellinger said, "There is some uncertainty…. as to just where these agents will fit in. Early experience will likely chart the course." Dr. Hirsch said, "In their favor is the fact that there is currently no marketing for SFUs except for combo products (e.g., Glucovance and Metaglip.)"

We think the DPP-4s have the potential to open up a market of either newly diagnosed or perhaps ultimately, even pre-diabetic patients. More studies are required. Over the long term, catching these patients early might delay their need for other treatments.

**Big picture view?** These drugs are coming at an exciting time. We are learning that physiology can be changed for the better – just look at Byetta's capabilities, not only for lowering A1c's, but also inducing weight loss and possibly preserving beta cell function. Time will tell. And, now, with the Januvia and the other DPP-4s, we finally have a class of drugs that seems easy for primary care doctors to prescribe and easy for patients to take – we'll look forward to long-term data.

3. **DREAMING at EASD…**

They called it the DREAM trial, but the reality was mixed.

The results of one of the most heavily anticipated trials in years – the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) – were released several weeks ago in Copenhagen at the EASD meeting. At issue was whether these drugs, known as TZDs, could prevent type 2 diabetes in an at-risk population. With the global epidemic expected to increase from about 200 million patients today to 333 million by 2025, prevention is seen as the one hope to curb a worldwide public health crisis.

The DREAM study was large in both size and scope, with more than 5,000 patients enrolled over a three-year (and counting) period. The good news was that the trial showed a 60% reduction in incidence of diabetes, suggesting these drugs could indeed have a huge impact on slowing the epidemic. The bad news was that participants also experienced an increased risk of heart failure, raising obvious concerns about their use in patients who could achieve the same risk reduction for diabetes though lifestyle changes.

We doubt that the results will cause an immediate change in the use of TZDs, which are currently used as glucose-lowering drugs for type 2 patients. Physicians and payers probably need more studies to consider shifting the drug from care to prevention. Nonetheless, we believe that DREAM is an important study that highlights how our approach to diabetes is evolving. We now have data that clearly support aggressively treating patients as early as possible and results that indicate it is possible to change underlying physiology. If further research confirms and refines these findings, the future of this disease could well be changed.

Below we summarize results from the DREAM. Diabetes incidence and growth statistics are well publicized – an estimated 5% of the world's population and 7% of the US population have type 2 diabetes, and these numbers are expected to almost double in the next 20 years. The complications associated with diabetes impact major organ systems – eyes, kidneys, nerves, and blood vessels – and

make an already difficult disease even more challenging for patients, providers, and payers. We know that people with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) carry a higher risk of developing diabetes and its attendant complications. With an estimated 20 million diagnosed diabetics in the US, some estimate the number of "pre-diabetics" at roughly 40 million. This group of patients represents a clear clinical and commercial opportunity. We believe DREAM is likely to be the beginning of a coming wave of research into the prevention of type 2 diabetes and the damaging complications that come with it.

***Background*: DREAM's objective was to gauge whether patients with IGT and/or IFG can avoid developing type 2 diabetes by taking rosiglitazone or ramipril – in addition to improving lifestyle choices.** DREAM's inspiration came in part from the DPP (Diabetes Prevention Program), where troglitazone (Rezulin) showed positive early efficacy in delaying the onset of diabetes. Unfortunately, Rezulin caused liver damage in some patients and Warner-Lambert pulled it from the market. Still, these results offered some promise that another thiazolidinedione (TZD) might work. Rosiglitazone, trade name Avandia and marketed by Glaxo Smith Kline (GSK), is currently approved to help type 2 diabetics improve their glucose control by enhancing their sensitivity to insulin. This note focuses on the rosiglitazone arm, not the ramipril arm, which did not show efficacy in delaying progression to diabetes.

This international, multi-center, randomized, double blind trial began in 2001. The trial had a 2x2 factorial design, which in part means that patients in the rosiglitazone arm were also taking ramipril. (It was possible to conduct the study this way because the two drugs do not interact.) Of the 5,269 patients studied, 2,635 were randomized to 8 mg rosiglitazone taken daily and 2,634 to placebo. The primary endpoints considered were the development of type 2 diabetes or death from any cause. Secondary endpoints included micro- and macrovascular events as well as regression to normal glucose levels.

***On trial results – the good news*: On September 15, 2006, DREAM researchers presented three-year data at the EASD congress in Copenhagen.** We learned that 3 years of rosiglitazone therapy reduces the risk of developing type 2 diabetes by 62% with a high degree of statistical significance (p-value<0.0001). Of the rosiglitazone patients, 10.6% developed type 2 diabetes compared to 25.0% of those patients taking placebo. Looking at the composite endpoint of either developing diabetes or death, the relative risk reduction was 60% (p-value<0.0001). Rosiglitazone also increased the likelihood of returning to normal glucose by 70%. These patients also gained weight – 3%, 0.67 kg per year – compared to the placebo group. However, they maintained a consistent waist/hip ratio, suggesting that the amount of visceral fat dropped in favor of "the good fat." ALT (alanine aminotransferase) enzymes dropped as well. Because elevated levels of these enzymes are sometimes associated with a "fatty" liver caused by diabetes or obesity, this unexpected finding further suggests that the amount of fat in the liver dropped. The outcomes remained consistent regardless of gender, nationality, or body weight progression. During the study, 14 (0.5%) rosiglitazone patients developed congestive heart failure (CHF) compared to 2 (0.1%) in the placebo group.

In an interview, Dr. Bernard Zinman of the University of Toronto, a member of the DREAM Trial steering committee, described the results as follows: for every 1,000 patients treated, 240 will return to normal glycemia from impaired fasting glucose (IFG), 144 patients who would have progressed to diabetes will not, and the attendant risk is that 4 patients might develop CHF.

Dr. Zinman also noted that DREAM showed that rosiglitazone worked for everyone, but was more effective in obese patients. In the placebo group, the absolute risk of diabetes increased with weight, but in the rosiglitazone arm, the risk stayed constant across weight categories. In other words, rosiglitazone seemed to neutralize the impact of weight.

***On trial results – some concerns:*** **We are enthusiastic about the possibilities these results suggest – that it might be possible to change physiology, not just to prevent diabetes but also to move people back to normoglycemia – but questions linger.** The side effects are a bit troubling and clearly an issue for some of the doctors we've talked to since the results were announced. Specifically, we worry about CHF, weight gain, and edema.

**Let's tackle CHF first.** The rosiglitazone arm showed a 7-fold increase in the risk for CHF, which was made more confounding by the low risk study population. We can't help but wonder what the risk of CHF would be in a more general population with more diverse co-morbidity risks. Perhaps we should step back and consider CHF more fundamentally. We know that congestive heart failure results from reduced heart muscle function leading to a back up of fluid in the lungs and extremities. When the heart gets stiff – as might occur from the kind of fluid retention a TZD might cause – or weak, it can't pump out as much blood with each beat. Pressure builds and blood starts to accumulate in the heart, and ultimately the lungs. Patients might experience fatigue and shortness of breath with exertion, or even at rest, depending on the severity. In severe cases, the lower blood output can cause brain damage or kidney dysfunction. Causes include coronary artery disease, hypertension, and certain medications. CHF is reversible, so long as the underlying cause is reversible.

In the case of TZDs, we note that researchers said that if patients who experienced CHF stop taking rosiglitazone, their heart function returns to normal. We interviewed Dr. Steven Kahn, Professor of Medicine Division of Metabolism, Endocrinology and Nutrition at the University of Washington about the trial results. Although an experienced researcher, Dr. Kahn was not involved in the DREAM trial. With respect to CHF reversal, he was surprised but convinced: "[Patients] recovered when taken off the drug, which I didn't expect."

We note that while the hazard ratio for CHF points to a 7 times increase in risk, the absolute numbers of CHF were very small. Of the over 5,000 patients studied, only 16 patients developed CHF – 14 on rosiglitazone and 2 on placebo. We discussed these results with Colleen O'Neill, Senior Director of Clinical Programs in the Cardiovascular/Metabolic Medicine Development Center at GSK, who pointed out that some statisticians might not state the risk in such aggressive terms given so few cases.

**Also of concern, patients gained weight – an average of 3% body weight or 0.67 kg/year.** While researchers tried to add the spin that "it's the good kind of weight" (hip as opposed to abdominal fat), we expect this issue to be a very hard sell to patients and an inconvenient selling point for caregivers who continuously beat the drum of "lose weight" to most of this prospective patient population. We spoke with one researcher who left us with the impression that so long as the weight isn't visceral fat, weight issues become more aesthetic or orthopedic in nature. We think there is more to it than that for patients. Will patients be willing to take a medication that will cause them to gain weight *and* might cause heart damage to prevent a disease they might not get anyway?

**Another significant concern is the cost of prevention, especially given the less-than-ideal side effects.** We are obviously in favor of anything that mitigates the destructiveness of diabetes, and especially any treatment that prevents it altogether. However, we also acknowledge that TZD therapy does not come cheap – it costs approximately $3,000 per year. For large numbers of people to benefit, we know that large numbers would need to be screened and treated. Diabetes – and pre-diabetes – is frequently an asymptomatic disease. Metabolic systems progressively deteriorate without the patient knowing because the body doesn't offer a pain signal to let people know that something is wrong. So, there's an added conundrum – and cost – to finding this pre-diabetic population and bringing them into a treatment loop.

We asked GSK whether cost-effectiveness studies were underway given the positive results. We learned that while GSK financially supported DREAM and will ultimately have access to the data set, McMaster

University, the center that headed up the trial, controls it. At this point, GSK plans to wait until the data is transferred and it can conduct its own analysis. Based on our conversations, we don't expect to hear much from GSK on this topic for a while.

Nick Wareham, in his scheduled independent critique of the results, also questioned the value of TZDs, given equivalence to lifestyle changes, and whether the effect would last once treatment stopped. The presumption is that once a pre-diabetic goes on a TZD, the patient remains on therapy. But we really don't know yet. We spoke with one researcher, Dr. Rury Holman, who was hopeful that the effect might be sustained given the effect on liver enzymes, which suggested to him that the drug might be affecting an underlying physiology.

Another thought leader, Dr. Jay Skyler – a known critic of TZDs – pointed out that the results suggest a 12-18 month delay to diabetes, not prevention. Still, one PI, Dr. Yusef Salim, responded that it's a 12-18 month delay out of three years, suggesting that we have to start somewhere.

