DIABETES CLOSE UP

Diabetes Close Up
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Galvus Interruptus - FDA Demands More Data from Novartis

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

From the Editor:

We just received yet another reminder that the march toward improved drugs and therapies is anything but steady and predictable. Novartis reported this week (February 26) that it did not receive FDA approval for Galvus, leaving Merck's Januvia as the only approved DPP-IV inhibitor. Novartis said that the FDA wants additional data, including a clinical study in patients with renal failure. We have pointed out before that the long-term safety of this entire class is still a question – there simply aren't enough data, and the underlying mechanism of these drugs remains unclear, in spite of all the class advantages (simplicity is the one we most admire, all else equal – which, of course, it's not, yet). Nonetheless, we believe the FDA's request is a reason to pause, not to panic. The agency, after all, didn't halt the GALIANT (head to head Galvus vs TZDs, 80-center, 3-month ongoing) trial. You can read our complete take on the Galvus news on page 15 of this month's DCU.

We feel more upbeat about our travels to New York for the ADA Postgrad meeting. For years, we've heard the mantra that type 2 patients will receive earlier, more aggressive therapy, so that's by no means new, but we believe clinicians (especially the good ones) are ready to make that a reality. They seem more thoughtful and deliberate in how to initiate and intensify treatment, and of course they also have a growing list of therapeutic options, many of which are easier to tolerate for patients. Notwithstanding Galvus's troubles, Januvia stands as a key new early treatment, Byetta remains red hot, and combo therapy continues to gain traction. Given how fast the type 2 epidemic is growing, given how much better diagnoses are getting, given how much more serious that HCPs are becoming about not just early treatment, but treatment at diagnosis (forget diet and exercise as a start without drugs – the ADA nixed that last August in its guidelines), given how many drugs each person will start *taking at diagnosis, and will start taking more* quickly*, given how much the trend is moving toward adding drugs more quickly when the first combo therapy doesn't work, given how guilty people are starting to feel about A1cs over 7 (okay, right, sorry, that's not happening yet), given how many important outcomes trials there are to be executed and reported on in the coming years, given how big the potential is for direct-to-consumer (and can you imagine the impact of* good *direct-to-consumer marketing?), it really does make one feel a little delirious to sit and ponder how much better patients* could *get and how big the commercial potential of these therapies could really be.*

Anyone else notice that the US presidential campaign has started? We wish we could report that one of candidates, even a marginal one, was making a major address on diabetes, but instead we can report on perhaps the next best thing, Bill Clinton will deliver the keynote address at the Global Changing Diabetes Leadership Forum, in New York on March 13, sponsored by Novo Nordisk (we love how Novo is always pushing the envelope). Our hope is that the former president learns a great deal about diabetes ... and then tells his wife about it.

– Kelly L. Close

MAJOR HEADLINES, DCU #66

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<u>Quotable Quotes from February's DCU:</u>

Dr. Zachary Bloomgarden, Mount Sinai School of Medicine, and endocrinologist extraordinaire:

- *On Januvia: "Everything looks like Januvia ought to be a really good drug for diabetes. It gives the same benefits as Byetta, with glucose-dependent insulin secretion, and with no need for titration. There's one dose for everybody, and it's not associated with weight gain, although not giving weight loss in the way seen with Byetta. I have found that there's some heterogeneity in patient response to Januvia, so that some have very good responses and other patients with type 2 diabetes really don't show quite as good a response."*
- *On SMBG: "Monitoring the blood glucose should be seen as something that's empowering, and that helps the person with diabetes to understand how the diabetes is doing, rather than seen as a burden … that people have to put up with. I just don't see how you can manage diabetes in anyone, whether on oral agents or insulin or combinations, without home glucose monitoring."*
- *On rimonabant: "Rimonabant might be very important. I think there's a lot to worry about with depression and anxiety as potential side effects, but as far as the blood sugar benefit, in the RIO-Diabetes study, which appeared several months ago in Lancet, there was tremendous benefit of rimonabant in people with relatively early diabetes, three quarters on metformin, one quarter on sulfonylureas. Their mean A1c was 7.2%, and they had a 0.6% fall in A1c with rimonabant. That's huge. There appear to be rather complicated political reasons making it difficult for the FDA to approve rimonabant as a diabetes drug, but it appears hypocritical."*
- *On CGM: "I think it's ready. I think the technology is basically here. Those of my patients who are using it are absolutely getting less hypoglycemia. When the blood sugar really goes up and down all the time, testing fingersticks 20 times a day is not as good as getting a readout 1,400 times a day. In a day-to-day sense, people with type 1 diabetes need CGM."*

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.