***On DREAM's trial design:*** **We believe the study was well designed and fairly presented but it was not all encompassing.** Though it makes sense that TZDs could prevent micro- and macrovascular complications, this study wasn't designed with enough powered to assess that. We still need to see analysis on the cost-effectiveness of prevention therapy, which will be a factor for reimbursement. We also need to see more lipid data. It would be useful to see how TZDs affect the "hard" endpoints of CVD events and stroke in addition to diabetes. Finally, we need to see washout data to determine if the effect of TZDs is sustained. This data will be presented at the IDF meeting in December. If TZDs are actually delaying the pathophysiology of diabetes progression, then the intervention group should continue to have a lower prevalence of diabetes than the placebo group. If it is not, then the intervention group's prevalence of diabetes should catch up to the placebo group during the washout. Though patients on TZDs would never actually stop taking them, the knowledge is still medically useful. We expect this dataset to be very important to GSK as it decides what the best next steps for Avandia might be.

***On DREAM's impact on clinical practice*****: From a clinical standpoint, we don't see practice patterns changing that much in the near term absent a label change and/or a clear reimbursement pathway.** Given the risks we discussed above, we think the provider community will adopt more of a "wait and see" approach to DREAM's findings. Even the researchers themselves weren't advocating an aggressive change in practice style. One investigator we spoke to said he didn't expect to change his practice at all – he viewed these results as an exciting *first step*, not a definitive answer. However, we also learned from Dr. Zinman that he is worked with primary care providers who are very interested in diabetes prevention and willing to experiment with metformin and TZDs off label. While he doesn't anticipate a dramatic change in practice, he thinks that some physicians might experiment with lower doses than 8 mg, possibly mitigating both CHF risk and weight gain while most likely preserving some of the protective benefit. However, while clinical practice for pre-diabetics might not change much, we could see the DREAM results encouraging physicians to embrace TZDs earlier in the treatment cycle for their diagnosed diabetic patients.

***On DREAM's impact on patients:*** **So, to whom should patients listen? Their endocrinologists? Their cardiologists?** DREAM's message is clearly a rose with several thorns. We've been writing about disease cross talk with respect to diabetes and other co-morbidities – namely cardiovascular complications. DREAM may force the issue to the provider level given the challenging questions it leaves for patients who will need to balance the benefit of preventing diabetes with the added risk of heart failure.

***On reimbursement:*** In the mean time, reimbursement is a sticky wicket, especially given that DREAM's results were in line with the effect of lifestyle changes (over 50% reduction in risk) as observed in the DPP. And, Dr. Kahn pointed out that in the DPP, lifestyle changes were more cost effective than

metformin. Lifestyle changes are "free" – at least to payers. We know, however, that in the real world, lifestyle changes aren't easy for most people and can be quite costly for some (e.g., fresh food is more expensive than processed, social and caregiver support has hidden costs, etc.). For the foreseeable future, using TZDs for prevention will be off-label – a difficult status from a reimbursement perspective. And, as mentioned above, TZDs aren't cheap.

***On the commercial impact of DREAM:*** **Translating the impact on clinical practice into potential commercial opportunities**, we believe these outcomes are certainly positive for GSK and Takeda (Dr. Zinman also anticipates, albeit unproven, a class effect for TZDs). We've learned that 12-18 months is adequate to secure a prevention label from the FDA – a much shorter trial horizon than we initially thought. Although we think another study is warranted because of safety concerns, the 2011 patent expiry clock is ticking.

It is apparent from our conversations with GSK that the company is excited about the trial results – which O'Neill described as "definitive" – but has almost as many outstanding questions as we do. When peppered with questions about conducting additional trials and filing for a label extension, the consistent reply was that nobody knows yet because GSK hasn't seen the raw data. O'Neill replied that at this point in time, GSK has no plans for more large outcomes studies for pre-diabetes but continues to conduct studies in diabetes – namely ADOPT, which is following newly diagnosed diabetics not yet on drug therapy.

With respect to the work GSK can do with DREAM data and how long it might take, we know that the washout period data is important to this process, which puts us until the end of the year. Assuming the data transfer and internal analysis will take several months to complete, we would be surprised to hear news from GSK until mid-2007. If we assume the decision is to file for a prevention indication on the existing dataset, the likely FDA turnaround for label extension requests is about 10 months. Continuing with the assumption that all goes well from a regulatory standpoint – and the FDA is never a shoe-in – the earliest we might see rosiglitazone marketed for diabetes prevention is probably mid- to late 2008. If this scenario plays out for GSK, the label change will certainly help with reimbursement and physician acceptance. In the meantime, though, we do not expect significant shifts in prescribing patterns.

As for other pharma companies, we hope these trial results are a bellwether for future interest in studying and developing prevention therapies. Clearly, the DPP-4s (MRK, NVS) and GLP-1 analogs (AMLN/LLY, Novo Nordisk) spring to mind – effective in lowering glucose without inviting the same side effects. On this topic, Dr. Zinman thought agents that promote weight loss specifically could show benefit in preventing onset. The clear winner in this respect is AMLN/LLY's Byetta – the only approved agent that frequently causes significant, sustained weight loss. Even more promising in terms of patient convenience and adoption is AMLN/LLY's once weekly formulation, and NovoNordisk's once daily liraglutide. But we are likely to see the first endocannabinoid agent launch soon, perhaps even this year – rimonabant by Sanofi-Aventis. While this drug has been associated with increased depression as a side effect, we won't know the market impact for a while. As yet, the FDA has not requested a panel meeting, so we aren't certain as to potential launch dates. Speaking to prevention specifically, at present, we count only a couple of companies with ongoing studies on prevention of type 2 diabetes: Sanofi-Aventis with rimonabant, and Merck with vildagliptin.

***Conclusion*****: Having been in the room while the DREAM results were presented, we can't possibly express the excitement we felt being part of the event. We believe DREAM is the beginning, not the end of changing approaches to helping patients avoid or better manage their type 2 diabetes.** But we don't expect physician behavior with respect to prescribing TZDs for pre-diabetics to be like flipping a switch. Time will need to pass for the data to disseminate and conversations to start about how best to incorporate what we are learning. We might be able to argue nickels and dimes with respect to the short-

term market impact for involved companies. But, bigger picture, we believe DREAM's message is a variation on a theme we continue to hear in our conversations and travels and is positive for all committed players: early, more aggressive therapy reaps significant benefits for patients, providers, and payers.

*—by Cindy Glass and Kelly Close*

**4. Dual PPARs: And then there were none**

After last spring's fairly spectacular and high profile glitazar (PPAR) failures – Pargluva (muraglitazar) by Bristol-Meyers and Galida (tesaglitazar) by AstraZeneca, Eli Lilly has quietly dissociated itself from its naveglitazar development relationship with Ligand. No splashy news releases, just a Reuters brief that led us to a blurb in a Ligand 10Q stating that:

"In May 2006, after review of all preclinical and clinical data including recently completed two year animal safety studies, Lilly informed the Company that it had decided not to pursue further development at this time of LY818 (Naveglitazar), a compound in Phase II development for the treatment of Type II diabetes. Naveglitazar, a dual PPAR agonist was developed through the Company's collaborative research and development agreement with Lilly. This decision is specific with regard to Naveglitizar and does not affect the ongoing development activities of LY674 or the status of preclinical PPAR agonists."

But we've also learned – practically by accident given the complete absence of information on either Eli Lilly's or Ligand's websites – that LY674 has been place on "internal hold."

This new class of drugs started with great promise -- a simultaneous ability to lower cholesterol and improve glucose levels. But in the summer of 2004, the FDA requested that all companies with PPAR programs intended to last longer than 6 months submit 2 years of toxicity data in a rodent model due to concerns about tumors. Bristol-Myers and AstraZeneca had both completed the required toxicity studies, so Pargluva and Galida were allowed to move into Phase III testing while other companies were slowed.

Although several companies had already abandoned PPAR programs at the Phase 2 stage due to safety concerns (Takeda, Glaxo Smith Kline, and Novo Nordisk), the September 2005 FDA request for long-term studies on cardiovascular risks for Pargluva (submitted to the FDA in 2004) put the class into a tailspin. After a damaging JAMA article that reinforced the FDA's concerns about a higher incidence of death, myocardial infarction, or stroke in the muraglitazar group, Bristol-Myers and Merck decided to abandon their investment given the burdensome cost of another long-term trial (5 years) with an uncertain safety outcome. A few months later, Astra Zeneca also abandoned Galida because of increased creatinine levels, which suggested renal toxicity issues.

We aren't surprised to see that another PPAR sponsored by another major pharmaceutical company has failed. Given the lack of news releases on either Eli Lilly's or Ligand's websites regarding either one of these programs in almost a year, we can only surmise that these programs have been dying a slow death of neglect since the FDA's decree 2 years ago followed by high-profile disappointments for Pargluva and Galida. And the dearth of current information on these discontinued programs does little to dispel this notion of abandonment.

*—by Cindy Glass*

**5. Cleveland Clinic Obesity Conference – outstanding meeting reinforces tremendous interest**

We were excited to attend the first Obesity Congress at the Cleveland Clinic, held on October 12-14. The Congress was co-directed by Dr. Philip Schauer and Dr. William Carey of the Cleveland Clinic and it featured Dr. Richard Carmona, former US Surgeon General (2002-6) as keynote speaker. We heard that the organizers hope to make this conference an annual meeting in the future – we take this as yet another example of the many new meetings that have sprung up in recent years to address the problem of obesity.

Overall, the program was extremely well organized, and we found the talks to be of uniformly high quality.

The conference had about 200 registered attendees, the majority of which were doctors. There were also a few (maybe two dozen) registered nurses. Among the doctors, most seemed to be clinical care providers but there was also a strong minority of surgeons. Overall, the conference focused on treatments and clinical outcomes, with attendees asking very specific questions about treatments and surgical techniques.

About a dozen companies had exhibits at this conference. The majority were medical device companies but there were also a few drug companies, including Olympus, Mediflex, and Bodymedia,Takeda (advertising Actos and Actoplus Met) and Amylin. The main sponsors for the conference were (in order): Ethicon Endo-Surgery (owned by J&J – we expect to be hearing more from Bariatric Edge, the old Obtech, the Swiss company purchased in 2002), Stryker, Autosuture, Invacare, Nestle, Sanofi-Aventis, and Takeda. Baxter, Inamed, Allergan, Storz, and KCl were also sponsors.

**Themes: Our Main Takeaways**

- **Treatment for obesity should begin with lifestyle modification, then pharmacotherapy, and then surgical intervention**. This course of treatment was somewhat debated, but this seems to be the general consensus. Doctors we spoke to tended to be very interested in surgery but most clinicians would only refer patients to surgeons after all other treatments had repeatedly failed. At the same time, we sensed that clinicians (or at least their patients) are not satisfied with the results of lifestyle modification (can't keep off the weight) and pharmacotherapy (weight loss tends to be moderate) and feel that current medical treatment for obesity is simply inadequate in general.
- **We need more effective weight-loss drugs that are clinically proven to reduce long-term complications (CVD, mortality, etc.)**. All three currently approved classes of drugs – stimulants (phentermine), appetite suppressants (sibutramine), and fat absorption blockers (orlistat) – are only moderately effective and cause problematic side effects. Long-term studies haven't been conducted. In terms of new drugs, there was interest in rimonabant (PI Dr. F. Xavier Pi-Sunyer spoke about the RIO North America trials) as well as other drugs earlier on in the pipeline. In phase 2 or 3 are 5HT-2C receptor agonists (Arena's locaserin), NPY5 antagonists (Shionogi's S2367 and MK 0557), combination drugs (Vivus, Orexigen), seizure medications that are currently used off-label to treat obesity (Bupropion, Topiramate, and Zonisamide), and CB1 antagonists (other than rimonabant) that are being developed by companies including Pfizer, Merck, and Solvay/BMS. Exenatide was mentioned as a potential weight-loss agent as well; there is also interest, of course, in Symlin, which we expect to be moving into Phase III for obesity shortly. There was also interest in earlier-stage drugs like Cetilistat, PYY 3-36, and oxyntomodulin.
- **Obesity is a chronic disease, not a failure of will power**. We kept hearing the mantra, "Anyone can lose weight… it's maintaining the weight loss that's hard." There was no evidence of patient-blame throughout the conference; the general consensus was that obesity is caused by a number of factors that are often beyond patients' control. Actually, while several excellent talks covered the causes of obesity in the "Nature or Nurture" section of the program, in general less attention was paid to causes than to treatments, which makes sense. This conference was intended as a continuing education course for healthcare providers in obesity, and they tend to be less interested in etiology than basic scientists or clinical researchers are.
- **Bariatric surgery is hugely underused and very effective but is not a magic solution; it only helps motivated patients make the necessary lifestyle changes to reduce weight**. Bariatric surgery was much-discussed at this conference – Dr. Schauer is a leading bariatric surgeon – and some themes that came up included the need for better training programs, more flexible and patient-tailored guidelines for treatment, and the importance of patient selection. Experts put forward the view that patients who aren't "compliant" on lifestyle and pharmacologic treatments tend not to do well after bariatric surgery because they expect to be 'cured' without effort. We heard one speaker calculate that

the penetration of the market for bariatric surgery is somewhere around 2% - this is based on BMI, we presume. Another interesting calculation by Dr. Henry Buchwald (one of the pioneers of bariatric surgery): because it resolves so many comorbitidies, surgery actually becomes cost-effective at 3.7 years after the procedure – Dr. Buchwald opined that the reason payers remain reluctant to reimburse is that they can't hold their customer base that long to being reaping the benefits. Probably true – we're all-too-familiar with the similar lack of interest in prevention programs in diabetes. But if radical steps aren't taken, all the insurers will end up paying for the costly consequences of excessive weight.

**Other Highlights**

- **Life surgical demonstration**: We were quite impressed by the live demonstration of a Roux-en-Y divided gastric bypass surgery performed by leading bariatric surgeons Dr. Philip Schauer and Dr. Bipan Chand of the Cleveland Clinic on the last day of the congress – we were very taken with the tools used and the speed at which the surgery was done. Dr. Schauer, Dr. Chand, and Dr. Buchwald explained the procedure in real-time and answered questions from attendees in the conference auditorium.
- **Patient forum:** The conference ended with success stories from five obesity patients who had undergone pharmacologic and/or bariatric surgery treatments. All are normal weight or at most overweight now. Their stories strongly reflected the frustration of motivated patients who are unable to maintain weight loss. One man, an army soldier who has been deployed in Iraq, was overweight despite getting what most Americans would consider an immense amount of exercise. However, he did successfully lose weight on Xenical – he originally lost 27 lbs over six months (starting Dec 2004) but has gained back about 15 lbs now. Another man was able to drop 85 lbs on a modified protein diet but has had to work extremely closely with a dietician to keep a majority of that weight from returning. Three of the women who spoke were variously, yo-yo dieters or had family history of obesity (one woman said she'd been obese since she was four) and were simply unable to keep off weight loss despite numerous dietary and pharmacologic treatments. One of them had a particularly touching story – she told the audience that she had been Dr. Jay Skyler's PA for 17 years and helped him develop diabetic carbohydrate counting programs, so her problem was not one of lack of education or inability to monitor calorie intake. Another woman said that diets worked well for her but she always plateaued after losing about ten percent of her weight and then gained it all – and more – back. All three of these women finally underwent bariatric surgery with Dr. Schauer and have lost a great deal of weight and kept it off. One of them said that the surgery was "a tool to undergo behavior and lifestyle modifications that she needed."

## 6. One Doctor's Plea: Making Preventive Care a Priority

Dr. Anne Peters is a highly regarded diabetologist in Beverly Hills with some of the best-heeled patients in America, but every time she treats someone, she loses money.

"I'm very good," she says, "at losing money."

Peters can maintain her practice through contributions from donors, but her predicament highlights the perverse financial incentives that plague diabetes care in America: while insurers generously reimburse acute care – surgeries, procedures, etc.– they spend relatively little for chronic care. Unfortunately, these are the very needs – education and disease management – that diabetics require.

But in recent years, "chronic care models," which emphasize keeping people healthy through preventive care, have been introduced in communities around the country. Whether sponsored by government or health maintenance organizations, their premise is that preventive care ultimately saves money as well as lives.

Some of these programs, including one involving Dr. Peters, are directly geared for diabetics, and if they gain momentum, they would be an obvious boon to the companies that provide diabetes' products. But even if these programs demonstrate clear improvements in outcomes, that does not mean health care reform is inevitable or even likely. The sprawling $1.9 trillion health care system resists fundamental

change of any kind, particularly for chronic diseases, which providers have historically spurned. (So-called "incurables" were expensive to treat, their cases were depressing, and they failed to satisfy physicians' desire for closure.)

Nonetheless, the scope of the diabetes epidemic could make reform possible. According to Dr. Mark McClellan, the administrator for the Centers for Medicare and Medicaid Services (CMS), diabetic patients make up 20 percent of Medicare and Medicaid beneficiaries, but those individuals (many of whom have other diseases as well) receive 50 percent, or $300 billion a year, of all Medicare and Medicaid expenditures. And much of that money goes for the treatment of diabetic complications that can either be eliminated or delayed through preventive care.

"We pay more when we get worse care," Dr. McClellan told us in an interview. Last year, CMS introduced voluntary chronic care improvement programs that emphasize preventive care. "We ought to pay more for what we want," he said.

There is some evidence that momentum for change is building. This month PBS is running a four-part series, *Remaking American Medicine . . . Health Care for the 21st Century*, which explores the "quality crisis" in health care and examines innovative solutions that have been undertaken across the country. (The series' lead sponsor is the Amgen Foundation, with major underwriting from The Robert Wood Foundation; see www.RAMcampaign.org.)

"We're inaugurating a national movement," says John Hockenberry, the former NBC and NPR reporter who serves as the series' host. To help launch the series, Hockenberry moderated a recent health care symposium in Washington D.C., and he spoke from his own experiences – he's been a paraplegic for 30 years – when he discussed who must lead this reform movement. "It must be a consumer-led, demand push movement, with patients taking management in their own hands," he says.

The segment that most interests us is about diabetes, titled "The Stealth Epidemic," which will air on October 19. We highly recommend it. It features Dr. Peters' work for the Los Angeles County Department of Health Services, which has received government funding for several disease management programs for uninsured patients, including those with diabetes. Los Angeles County has an estimated 70,000 uninsured people with diabetes, mostly type 2.

The show captures the heartbreak of the disease. It features people being admitted to hospital emergency rooms, only to learn that they have diabetes and will be forced to make dramatic changes in their lifestyle. It shows the struggles of an obese Hispanic woman who desperately wants to lose weight so her young daughter doesn't have a "diseased mom." It profiles a young man whose poor control landed him in the emergency room three different times. The doctors "had no reason why I was still here," he said. He got his health back on track after he joined a diabetic support group and began eating correctly and monitoring his diabetes.

The PBS segment also showcases the disease management program in Los Angeles County; we were interested enough to talk directly to some of the principals, including Dr. Peters.

The effort itself, centering on diabetes care at the Roybal Comprehensive Center, began about five years ago. Given the size of the population, patients are only supposed to be in the program for six months, but the average time is about one year. (Many patients have "special circumstances," and the county itself lacks tracking data to discharge patients on time.)

Officials hope that the program proves its value sufficiently so that it not only continues in Los Angeles but is replicated elsewhere in the country. It consists of several components, according to Dr. Jeffrey Guterman, medical director of Clinical Resource Management for the Los Angeles County Department of Health Services.

The program first required bringing together the area's "thought leaders" to forge an agreement on the best ways to deliver care and on what goals should be met. Although this process is time consuming, Guterman believes that it is an essential first step before any legitimate reform can occur.