- **February 26: Novartis' Galvus – FDA prolongs the agony**
- **February 22: Avoiding burn out: one man's story**
- **February 21: What do you think of my genes?**
- **February 21: What the FDA's sharper claws mean for us lab rats?**
- **February 20: Byetta pens no longer need refrigeration**
- **February 21: A godsend or a scare: results can vary widely with weightloss surgery**
- **February 8: A potential new correlation between white blood cells and type 2 diabetes**
- **February 6: Squeezed again: political leadership needed to reverse budget trends in diabetes**
- **February 5: Mind over matter**
- **February 2: Can government help Americans lose weight? Here's how to start**

Coming soon in DCU…

- **PTP1B primer: more help on insulin resistance**
- **Conference reports from Diabetes UK in Glasgow, ADA islet research symposium in Georgia, and American College of Cardiology conference in New Orleans**

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

1. DCU Company Watch

- **DexCom – Hopes for a successful seven-day sensor, starts new discussions of IV hospital product:** DexCom's February 27 call was disappointing in our view. Revenues for the fourth quarter were flat sequentially at $835,000 versus $841,000 in the third quarter, as had been announced at the JP Morgan conference last month, and management conceded revenues likely wouldn't increase much this quarter. We agree, given that its credibility with healthcare providers and patients has suffered. Gross margins remain very negative – for the year, cost of goods sold was $11 million, on $2.2 million of sales. CEO Andy Rasdal also suggested revenue was slower because people are waiting for the seven-day sensor, which we do believe is the case. (We're waiting for it.) We actually wonder if some people might "stock up" on the current sensors, which can be reused – how certain the "shut-off" will be for the seven-day sensor is uncertain, but we imagine the company has made this more difficult. Rasdal noted that supply constraints from 4Q06 were resolved in January and that DexCom now has product inventory and has been able to meet demand. We assume that supply difficulties were at least partially due to the higher-than-expected replacement requests – this must have been difficult for the sales reps. DexCom's loss for the year was $47 million, and it now has just around $55 million in the bank – right around the loss estimate for 2007. The report of 840 new customers in the fourth quarter seems low, which is not surprising given both the product reliability and quality issues and the lack of reimbursement. It is critical in our view for the seven-day sensor to perform much better than current ones on this front. On the manufacturing front, DexCom's passing a January FDA inspection of manufacturing facilities represented an important bright light, as did the FDA approval in the automation of two of three steps that represent current "bottlenecks" in the manufacturing line. On reimbursement, Rasdal expected that DexCom's and Medtronic's January HCPCS application would receive a decision at the end of Q1 or beginning of Q2 with final determination in late fall. We aren't confident that the data will emerge the first round, and we don't think isolated individual cases of reimbursement for patients are or will become much more common anytime soon. Management noted that the JDRF trial, which began enrollment recently, should be good evidence for stronger reimbursement – as we understand it, DexCom is providing seven-day sensors for this trial, an apparent positive for the patients. As for the seven-day sensor approval timing, DexCom is talking with the FDA, and Rasdal believes this device will be approved in 2Q07. DexCom intends to launch as shortly after approval as possible as it did with the three-day. Fortunately, the device is made on the same manufacturing lines so DexCom can switch over "almost instantaneously." We were excited to hear that DexCom's in-hospital product was IV-based, and we certainly agree this is an important market. Rasdal said that initial human studies of the product are positive and that compared to YSI measurements, the hospital product is more accurate and reliable than traditional BGM – it wasn't stated what the comparator was. DexCom intends to enroll patients in feasibility trials soon. Rasdal called the hospital application a "standing opportunity for partnering" and said that DexCom will pursue partnerships in other products as well.

- **Emisphere – To reformulate its oral insulin and partner its diabetes drugs:** At the year-end call on February 27, CEO Lewis Bender reviewed what the company termed the year's diabetes milestones: results released from a phase 2 oral insulin trial and full rights to the oral GLP-1 patent granted by a U.S. district court from previous partner Lilly. A panel of diabetes-focused HCPs had reviewed oral insulin data at the time the results were released and are now expected to become a scientific advisory board to the program. Emisphere announced it will move forward with the development of the oral insulin product, but, since it's "a drug delivery company rather than a diabetes company," it intends to partner the product with a pharmaceutical company as soon as possible. We don't look for quick movement on this front. The expert panel had recommended that

Emisphere reformulate the insulin to "strengthen the signal" in terms of the amount of insulin put into the blood as well as the extent to which blood glucose is lowered, particularly in the lunch and dinner doses. Bender said he believes the company can do this. Emisphere plans to systematically test various reformulations in animal and "some" human studies to get to a point at which additional efficacy studies are appropriate. As far as its phase 1 oral GLP-1 product and also its oral PYY product for obesity, the next step is to generate some human data in order to partner them – were it only so straightforward!