The next step is the "clinical content" – creating the right organizational and structural tools for providers to ensure quality care. These are often simple things. For example, a diagram on how to use a monofilament, or a "structured prescription pad," which clearly delineates the medication, dose, and frequency to reduce medication errors. "It's just on paper," Guterman says. "It's a low-tech approach (see

below for the prescription pad – there is another one specifically for insulin). But the less expensive drugs applied well will have more impact than the latest drugs applied incorrectly."

| *Rx* | **Los Angeles County Department of Health Services<br>Edward R Roybal Comprehensive Health Center USC Clinical Diabetes Program<br>245 South Fetterly Avenue, Los Angeles CA 90022 (323) 780-2398** |
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| | | |
|---|---|---|
| ☐ Anne Peters Harmel, M.D. | CA: | DEA: |
| ☐ Ruchi Mathur, M.D. | CA: | DEA: |
| ☐ Paula L. Situ, N.P. | CA: | DEA: |
| ☐ Barbara Dominguez, N.P. | CA: | DEA: |
| Prescriber Name: | License: | DEA: |
| Allergies: | Diagnosis: | |

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| ☐ **Aspirin**<br>☐ 81mg EC ☐ 325 mg<br>☐ 325 mg EC<br>1 PO Daily ☐ 100 days<br>Refills: ①②③ | ☐ **Atenolol**<br>☐ 25 mg ☐ 50 mg<br>☐ 100 mg ☐ __ PO Daily<br>☐ 90 days ☐ __ days<br>Refills: ①②③ | ☐ **Atorvastatin**<br>☐ 80 mg<br>1 PO Nightly<br>☐ 90 days ☐ ___ days<br>Refills: ①②③ |
| ☐ **Benazepril**<br>☐ 10 mg ☐ 20 mg<br>☐ 40 mg ☐ __ PO Daily<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **Ezetimibe**<br>☐ 10 mg<br>1 PO Daily<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **Furosemide**<br>☐ 20 mg ☐ 40 mg<br>☐ __ PO Daily ☐ __ PO BID<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ |
| ☐ **Fenofibrate (Micronized)**<br>☐ 43 mg ☐ 130 mg<br>1 PO Daily<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **GlipiZIDE**<br>☐ 5 mg ☐ 10 mg<br>☐ __ PO Daily ☐ __ PO BID<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **GlyBURIDE**<br>☐ 2.5 mg ☐ 5 mg<br>☐ __ PO Daily ☐ __ PO BID<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ |
| ☐ **Hydrochlorothiazide**<br>☐ 12.5 mg ☐ 25 mg<br>1 PO Daily<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **Losartan**<br>☐ 25 mg ☐ 50 mg<br>☐ 100 mg ☐ __ PO Daily<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **Metformin**<br>☐ 500 mg<br>☐ __ PO Daily ☐ __ PO BID<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ |
| ☐ **Metoprolol**<br>☐ 25 mg ☐ 50 mg<br>☐ 100 mg ☐ __ PO BID<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **Pioglitazone**<br>☐ 15 mg<br>☐ __ PO Daily<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ **Pravastatin (RESTRICTED)**<br>☐ 20 mg ☐ 40 mg<br>☐ ___ mg 1 PO Nightly<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ |

| ☐ **Simvastatin** | ☐ **Simvastatin/Ezetimibe** | |
|---|---|---|
| ☐ 10 mg ☐ 20 mg<br>☐ 40 mg 1 PO Nightly<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | ☐ 40/10 mg ☐ 20/10 mg<br>1 PO Daily<br>☐ 90 days ☐ ____ days<br>Refills: ①②③ | |

| DRUG NAME AND DOSE | QUANT. | DIRECTIONS | REFILLS |
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| Total number of prescriptions: ①②③④⑤⑥⑦⑧⑨⑩<br>☐ Spanish ☐ Easy open<br>_____<br>**Prescriber signature**<br>**Date: ___/____/_____**<br>_____<br>**Attending approval (if required)** |  |

What is also central to clinical content is the increased use of nurses or nurse practitioners in caring for diabetic patients. Such care requires time, and most physicians, however well intended, resist those demands because they are either too busy or are not adequately compensated. Diabetes does not lend itself to one-time, quick, therapeutic solutions, and in many cases, nurses are better trained to help patients manage the condition's emotional and psychological complexities.

"When I'm with a patient, time stops," says Barbara Dominguez, a nurse practitioner at Roybal. "Communicating with the patient is built into the nursing model."

Dr. Peters is more explicit: "Our goal," she says, "is to empower nurses to be diabetologists."

The Roybal nurse practitioners manage patients on their own, following a protocol established by a physician. Nurses are allowed to adjust insulin doses, conduct physicals, and set up their own appointments. Perhaps more importantly, patients can come to the clinic for assistance on drawing up their insulin or giving injections. In doing so, patients receive what they often really need: moral support, encouragement, and a helping hand with the basics. "It all depends on patient needs," Dominguez says.

The program is also trying to improve communications between the provider and the patients. For example, while some diabetes clinics have developed Web-based systems to convey blood-sugar numbers, the Los Angeles program is developing voice recognition technology that can collect data from patients – "a great alternative to the Internet," Guterman says.

So how has the program worked? According to Guterman, more than 2,500 patients have participated, and "of those 2,500 who have been treated through the Roybal program, the data has shown an improvement in their [A1c] values with a decrease from 9.3% to 7.8%. For LDL, there was an improvement from 111 mg/dl to 90 mg/dl."

The improvement is impressive, though we would like to see more complete data published in a medical journal. Only then can the outcomes be scrutinized and can public health officials elsewhere consider investing money into similar programs.

For all the Los Angeles program's short-term success, many patients who were discharged from the program reverted to their old ways: not surprisingly, glucose levels rose. This mimics the results of numerous studies, including the DCCT, in which patients who were in intensively managed saw their blood sugars rise once the study was over. "This is our big challenge," Peters says, "To find ways to help

PCPs continue to provide the care patients need, because we can't possibly afford all the nurses we need to keep all in the program continuously."

Dominguez says that of her 383 patients, she has few with A1c's below the ADA's recommended level of 7.0 percent, but she's realistic about her goals. "Because it's a chronic disease, you can have good stretches, but then you can hit the wall."

Even with additional evidence of success, the case for preventive care won't be easy to make. Employers and insurers (both public and private) already believe they are spending too much on health care and will resist spending more. "Even once you have a provable intervention, it takes 10 years to get it reimbursed," says Carolyn Pare, chief executive officer of Buyers Health Care Action Group, which assists companies on health-care purchases. "It's all about the money."

Guterman also notes that the entire medical field is geared toward acute care, not chronic care, and doctors are rewarded accordingly – by patients as well as insurers. "There are no awards for those who prevented the most heart attacks," he says. "I spent a decade in emergency medicine, and I also trained as an internist. No patient ever thanked me for giving them a cholesterol-lowering drug. It cost money, and it didn't make them feel any better. But every patient who is brought to you who is barely alive, and you save them, they are indebted to you forever."

A cynic might also suggest that those who benefit the most from bad diabetic outcomes – surgeons, cardiologists, and other specialists – have no incentive to see more money invested in preventive care, and they use their own financial and political clout to maintain the status quo. What's certainly true is that in the medical world, diabetologists are the patron saints of lost causes, and few fit that bill better than Anne Peters. A self-described "good Unitarian Buddhist," she had planned on joining the Peace Corps when she was in medical training, but an advisor told her that if she wanted to help poor people, she should practice in Los Angeles.

"Who would go into diabetes?" she asks. "I see blind 25-year-olds and young people on dialysis all the time, and it's terrible." But the very challenge to patients, particularly the underprivileged and underserved, is part of its appeal. "I love the underdog," she says.

Peters says the relative success of the diabetes program at the Roybal clinic demonstrates the importance of establishing standardized formularies and consistent treatment protocols. The program also shows the benefits of shifting responsibilities to non-physician providers. "We can shift the cost of prevention," she says. The key to diabetes care often comes down to access and motivation, which can be done cost-effectively. "You can give me the simplest tool, and I can make your diabetes better," she says. "But you have to come back and be willing to work with me."

To develop a rapport with her patients, she tells them that she is their partner. "I try never to judge and to always make people know that you believe in them," she says. "So often people feel like a failure, and once you feel like a failure, then it builds. They say, 'I disappointed you. I failed you.' I say, 'You're not allowed to use those words.'

Peters recognizes that type 2 diabetes is as much about lifestyles as it is about biology, so she is part of a small but growing chorus of health care professionals urging for community change. This includes getting rid of snack and soda machines in schools; bringing farmers' markets to urban centers so residents can buy fresh produce; restoring physical education classes in schools; building bike paths and ball fields in local parks; and introducing safety patrols so children can play outside. "You can't go out and exercise if you're afraid you'll get shot," Peters says.

The health care system won't make preventive care a priority for many years, but individual citizens can do their part to make a difference. "We have to change communities," Peters says, "to make them healthier to live in."

*—by James S. Hirsch*

## 7. New therapies discussed at Dr. Steve Edelman's TCOYD conference

We had the pleasure of attending the Taking Control of Your Diabetes (TCOYD) convention at the Santa Clara Convention Center on October 8. Dr. Steve Edelman began the program 11 years ago to educate patients about their diabetes. Since it's founding in San Diego, Dr. Edelman has directed its growth to many additional cities with great success. We're huge fans because the program educates patients about diabetes management in a way that their health care providers simply do not have the time, resources, or (sometimes) the knowledge to do. TCOYD will hold 10 conferences next year, beginning in Honolulu on February 11 and ending in San Diego on November 18.

This particular TCOYD conference, the second annual for Silicon Valley, featured opening remarks by Bruno Figueroa, Consulado General de Mexico, and marked the start of Bi-National Health Week. The program included a wide array of doctors and specialists who spoke on topics including weight and glucose management, complications, and the emotional side of diabetes. Free retinopathy and neuropathy screening were available in the exhibit hall, and we were pleased to see that there was a full Spanish-language program running in parallel to the English one – appropriate considering the size of the Latino community in California and how susceptible Latinos are to diabetes – but unfortunately we saw almost no African Americans in attendance. We were happily surprised to note that a number of attendees had prediabetes and were there to learn how to avoid full diabetes. Prevention – yes! We knew TCOYD catered to a motivated audience, but this level of interest was still gratifying.

The conference closed with a fascinating crossfire panel on the newest treatments for diabetes. The panel was moderated by Dr. Edelman and also included Sunnyvale endocrinologist Dr. Todd Kaye, Dr. Marc Jaffe of Kaiser Permanente, and Dr. Patrick Kearns of the Santa Clara Valley Medical Center. Dr. Edelman led the panel through discussions of continuous glucose monitoring (CGM), pramlintide, exenatide, and inhaled insulin. Non-invasive glucose monitoring and disposable insulin pumps were briefly mentioned but not discussed due to time limitations.

### Continuous Glucose Monitoring

Dr. Edelman discussed CGM in some detail before opening the floor to comments from the other panelists. He focused mainly on the DexCom STS, though he also introduced the competitors – MiniMed's Guardian and Paradigm Real-Time Sensor and Abbott's upcoming Navigator – and explained the features that distinguished each sensor. Dr. Edelman explained that CGM is for type 1 and type 2 patients who use insulin, especially patients who don't feel lows, and presented compelling data from clinical trials showing improvements in glucose control over just six days when patients using CGM were able to see real time data from their sensors.[1] However, the other panelists were generally less enthusiastic about the technology.

Dr. Kearns, who works in a county hospital with mostly overweight and often disabled patients, said that for his patients CGM would be information overload. He conceded that CGM may be useful for patients who already exercise and have good eating habits, but all in all he would rather have seen the $1.2 billion that went into the development of this technology spent on health club memberships for all the people who need them. The audience clapped approvingly.

Dr. Jaffe, who spoke next, disagreed with Dr. Kearns. Though he believes many patients aren't ready for CGM, others are. He has patients who have used it and has seen the difference it makes; the technology is exciting and as the bugs are worked out, he hopes it will be more used more widely. Dr. Kaye noted that CGM is really more for type 1 patients, who tend to have a lot more variability in their blood glucose. He believes it has particular utility for patients who are afraid of hypoglycemia, and though every treatment is only good for some patients, we need all the help we can get with diabetes. Dr. Edelman agreed.

[1] Garg et al. *Diabetes Care* 2006; 29:44-58.

Though some doctors think continuous numbers make patients anxious, for him it tends to relieve anxiety when he can see what direction he's going. The technology is not perfect, but he does expect that it will benefit a certain subset of patients.

**Pramlintide**

Dr. Edelman gave a quick introduction to amylin, explaining the hormone's natural actions in the body and what its synthetic analogue pramlintide does as a therapeutic agent: decrease glucose fluctuations. Dr. Kaye said that of all the new products, he is the least excited about this one because it requires three injections daily; his approach would be to use a fast-acting insulin to address postprandial excursions, and he believes that pramlintide really only caters to a small niche of people who are already taking insulin and still having trouble with postprandial highs. Dr. Jaffe added that though it is a great tool for people who are already exploiting other tools, most people don't like it very much when they realize how difficult it is to take. Dr. Edelman agreed that it targets a niche, but added that Amylin is now doing phase 3 studies on pramlintide for obesity because it is so safe, and that short-term results have been good so far. Dr. Kearns again opined that as a new technology, pramlintide is very novel, but what is really needed for people with diabetes is a focus on the basics. While treating blood glucose is great, he thinks the first target should be hypertension. The other doctors agreed, but Dr. Edelman reminded him that this was a session on new information.

**Exenatide**

Dr. Edelman next showed an ABC news segment on exenatide as an introduction to Byetta. Dr. Jaffe said that exenatide is great, but one caveat is that it's necessary to be realistic about the weight loss; the average loss in clinical trials was twelve pounds over two years. Also, people with type 2 diabetes need many medications, so while exenatide has a role, its cost and the hassle of injections are disadvantages. Still, he's more excited about this than about Symlin because it applies to more patients. Dr. Edelman pointed out that Amylin is developing Byetta LAR, the once weekly form of the drug. As a preemptive note, he reminded the audience that basics come first, and then he turned over the floor to Dr. Kearns, who simply said that he has not had experience with this drug yet. Dr. Kaye agreed with Dr. Jaffe that Byetta is more exciting and does more than Symlin. He noted that the needle is quite thin, which helps overcome the injection hurdle, but the pen does have to be refrigerated.. He also added that some patients do better than others on the drug and for those who do not lose weight he will often have them try something else. Dr. Edelman reminded him that usually lowering blood sugar always causes weight gain, so even a little weight loss is excellent.

**Inhaled Insulin**

Dr. Edelman explained that he thought inhaled insulin deserved extra attention because people are so interested in the technology, which was first envisioned as early as 1925. Some of the companies working in this area include Pfizer, Novo, Lilly, Kos, and Mannkind. With Pfizer's Exubera, freeze-dried insulin is packaged in "blisters;" and once inhaled, it acts much like a fast-acting insulin. In trials, taking a puff of Exubera three times a day for twelve weeks brought mean A1c's down from ~10% to ~7.5% in a group of type 2 patients. Long-term studies have gone on for as long as seven years now with no serious adverse effects; Dr. Edelman assured the audience that lung function was not adversely compromised in patients who received inhaled insulin in trials. In his anecdotal experience, all of his patients who have been in the trials preferred inhaled insulin to shots.

Dr. Kearns said that he has actually been surprised that there hasn't been more demand for conversion or inquiries about inhaled insulin from his patients. He believes that, given his setting, the reason is that most of his patients are looking for ways to deal with their weight – new treatments and cures – rather than just a way to fine-tune their blood sugar control. He said that his motto is TCOYD – which means

pushing back on the patients and making them take management of their own care rather than look for the magic bullet.

Dr. Jaffe said that Exubera represents a closer step to non-invasive insulin, but the inhaler remains clunky and there are issues with the blister dose size. He is excited about the idea because he sees it as an opportunity to move more patients onto insulin therapy sooner. He uses inhaled insulin as an opportunity to tout insulin itself as a drug – injected or inhaled – but he's waiting for something that fits into the pocket for true convenience,

Dr. Kaye added that Exubera is really meant for type 2 patients because the smallest dose size is three units, which is too large for type 1 patients to fine-tune their regimens. He's happy with whatever will help type 2 patients more readily accept insulin, but many of his patients choose insulin pens instead once they see the inhaler. Dr. Edelman agreed that everything depends on the patient's preference; the whole theory behind the developmental cost of inhaled insulin was that it would expand the toolbox for patients who want more options to fit their needs.

*—by Jenny Jin and Kelly Close*

**8. JDRF funds new research grants for artificial pancreas project**

On September 12, the Juvenile Diabetes Research Foundation announced a multi-year research program to accelerate the development of an artificial pancreas. The first year's funding exceeds $5.5 million. The JDRF launched the Artificial Pancreas Project in late 2005 to speed regulatory approval, health insurance coverage, and clinician adoption of promising new artificial pancreas technologies. The JDRF believes that an artificial pancreas will revolutionize diabetes care by allowing patients to more tightly control glucose fluctuations, which can lead to severe complications over time. Currently, even patients who aggressively monitor their blood glucose spend less than 30% of the day in the normal blood glucose range! Continuous glucose monitors are the first step toward more tightly controlling glucose fluctuations and developing a closed-loop system. In fact, research shows that patients using continuous glucose monitors spend 26% more time in the normal glucose range and have statistically significant improvements in their A1c levels.

To quantify the benefits of continuous glucose monitoring, the JDRF is funding the Continuous Glucose Sensor Human Clinical Trial. It will compare health outcomes, including A1c levels and avoidance of hypoglycemia, among people who use continuous glucose sensors and those who do not and assess the economic costs and benefits of sensor use over 12 months. It will also explore the impact of sensors on quality of life for both children using the devices and their parents. The trial will enroll both children and adults with type 1 diabetes.

The JDRF's second research initiative in this area, the Artificial Pancreas Consortium, will aim to speed and optimize the process of linking continuous glucose monitors and pumps. It will investigate potential algorithms to communicate between the two devices, as well as safety and efficiency of the technology, such as automatically shutting off insulin pumps during severe hypoglycemia. Although the JDRF is funding this research independently, it is also working with government agencies to accelerate the availability of these technologies. In the last six months, 68 U.S. Senators and 244 U.S. Representatives signed a letter highlighting the promise of these technologies; the FDA included the artificial pancreas on its "Critical Path Opportunities List;" and the Centers for Medicare and Medicaid Services held an expert panel to advise on future research using these technologies in Medicare patients.

The JDRF's new research grants are clearly an important driver in accelerating the development of an artificial pancreas. In the meantime, the new research initiatives should help facilitate the adoption of continuous glucose sensors and hopefully speed health insurance coverage of those devices.

*—by Rachael Hartman*

## 9. DCU Lit Review – Hot target Adiponectin gains greater visibility

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 *Archives of Internal Medicine, Diabetes Care, Diabetes Educator, NEJM, Lancet, JAMA,* and more.

- *Annu Rev Med* - Therapeutic approaches to preserve islet mass in type 2 diabetes - Baggio, Drucker: A detailed scientific look at five classes of compounds that have potential in beta cell preservation: GLP-1 receptor agonists, GIP, DPP-IV inhibitors, thiazolidinediones (TZDs), and epidermal growth factor (EGF) and gastrin.
- *Arch Intern Med* - Diabetes mellitus and the risk of cancer- results from a large-scale population-based cohort study in Japan - Inoue et al: This study showed a link between diabetes and the risk of total cancer, particularly cancer of the liver, pancreas, kidney, and ovaries.
- *Arch Intern Med* - Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus - Knutson et al: This study, part of an entire *Arch Intern Med* issue devoted to sleep disorders, linked poor sleep duration and quality to higher A1c's in patients with type 2 diabetes.
- *Arch Intern Med* - Effect of medication nonadherence on hospitalization and mortality among patients with diabetes - Ho et al: Unsurprisingly, the authors here found that medication nonadherence is prevalent in diabetic patients and is associated with adverse outcomes.
- *Arch Ped Adol Med* - Measuring effectiveness of dietetic interventions in child obesity: a systematic review of randomized trials - Collins et al: This meta-analysis of studies that looked at the effectiveness of dietary interventions either alone or in combination with lifestyle changes and psychological counseling revealed the dearth of studies in this important area.
- *Diabetes Care* – A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes – Edelman et al: This study showed that increasing pramlintide doses with reduced mealtime insulin cut incidence of nausea and severe hypoglycemia during initiation of pramlintide therapy.
- *Diabetes Care* – Flexible intensive insulin therapy in adults with type 1 diabetes and high risk for severe hypoglycemia and diabetic ketoacidosis – Samann et al: This study showed that patients at high risk for severe hypoglycemia or ketoacidosis benefit from standard diabetes treatment and teaching programs. Arguably, all patients should take these programs... this is good evidence.
- *Diabetes Care* – Psychological outcomes of patients with screen-detected type 2 diabetes: the influence of time since diagnosis and treatment intensity – Thoolen et al: This Anglo-Danish-Dutch study found that early and intensive treatment actually causes more anxiety and less self-confidence about disease management in the 1st year after diagnosis in diabetes screening-detected patients without necessarily improving self-care. It's not clear whether this applies in general or is specific to the protocols in this study…
- *Diabetes Care* – Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus – Zhang et al: This study found that prepregnancy diet may affect GDM risk; low fiber and high glycemic load diets seem to be associated with an increased risk of GDM.
- *Diabetes Care* – Premeal insulin treatment during basal-bolus regimen in young children with type 1 diabetes – Cherubini et al: The authors found that regular insulin may actually be more effective at mealtime than NPH or rapid-acting insulin for prepubescent patients.
- *Diabetes Care* – A high-carbohydrate, high-fiber meal improves endothelial function in adults with the metabolic syndrome – Brock et al: This is the first study to actually show the positive effect of a high-fiber, mixed meal on endothelial function in patients with metabolic syndrome - support for the idea that lack of dietary fiber contributes to metabolic disease.
- *Diabetes Care* – Gut hormones and related concepts – Bloomgarden: This excellent review covers subjects including GIP, enterostatin, granulocyte/macrophage–colony stimulating factor, DPP-IV inhibitors, exenatide, liraglutide, and BIM51077.