- **Novartis—Galvus awaits approval, but likely not 'til 2008:** On February 26, Novartis announced an approvable letter for Galvus, requesting "additional data, including a clinical study in patients with renal impairment." This surprising delay suggests that the DPP-4 inhibitor likely will not be on the market before 2008. Is this simply great for Merck (and its approved, first-in-class Januvia) or will it cloud the class? See our story below.

- **Matria 4Q06– A solution to close care gaps:** Health enhancement company Matria held its year-end conference call on February 23rd. The company released its new Physician-Patient Care Alerts system earlier in the month. They expect it to be a program that uses Matria's health records and informatics capabilities to improve adherence and outcomes by identifying "no less than" a quarter million significant care gaps per million covered lives per year. Types of alerts include preventive health screenings, diagnoses, drug incompatibilities, patients not under lab surveillance who are on drugs that require them, and patients who are underutilizing treatments. This has potential to help many patients with diabetes in particular and to cut down on costs to employers and health plans. They mentioned possibly approaching Medicare, Medicaid, and the uninsured, which they estimated was about 130 million Americans. With diabetic patients having to juggle many health care providers and treatments, we think Care Alerts could reduce less-than-optimal care.

- **Lilly—Memoir pen introduced**: Lilly launched its new Humalog pen, called Memoir, on Feb 22. Memoir is being marketed as a smart new way for patients to manage their diabetes because it 'remembers' the last sixteen insulin doses, allowing patients to check their doses if they forget to log their numbers. We think that anything to get people to insulin faster is positive, and this may help on the margin if Lilly's sampling is generous enough. The pen is very expensive at $100 (not including cartridges), however, and while intensively managed patients pay up for some extras, we don't know that the average insulin-naïve patient will spend the money, and we assume that's the main target for the pen. Clearly, Memoir is not going to turn around Lilly's insulin franchise, especially when only a fifth of US patients on insulin use pens, but we do view this as an innovative product. What we like best is the possibility that it might lead to more prandial insulin and testing, which would be great – we've heard from doctors that too many people right now essentially overdose on Lantus as they are avoiding the mealtime shots. We do wonder why the pen only remembers sixteen doses if Lilly has already gone through the trouble of putting the electronic bells and whistles in place… then again, we'll hope this is only the start of the smart pens.

- **Arena 4Q06—Lorcaserin obesity trial enrollment complete; no partner expected this year**: The big news in Arena's February 21 earnings call was the January completion of enrollment for the BLOOM trial, the first of three phase 3 pivotal studies for lorcaserin, the company's lead candidate for obesity. Enrollment finished with 3,180 patients, a bit ahead of plan, we assume due to the expected dropouts seen in virtually all obesity trials to date. *In our view, the next piece of key data will be information from a six-month safety review in Q307, on which the future success of the compound hinges.* Management said a partnership deal for lorcaserin in 2007 is unlikely - we assume it's a matter of Arena looking for a bigger valuation step-up and the potential partners waiting to see safety data prior to a deal. This isn't too surprising, and so 2008 appears likely timing for a partnership deal, probably before the planned 2009 NDA filing, which said to be still on track. Arena

will initiate two additional one-year phase 3 trials this year, and the 12-month data safety monitoring board (DSMB) review for BLOOM will occur in 1Q08 – no doubt this will also be closely watched. Management said that the development program for lorcaserin will be unaffected by the FDA's new draft guidance on obesity drugs, issued last week (see separate story on this below). No news was provided on Arena's partnership with Ortho-McNeil to develop APD 668, a glucose-dependent insulinotropic receptor (GDIR) agonist for type 2 diabetes, currently in phase 1 studies. However, CEO Jack Leif made the interesting remark that APD 668 may affect glucose-dependent insulin secretion both directly by acting on β-cells to increase insulin secretion and indirectly by acting on L cells and K cells to increase GLP and GIP secretion. We believe this would give this novel molecule a significant scientific boost if it can be proven in clinical trials; so far the evidence for an incretin effect is only preclinical.