- *Diabetes Care* – A continuous metabolic syndrome risk score: utility for epidemiological analyses – Wijndaele et al: This paper concludes that, from an epidemiological standpoint, a continuous metabolic syndrome risk score is more appropriate and useful than the current yes/no classification.
- *Diabetes Care* – The effect of pioglitazone on the liver: role of adiponectin – Gastaldelli et al: This study looked at the effect of pioglitazone on liver gluconeogenesis (GNG) and concluded that TZDs reduce fasting GNG and that this effect may be mediated through a rise in adiponectin concentration.
- *Diabetes Educator* - Update in the pharmacologic treatment of diabetes mellitus - Focus on Pramlintide and Exenatide - Odegard, Setter, Iltz: We were impressed to see an exhaustive 20-page paper on pramlintide and exenatide drug mechanisms, clinical trial data, and prescribing information . This will be very useful for CDEs.
- *Diabetic Medicine* - Performance of CGMS during development of ketosis in patients on insulin pump therapy - Pfützner et al: This article confirmed that the CGMS remains reliable and accurate during hyperglycemic and ketotic conditions - good to know.
- *JAMA* - Tight blood glucose control pays off in reduced cardiovascular risk in diabetes - Friedrich: This news article reminded AMA readers again of the results of the DCCT/EDIC, which proved the benefits of intensive control for type 1s. It also updated readers on the VADT, an ongoing trial devoted to proving the same for type 2 patients. It will be completed in December of 2007.
- *Lancet* - Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose - The DREAM Trial Investigators: The results of the rosiglitazone arm of the DREAM trial showed a 62% reduction in progression to diabetes, though there was no difference in all-cause mortality or composite cardiovascular events. There were 14 heart failures in the rosiglitazone group compared to placebo.
- *Lancet* - Editorial: Glucose lowering and diabetes prevention: are they the same? - Tuomilehto, Wareham: The authors caution against the use of rosiglitazone in diabetes prevention and question whether TZDs actually slow disease progression or merely lower glucose.
- *Lancet* - Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study - Villamor, Cnattingius: This articles reports, surprisingly, that weight gain between pregnancies is linked to increased risks for maternal and perinatal complications, even for women who are not overweight.
- *Lancet* - Editorial: Obesity, weight loss, and pregnancy outcomes - Caughey: This editorial says the results of the Villamor and Cnattingius study should "lead to a call for more randomized trials of weight loss interventions before pregnancy, as well as weight loss post partum"
- *NEJM* - Effect of Ramipril on the Incidence of Diabetes - The DREAM Trial Investigators: The results of the ramipril arm of the DREAM trial showed no change in progression to diabetes or death, though there was a higher rate of regression to normoglycemia in the ramipril group compared to placebo.
- *NEJM* - Editorial: Angiotensin-Converting–Enzyme Inhibitors for Impaired Glucose Tolerance — Is There Still Hope? - Ingelfinger, Solomon: The authors suggest that the relative health of the DREAM participants explains the negative outcome of the ramipril arm of DREAM. They believe ACE inhibitors probably do improve glucose metabolism and this will remain a benefit for those type 2 patients who take them for others indications, like hypertension or congestive heart failure.
- *NEJM* - International Trial of the Edmonton Protocol for Islet Transplantation - Shapiro et al: This trial of 36 type 1 patients who underwent islet transplantation showed that transplantation restores long-term endogenous insulin production and glycemic stability, but insulin independence is usually not sustainable. But the authors say that persistent islet function even without insulin independence protects against severe hypoglycemia and improves A1C.
- *NEJM* - Editorial: Diabetes Cure — Is the Glass Half Full? - Bromberg, LeRoith: This editorial goes through the history of diabetes treatment/cure and concludes on a kind of mixed note, noting that we've come far with transplants, but poor long-term results, high costs, and serious adverse events limit the usefulness of the procedure.

This month we feature an original research article on adiponectin, a very hot topic of late in diabetes and obesity research. Published by a research group in Germany, the study helps explain why adiponectin research often yields inconsistent results in the protein's relationship with various markers of metabolic function. It also posits an intriguing explanation for why some drugs work better in obese individuals, as was the case with rosiglitazone in the DREAM study.

***Kantartzis K, Rittig K, Balletshofer B, Machann J, Schick F, Porubska K, Fritsche A, Häring H, Stefan N. "The Relationships of Plasma Adiponectin with a Favorable Lipid Profile, Decreased Inflammation, and Less Ectopic Fat Accumulation Depend on Adiposity." Clin Chem Oct 2006. 52(10):1934-1942.***

**In this paper, Kantartzis and colleagues from Eberhard-Karls-University of Tübingen, Germany, demonstrate that there is a relationship between high plasma adiponectin and better lipid profiles, less inflammation, lower markers of atherosclerosis and endothelial function, and less ectopic fat accumulation, and that these relationships seem dependent on overall adiposity**. Adiponectin is a protein mediator of glucose and lipid metabolism that is released by adipocytes; low plasma levels of adiponectin are usually associated with insulin resistance and are predictive of type 2 diabetes and increased risk of developing cardiovascular disease. However, previous human studies on the role of adiponectin in metabolism have often yielded inconsistent results; the authors hypothesized that this is because the beneficial effects of adiponectin on metabolism manifest only at higher levels of adiposity; studies with lower weight individuals tend not to show significant correlation. They cite animal studies to support this view, such as findings that adiponectin knockout mice only develop insulin resistance when fed a high-fat and high-carbohydrate diet.

**Study participants included 242 nondiabetic Caucasians from southern Germany**. All met at least one of these inclusion criteria: family history of type 2 diabetes, BMI > 27 kg/m$^2$, or previous history of impaired glucose tolerance or gestational diabetes. None took glucose-lowering drugs, though 5% were on lipid-lowering drugs and 4% were on aspirin. Eleven percent smoked. None drank regularly and all were considered healthy from physical exams and standard lab tests.

**The authors measured the participants' body composition, fat distribution, glucose tolerance, and plasma levels of metabolic markers**. Total body fat was measured by bioelectrical impedance, a method where the electrical resistance of a person's body is measured and used as a proxy for their level of body fat; higher resistance signifies more fat. Fat distribution was determined by measuring levels of visceral, liver, and calf muscle fat by magnetic resonance imaging (MRI). Glucose tolerance was assessed by a 75-g oral glucose tolerance test. The authors measured participants' plasma levels of glucose and insulin as well as markers for lipids (including lipoproteins, apoB$_{100}$, apo A-I, total cholesterol, HDL cholesterol, and LDL cholesterol), subclinical inflammation (including hsCRP[2], TNF-□[3], and IL-6[4]), and endothelial function (including soluble E-selectin, sV-CAM[5], and PAI-1[6]).

**The authors divided participants into 'lean' and 'obese' groups on the basis of median percent body fat (cutoff was 26% for males and 36% for females) and did correlation analyses of adiponectin with various metabolic measures separately for the two groups**. Mean BMI was 26.43 kg/m$^2$ in the lean group, compared to 31.82 kg/m$^2$ in the obese group. Mean percent body fat was 26.51% in the lean group and 36.15% in the obese group.

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[2] hsCRP: high-sensitivity C-reactive protein
[3] TNF-α: tumor necrosis factor-α
[4] IL-6: interleukin-6
[5] sV-CAM: soluble vascular intercellular adhesion molecule 2
[6] PAI-1: plasminogen activator inhibitor 1

**Correlations between adiponectin and metabolic measures were stronger in the obese group than in the lean group**. In **lipids**, the authors found a strong positive correlation between adiponectin and HDL (r = 0.39) in the obese group, as well as strong negative correlations between adiponectin and LDL (r = -0.21) and triglycerides (r = -0.29). These correlations were weaker in the lean group, where r = 0.26 for HDL, r = -0.09 for LDL, and r = -0.07 for triglycerides. In **inflammation, atherosclerosis, and endothelial** function, they observed negative correlations between adiponectin and leukocyte count, hsCRP, IL-6, PAI-1, sE-selectin, sV-CAM-1, apo $B_{100}$, and apo A-I/apo $B_{100}$ ratio in the obese group. In contrast, there were no significant correlations observed in the lean group. The negative association of adiponectin with **ectopic fat** was also stronger in the obese group than the lean group, both for liver fat (r = -0.28 versus r = -0.21) and muscle fat (r = -0.22 versus r = -0.13).

**Visceral fat was also correlated with most of the same metabolic measures as adiponectin**. Adiponectin concentration was more strongly correlated with visceral fat in obese (r = 0.41) than lean (r = 0.28) individuals. The authors cited this as evidence that visceral fat is strongly predictive of low adiponectin concentrations. We're not sure how they decided this was the direction of the causal relationship… if indeed there is a causal relationship at all rather than some indirect link between the two. In any case, once the effects of visceral fat on all the metabolic measures were factored out, the relationships of adiponectin with leukocyte count, HDL, triglycerides, and apo $B_{100}$ still remained significant. This suggests that the association of low adiponectin with poor lipid profile is at least partially independent of the visceral fat level. Interestingly, the authors concluded that low adiponectin is a cause of ectopic fat since adiponectin regulates AMP-activated protein kinase, which is involved in fatty acid oxidation. Again, we think it is a bit of a leap to draw causative relationships from the data, considering that this is an observational, not an interventional study. Nonetheless, the correlation relationships presented in this study are intriguing.

**We think this study is significant because it suggests why drugs like TZDs that increase adiponectin (among other things) are more effective in obese than lean patients, as was seen in the DREAM study**. If the protective effects of high adiponectin only 'kick in' under conditions of metabolic stress (i.e. high adiposity), it would make sense that the relationship between high adiponectin and more favorable metabolic measures is stronger in obese than lean individuals. Unfortunately, TZDs cause other problems for obese patients (congestive heart failure), limiting their clinical utility in such individuals. Regardless, the theory presented by the authors in this study is compelling and worth pursuing, perhaps in the form of future drugs that aim to reduce cardiovascular risk by directly increasing adiponectin levels.

*—by Jenny Jin and Alyssa Shell*

**10. Upcoming Conference Preview – most exciting fall we can remember …**

We can't believe how many excellent meetings there are this fall; our team will be busy reporting all the news as we fit **three brand new** conferences into our schedule (Cardiometabolic Health Congress in Boston, World Congress on Controversies in Obesity, Diabetes and Hypertension in Berlin, and Insulin Congress in DC) along with annual meetings of significant interest like CDA, NAASO, and DTT. We know the growing number of diabetes-related meetings is yet another indication of growing awareness of diabetes and obesity as serious health issues.

- **Canadian Diabetes Association and Canadian Society of Endocrinology and Metabolism Professional Conference and Annual Meetings (CDA/CSEM), Oct 18-21, Toronto, CA http://www.diabetes.ca**

Always a good time, the CDA meeting kicks off on Wednesday with a series of four satellite symposia. The morning symposium, sponsored by Merck, will be chaired by Dr. Bernard Zinman and Dr. Gary Lewis of the University of Toronto and will focus on "Beta cells, Incretins, and DPP-IVs" – certainly the hot topics of today. Dr. Steven Kahn will also participate, focusing on beta cell function –

this is reason enough to go to Toronto! Dr. Jens Juul Holst will speak next on incretins and GLP-1 agonists – we heard him speak at length at EASD and we were always impressed. Next, Dr. Christopher McIntosh will give the lowdown on DPP-IV inhibitors.

The second symposium of the day, sponsored by Sanofi Aventis, focuses on insulin rather than rimonabant, which we found surprising. Dr. Hertzel Gerstein will discuss the INSIGHT Trial and how best to initiate and titrate insulin – and he'll likely receive a number of questions on DREAM. Then Dr. Zinman will speak again, this time on whether new therapies present an advantage in controlling hypoglycemia – we're curious about how much he'll discuss CGM here.

The last two symposia of the day are also worth going early to get a seat. The first, hosted by Lilly, Medtronic, and BD, is "New Clinical and Technological Approaches to Reducing Glycemic Variability." Dr. Michael Vallis will speak on the psychological impact of hypoglycemia, Dr. Margaret Lawson on innovations in device technology and strategies to reduce variability, and the ever-so-sharp Dr. Patrick Boyle on therapeutic interventions to reduce variability.

The second symposium, hosted by Sanofi Aventis, is titled "Innovative Strategies to Reduce Global Cardiometabolic Risk." Here's the rimonabant offering! Dr. David Lau will talk about the Canadian obesity clinical practice guidelines, Dr. Hertzel Gerstein about whether inhibition of the renin-angiotensin system has favorable glycemic effects, and Dr. Lawrence Leiter about whether clinical practice guidelines should be modified to reflect recent advances in the management of cardiometabolic risk.

Thursday opens with breakfast sessions, opening ceremonies, and a plenary lecture. This day, the morning symposium on "Brain and Metabolism," where Quentin Pittman will speak about the endocannabinoid system, is what we're really watching out for.

Friday morning will feature an early breakfast panel session, hosted by Pfizer, on diabetes and cardiovascular disease management. Included on the panel are Drs. Lawrence Leiter, Michele MacDonald Werstuck, and Marian Wheeler. Later in the afternoon are two very intriguing sessions. The first is a debate about the usefulness of frequent glucose monitoring in type 2 patients; Dr. Sumit Majumdar will argue in favor and Dr. Ehud Ur, against,. Whenever we see these debates, whoever is arguing against frequent measurement always says something like "Actually, we think the same thing and I don't want to downplay testing …" Right afterwards, for those that missed Copenhagen, is a "Hot Topic Lecture" by Hertzel Gerstein on the DREAM trial.

On Saturday, catch the symposium on beta cells in type 1 diabetes chaired by Dr. Diane Wherrett, in which Peter Butler will speak on the evidence for long-term beta cell turnover and Alex Rabinovitch on beta cell regeneration. Star researchers Dr. Kevan Herold will also speak on the potential for restoring beta cell function with immune system modulation.

- **Cardiometabolic Health Congress, Oct 19-21, Boston, MA**
  **http://www.cardiometabolichealth.org**

The keynote on Thursday, October 19, marks the inception of this new conference, which seeks to replace the controversial term "metabolic syndrome" with "cardiometabolic risk." Dr. Jean-Pierre Després will speak on "Assessing Global CVD and Type 2 Diabetes Risk: From Metabolic Syndrome to Cardiometabolic Risk." Dr. Robert Eckel will follow with "Biomarkers for Cardiometabolic Risk Assessment in Clinical Practice." Dr. Christie Ballantyne, one of the chairs of the meeting along with Drs. Richard Nesto and Jay Skyler, will cover hot topic "Inflammation: Etiology and Biomarkers."

We definitely plan to catch the clinical trials update later that morning, where Dr. Ballantyne will moderate a series of talks on current and emerging therapies for obesity (with Dr. Louis Aronne), hypertension (with Dr. Matthew Weir), dyslipidemia (with Dr. Christopher Cannon), and type 2 diabetes (with Dr. David Nathan).

For lunch, Drs. Aronne, Eckel, and Nesto will discuss "Cardiometabolic Risk Reduction: Targeting Abdominal Adiposity and the Endocannabinoid System," and then Dr. Jorge Plutzky will discuss "Glitazones: What Is Their Role in Cardiometabolic Risk Management?" Afternoon sessions focus on diabetes, with Dr. Vivian Fonseca discussing "Prevention, Treatment, and Control of Type 2 Diabetes," and Dr. Nesto speaking on "The Patient with Diabetes and Heart Disease: Strategies to Prevent

a Second Coronary Event."

On Friday, good debate is promised in the morning panel titled, "Do Current Guidelines Accurately Identify Cardiometabolic Risk?" Dr. Nesto will moderate and the panelists include Drs. Ballantyne, Eckel, Richard Kahn, and Xavier Pi-Sunyer. During the concurrent afternoon sessions, we plan to hit "Strategies for Improving Patient Compliance to Diet, Lifestyle, and Medical Therapies," moderated by Dr. Pi-Sunyer and presented by Dr. Kraus and Nancy Miller. Friday's closing session features Dr. Skyler speaking on strategies for the prevention of heart disease in patients with type 2 diabetes.

- **NAASO, Oct 20-24, Boston, MA http://www.naaso.org**

Overlapping with the Cardiometabolic Health Congress in both date and location is the Obesity Society's annual scientific meeting, with five days of lectures and workshops and over 900 abstracts. On Friday, October 20, we wouldn't miss the Pre-Conference Session on "Pharmacotherapy for Obesity." The session will include Dr. Alain Baron of Amylin discussing the "Bench to Bedside Life of an Anti-Obesity Drug," Julie Golden presenting an "Overview of the FDA Approval Process for Anti-Obesity Drugs," and George Bray telling "Cautionary Tales in the Pharmacologic Treatment of Obesity." Right afterwards, the conference will officially open with the president's lecture. Even before it opens, it'll have been absolutely worthwhile!

On Saturday, leptin will be the focus in the symposium on "STAT and SOCS in Energy Expenditure," with Dr. Martin Myers discussing the "Role of STAT3 in Leptin Signaling" and Dr. Brad Lowell discussing "Hypothalamic Targets of Leptin." Later that afternoon, in the population studies track, there will be a clinical workshop on the "Use of Pharmacologic Agents for the Treatment of Obesity" with Drs. David Arterburn, Kenneth Fujioka, and Holly Wyatt.

Sunday afternoon, a clinical studies symposium focuses on bariatric surgery, involving animal models, effects on the endocrine system, and a cost-benefit analysis, with bariatric surgery stars Drs. Lee Kaplan, David Cummings, and Eric Finkelstein. We're very curious about how much the issue of diabetes and other comorbid conditions will be addressed in this session; hopefully, more than at the ASBS meeting earlier this year.

Monday afternoon, there will be two competing afternoon symposia, but we think "Gut Hormones and the Treatment of Obesity" will have to win out – these are the star drugs of today. Dr. Andrew Young will talk about "Exenatide for Obesity Treatment," Dr. Remy Brucelin about "Incretins (A Link between Nutrients and Well Being)," and Dr. Jens Holst about "GLP-1 and Obesity," and Patricia Brubaker about "Nutrient, Neural, and Endocrine Control of Gastrointestinal Hormone Secretion." The competing session is just as much worth mentioning: a symposium on the Look AHEAD study (Action for Health in Diabetes).

On Tuesday, October 24, the last day of the meeting, we plan to catch the key lecture in the cell & molecular biology track by Susan Fried on "Regulation of Adipose Tissue – Adipokines in Obesity: What are the Signals?"

- **The World Congress on Controversies in Obesity, Diabetes and Hypertension (CODHy), Oct 26-29, Berlin, Germany http://www.codhy.com**

This is another new meeting for this fall, with an incredible number of what look to be outstanding sessions and internationally known doctors. Like NAASO, it will be organized into several parallel tracks: Diabetes; Diabetes, Hypertension and Related Complications; and Diabetes, Obesity and Related Complications.

Friday morning will feature what look to be some stellar talks and debates. To start, "Hypoglycemia, or Tradeoffs in Achieving Normoglycemia" will be chaired by Francine Kaufman and Dr. Shestakova from Russia. Afterwards is a discussion of first-line therapies in type 2 diabetes that have the potential of preserving or restoring beta cell function; Dr. Del Prato argues that PPAR agonists should be first-line therapy, and Dr. Raz argues that they should not. We expect this will become quite controversial. In the afternoon will be a series of debates on the best way to achieve weight loss, the first

featuring Dr. Mitrakou arguing for behavior and lifestyle against Dr. Toplak arguing for pharmacotherapy; the second features Dr. Schernthaner giving an internist's perspective and Dr. Morton, from the US, giving a surgeon's view on surgical treatments for obesity.