- **Novo—GKA licensed to TransTech Pharma, Dr. Henrik Rasmussen joins team**: Novo announced February 21 that it has granted TransTech Pharma, a privately held company, an exclusive license to develop its glucokinase activator (GKA) program, which includes phase 1 and preclinical compounds. Glucokinase is the enzyme that phosphorylates glucose in β-cells and liver hepatic cells, facilitating uptake of glucose into these cells. Activating this enzyme allows hepatic cells to take up more glucose and β-cells to better sense glucose concentrations and secrete insulin in response. Thus, GKAs would act to reduce hyperglycemia through both the stimulation of glucose-dependent insulin secretion from β-cells and the stimulation of glucose uptake in the liver. We learned from Dr. Mjalli, the CEO of TransTech, that this particular program involves a more selective GKA that only stimulates glucose uptake in the liver. As noted on January 15, Novo is discontinuing development of oral drug candidates in order to focus on biologics, its area of expertise. We think this is a smart move, particularly if they can make liraglutide into a significant competitor against exenatide. In other news, Novo never stops when it comes to recruiting talent – it announced Feb 16 that Dr. Henrik Rasmussen will join Novo as VP of Clinical, Medical, and Regulatory Affairs and lead clinical research programs in North America, bolstering significant strong talent at the company in this area.

- **TransTech Pharma – Reacquisition of Novo's GKA program:** On February 21, Transtech acquired exclusive rights to Novo Nordisk's glucokinase activator (GKA) program. Curious about the details, we spoke with TransTech founder and CEO Adnan Mjalli about the acquisition. He said he was surprised – "pleasantly surprised"– that Novo Nordisk decided to focus exclusively on proteins and that on January 16 Novo Nordisk announced it would auction off all of its small-molecule programs. The GKA program was the leading program in terms of value, Dr. Mjalli said. He added that getting this program back was "a dream come true," maintaining that TransTech's GKA molecule will be critical for the treatment of diabetes, because there is no other anti-diabetes agent on the market that does what it does. GKAs generally reduce hyperglycemia by facilitating the uptake of glucose into hepatic cells and beta cells, causing the liver to take up glucose and increasing beta cell sensitivity to glucose levels. TransTech's molecule could be different in that it is said to be more selective, only activating uptake of glucose in the liver. Though Roche, OSI/Lilly, and AstraZeneca might argue that dual activation is a positive, Dr. Mjalli said that so far these molecules are plagued by severe hypoglycemia and that "the data will speak for itself." We love leading phrases like that … As far as development plans, TransTech will pursue development in the US (Novo was developing in Europe). TransTech is in the process of initiating human trials in the US, which will happen in the next 90 days. Though the type 2 segment is the main target right now, Dr. Mjalli mentioned impressive data in type 1s – type 1s may be able to take fewer insulin shots in a day, he said. Other TransTech programs in diabetes include a PTP1b inhibitor for insulin resistance (this is one of our new targets that we're investing a lot of time in – a primer will be in our next issue), an AgRP inhibitor for obesity, a GLP-1 receptor agonist, all expected to move into the clinic shortly, and a

fourth program targeting AMP-activated protein kinase expected to move into the clinic in six months or a year. TransTech can fund its pipeline from a deal with Pfizer in which it out-licensed compounds targeting the receptor for advanced glycation endproducts (RAGE), including a drug for diabetic nephropathy (TPP488). Whew! There could be more than meets the eye with any one of these compounds alone – we'll be watching closely.

- **Amylin—Byetta receives room temperature storage indication**: Excellent news: the FDA approved Byetta pens for room temperature storage by patients after first use. This is one of those announcements that sounds ho-hum, but is actually very meaningful. The label change came February 20, just a few days before ADA Postgrad, and we were already hearing from thought leaders at Postgrad about the extent to which this change would significantly increase patient convenience. We understand well how the difficulty of keeping pens refrigerated currently dissuades some patients from going on Byetta – this is definitely a hassle (though less of one depending on amount of weight lost!). Amylin plans to inform HCPs about the new storage indications over the next few weeks.

- **Medtronic 3QFY06—MiniMed sales growth impressive at 24 percent**: Medtronic reported on February 20 that for the quarter ended Jan 2007, MiniMed achieved sales of $226 million, up 24% from $182 million in 3Q06. Though this was an easier comparison than many (since the growth the same quarter a year ago had risen well under 10%), it is still an extremely impressive result for new MiniMed head Chris O'Connell. Prior to this, MiniMed has had only one quarter in sales over $200 million (last quarter at $212 million), so to be annualizing at just over $1.0 billion is certainly quite positive, especially if that growth can be sustained. President and COO Bill Hawkins highlighted solid double-digit growth of pumps in all geographies. The Paradigm RT was characterized as gaining customer acceptance globally; it is the only product available integrating pump and CGM technology. Medtronic doesn't break out sales of CGM individually, and we suspect that they are a very low part of overall revenue. Notably, revenue growth from disposables has recovered to double-digits. The MINI-LINK was approved, a transmitter about 1/3 the size of the current device – this approval came a bit ahead of expectations and may allow Medtronic to be more competitive against DexCom, although we believe sensor improvements are still necessary. The STAR 3 trial comparing sensor-augmented pumps to MDI (Lantus and rapid acting analogs) began enrolling in the third quarter.