After lunch, famed glycemic excursion expert Dr. Antonio Ceriello will speak on the pathophysiology of cardiovascular complications in diabetes. Also part of this session on glucose levels and glycemic targets is Dr. Davidson, from the US, who will argue that postprandial glucose should be the target focus in clinical practice against Dr. Gerich, also from the US, who believes fasting preprandial glucose should be the focus. This will be interesting – we know that fasting glucose is typically easier to address but for patients with lower A1c it's absolutely necessary to address postprandial excursions in order to impact the A1c. Dr. Monnier himself is speaking in the next session, called "Post-Prandial Glucose under Crossfire." We can't wait to hear his talk about whether we can and should prevent glycemic variability. He'll appear on the panel discussion at the end of the session as well, along with Drs. Ceriello, Hanefield, and Gerich. Meanwhile, Drs. William Polonsky and Richard Bergenstal will speak, respectively, on the behavioral aspects of postprandial SMBG in type 2 patients and on how far we are with changing monitoring guidelines.

Saturday will bring another packed day of exciting sessions, starting with a timely debate on whether we need alternative routes of insulin administration, like inhaled, in type 2 diabetes with Dr. Rosenstock arguing yes and Dr. Efendic from Sweden arguing no. Afterwards comes what we expect will be an interesting session on "Novel Treatments to Cure Type 2 Diabetes Mellitus." The main question will be whether we should change treatment goals and strategies; Dr. Nauck will be discussing the pathophysiology of T2DM and asking whether there is a fundamental incretin defect while Dr. Holst will be discussing the advantages of treatment with injectable GLP-1 analogs and whether GLP-1 or DPP-IV inhibitors are preferable. Dr. Stein is discussing DPP-IV inhibitors as well and whether they have a unique role in treatment of T2DM. Following that will be a lunch session on targeting the continuum of cardiovascular risk; Dr. Davidson will talk about coronary heart disease risk in diabetes and Dr. Ceriello about comprehensive CV risk reduction through integrated management of diabetes, obesity, hypertension and lipid disorders. Immediately after is yet another session to highlight, this one on whether we can improve CV outcomes through better glucose control. Drs. Milicevic, Del Prato, Schell, and Strojek will discuss the role of hyperglycemia on CVD in diabetic patients, prevention of CVD in people with dysglycemia, whether or not normoglycemia can improve CVD outcomes, and whether insulin treatment during and after acute stress has advantages beyond lowering blood glucose.

On Saturday, Dr. De Zeeuw, from the Netherlands, and Dr. Mimran, from France, will debate whether microalbumineria is the marker for nephropathy in diabetics, people with hypertension, and the general population. Next, a session on controlling obesity looks interesting, where Dr. Rondinone will moderate over the question of what causes obesity – "brain or periphery; gut or fat." Dr. Rubino will speak on the mechanism of action of gastric bypass surgery and the role of the small bowel in the pathophysiology of obesity and type 2 diabetes, and Dr. Smith from Sweden will ask whether fat-secreted factors can modulate human obesity and insulin resistance. Dr. Walker will ask if glucocorticoids can control fat deposition and Dr. Bloom, from the UK, will ask whether gut hormones can control appetite and prevent obesity.

Sunday, October 29 will be kicked off by a session on CGM. The central question to be addressed in this session is how far we are from normoglycation with Dr. Pickup asking whether we need alternatives for insulin administration and whether long-acting analogs can replace pump therapy, Dr. Heinemann discussing non-invasive glucose monitoring and asking whether the search for the "dream beam" will ever come to an end, and finally (and we'll be paying attention during this one) Dr. Kerstin Rebrin discussing the accuracy of Abbott's FreeStyle Navigator. The next session is all about type 1 diabetics, discussing the "what and how to" with regard to targets for glucose control. Dr. Francine Kaufman will talk about challenges in achieving A1C lowering in pediatric and adolescent patients, Dr. Howard Wolpert will discuss how to achieve endpoints with sensor augmented pumps, and Dr. Moshe Phillip will talk about progress in closing the loop. The session that follows, on "Different Forms of Insulin," is also of note. One debate we think will be very interesting is whether there is any advantage to

combined therapy. Dr. Riddle will be arguing pro and Dr. Massi-Benedetti will be arguing con.

On Sunday, there will be what looks like a very interesting session on oxidative stress, where the major question is whether oxidative stress is the link between insulin resistance, hypertension, obesity, and diabetes. Drs. Ceriello and Erdine will chair and Dr. Touyz, from Canada, will speak on whether it is possible to design interventions to ameliorate hypertension related to oxidative stress. Dr. Ceriello will argue that hypertension is caused by increased oxidative stress, while Dr. Heagerty will argue that it is not. A later debate by Drs. Gitt and Tschope will discuss a "polypill" for diabetes and CVD, which is a concept we're certainly interested in hearing more about. They will discuss whether every diabetes patients should be prescribed a statin and aspirin and whether it is time for a "polypill;" we think so, since these drugs are as important as glucose control in controlling macrovascular complications.

- **Diabetes Technology Meeting, Nov 2-4, Atlanta, GA http://www.diabetestechnology.org/**

As usual, the program for this year's annual meeting of the Diabetes Technology Society looks strong, featuring a survey of new technologies with emphasis on original data and practical information. We particularly like the first pre-meeting workshop this year on reimbursement strategies, with a panel on CGM featuring Drs. Robert Hoover, Gerald Silverstein, Satish Garg, Volker Lodwig from Roche, and Edward Dougherty. Another panel on insulin pumps will feature Edward Dougherty, Patty Curoe from Medtronic, Shawna Gvazdauskas from Insulet – whom we're excited about hearing – Mark Richert, and Gerald Silverstein. Also of note is that Robert "Jim" Henderson of Amylin will be speaking for the panel on drugs for diabetes and obesity.

The next pre-meeting workshop is on the physiology of interstitial fluid, which will be very good to hear as this topic is not well understood. Diane Burgess and Carol Herman, from the FDA, will moderate as Dr. Craig Kollman talks about lag time, Dr. Theodor Koschinsky about the AST-phenomenon, Dr. Thomas Pieber about microperfusion and microdialysis, and Dr. Aaron Vinik about advances in microvascular technologies. After the academic panel will be an industry panel featuring reps from Medtronic, Abbott, Roche, Bayer, LifeScan, and other companies. Of note is a concurrent workshop on "Diabetes and Databases," where Dr. Michael Engelgau from the CDC is giving the keynote address on the CDC diabetes database.

The meeting officially begins on Thursday evening with a reception and poster presentation. This is always the best time for connecting with old and new friends – half the beauty of the meeting! The first session on Friday, on metabolic monitoring technologies, will feature an introduction by Dr. David Klonoff, a discussion on improving inpatient blood glucose measurement accuracy by Dr. Kent Lewandrowski, a discussion on improving outpatient BGM accuracy by Dr. Lutz Heinemann, and a discussion on advances in A1C point of care technology by Dr. Bruce Bode. Session 2 will be on formulas for expressing continuous blood glucose data; it will feature Dr. Sharbel E. Noujaim from LifeScan speaking on accuracy requirements for a hypoglycemia detector. Session 3 focuses on the artificial pancreas, with Geoffrey McGarraugh from Abbott speaking on CGM hypoglycemia alarms and Dr. Stuart Weinzimer speaking on the "Sensor Augmented Pump for Closed Loop Control." Session 4 will cap off the day with the question of whether automatic glucagon delivery has a part in an artificial pancreas. Especially interesting in this session is Dr. Alan Cherrington's talk on the importance of glucagon in metabolic regulation. Also of note are talks by Dr. Ken Ward from iSense on "Closed-Loop Glycemic Control in a Model of Type 1 Diabetes" and Dr. Morten Donsmark from Novo Nordisk on the "Pharmacology of Commercial Glucagon Preparations."

Five more sessions occur on Saturday, November 4, many of which we'd like to attend. Session 5 on "Novel Technologies to Deliver Insulin and Other Metabolic Peptides" includes Dr. Sol Steiner from Biodel talking about Viaject and our very own James Hirsch speaking on the evolution of insulin delivery systems. Session 6 on "Inhaled Insulin" will include John Patton from Nektar speaking on the "Clinical Pharmacology of Inhaled Insulin," and Drs. Anders Boss from MannKind speaking on "Advances in Insulin Delivery," Teresa Quattrin doing a clinical overview of inhaled insulin, and Sultan Meo discussing pulmonary function in diabetic patients. The last session on "Hospital Management Technology" looks like it will be interesting, with Dr. Jan Wojcicki as the moderator, Dr. Paul Davidson

talking about a "Glucommander-Based Glycemic Protocol for Cardiovascular Surgery," and Dr. Lindsay Arnold speaking on "Inpatient Glycemic Control with Basal-Bolus Insulin Using Computerized Order Entry."

- **Insulin Congress, Nov 10-12, Washington, DC http://www.insulincongress.org**

This is the first meeting of the Insulin Congress! We are excited to learn more about how patients view and take advantage of today's spectrum of insulin-based treatment options. On Saturday, November 11, James Hirsch will speak on the evolution of insulin's impact, followed by Dr. Stephen Clement on the evolving role of intensive hyperglycemia management in the hospital. Then the agenda will break into two options. We're particularly interested in the first option, with Drs. Jeff Unger, Satish Garg, and Vivian Fonseca speaking, respectively, on using SMBG software to fine-tune insulin therapy, using CGM to improve diabetes management, and insulin and endothelial function. The second option, however, includes Dr. David Marrero on overcoming barriers to initiating insulin therapy; interestingly, he'll be talking about patient barriers and not physician barriers – though we tend to think that both are probably equally important in contributing to psychological insulin resistance.

Another track split will occur in the afternoon; it's difficult to choose between Option 1, which will feature Larry Blonde speaking about pramlintide, and Option 2, which also focuses on incretin mimetics with a talk by Robert Ratner. We are major Symlin fans but a lot of doctors aren't because of the hassle of vial and thrice daily injections. The evening debate on the best strategy for insulin initiation in type 2 diabetes seems a little fixed, but we are eager to hear Dr. Philip Raskin opine on why pre-mixed and Dr. Geremia Bolli on why basal/bolus.

Sunday brings forth a few more speakers we are excited to see. In the morning, complications expert Dr. Michael Brownlee will talk about how glycemic variability as a step in the evolution of our understanding of insulin therapy. Afterward, Option 2 is the way to go with Dr. Bill Tamborlane speaking on pediatric patients and Dr. Luigi Meneghini on maximizing pump therapy. At noon, Lutz Heinemann will give the closing session on "Future Directions for Insulin Therapy and Treatment of Diabetes."

*—by Daniel Belkin and Kelly Close*