- **Merck—FDA accepts NDAs for Januvia with SFUs and as initial combo with metformin**: Merck is on a tear, having announced Feb 15 that the FDA has accepted two new filings for Januvia. One is for add-on to sulfonylureas (SFUs), as was expected, and the other is for adjunct to diet and exercise in combo with metformin as initial therapy. The company expects to hear in mid-October. The SFU filing responds to the FDA's request for data with SFUs; these data haven't been presented yet, and we assume Merck has submitted them to this year's ADA. We think it was smart for Merck to try to get an indication for SFUs - we're surprised they didn't get this earlier, but their strategy was clearly to get fast approval, which has served them very well so far. Since SFUs are still widely used and prescribed, we think having an indication is just smart business, even if the talk is that DPP-4 inhibitors will just replace SFUs. But, especially with managed care, many patients will still need to fail SFUs or metformin before being allowed to try DPP-4 inhibitors. We also think it was smart for Merck to try to get an indication for *initial* combo therapy with metformin because: 1) There's been a lot more support of late for combo therapy and the company would do well to climb on this bandwagon and get a specific indication; 2) Payors may be more willing to pay for this than just Januvia monotherapy… we're not at all sure about this, but at least the data are better. We note, however, that as usual, we feel the trial data are a little suspect because even though there shouldn't be the typical problems with wash-out muddying the results (since there should have been no wash-out), the 2.1% A1c drop was a placebo-subtracted result, and we don't know what the placebo group did. Also, the starting A1c of 8.8% was rather high. We note as well that the combo is a twice-daily, not

once-daily, drug. On the bright side, side effects are lower than what is typically seen with metformin alone, supporting the notion that lower doses cause significantly fewer side effects even though the dose of metformin alone wouldn't likely be enough to prompt such a big A1c drop. On the other hand, we understand that many MDs slowly titrate their patients up on metformin to minimize side effects, and the fact that you can't do that with Janumet makes us believe the product may not be taken up as quickly with endos as with GPs – reimbursement, of course, will also play a role. In terms of efficacy, Merck will be able to market the fact that 66% on the combo achieved A1c's of less than 7%, compared to 38% on placebo; even though we're not sure the FDA cares about seeing data presented this way, we note some thought leaders support this and think it's a great way to level the playing field. Impressively, Merck is hard at work building the clinical data for other indication expansions, with phase 3 trials ongoing for add-on to insulin (Novartis has already done this for Galvus as part of its original submission), for initial combo with pioglitazone, and for triple oral therapy with metformin and pioglitazone.

- **Diabetes market expansion - insulin and insulin delivery lead to two new S-1s!** Insulet and Biodel both filed their S-1s on Valentine's Day. How excellent is that? We see Insulet's disposable pump as a breakthrough product and believe demand will be high as it expands its roll out – improved automation is the next big step for the small, innovative company. We've been impressed with many aspects of the products, but simplicity most of all ...no, the automatic insertion most of all... no, the absence of tubing most of all ... no, the user interface most of all ...hard to choose. Automation is hopefully up next, and it has some terrific experience on its board in terms of cutting costs, namely Charlie Liamos, former TheraSense CFO and COO. Big challenges, but we hope it's up for it. (Kelly would give you her cell phone before handing over her pod.) For Biodel, we can't wait to see if this potentially VRAI (very rapid acting insulin) really is more rapid - a large trial is enrolling now (we were called for it and were dying to do it, but we didn't stand a hope of passing the screening questions. To our dismay, the company didn't take patients on pumps, patients who weren't willing to be randomized to regular insulin, or pregnant patients - three strikes and we were out!) We'll be digging into the S-1s, and we encourage investors to check out these pure-play opportunities. Some high mountains to climb to achieve success, but we relish this sort of innovation - onward!

- **Sanofi 4Q06—Rimonabant delayed to July, cardiometabolic positioning intensifies**: Sanofi held a four-hour 4Q06 meeting on Feb 13, featuring detailed discussions of the company's pipeline in each of its major disease areas and an hour-long Q&A. The biggest news was another rimonabant delay, this time for another three months until July 27. The press release also said that SERENADE data (we reported on this in our December DCU – it was announced at IDF) have been submitted to the FDA. Management basically dodged all questions for more detail on this during the Q&A and expressed continued confidence that rimonabant will be approved "sooner or later" but hopefully in the course of this year – a very cautious assessment. We detected some defensiveness regarding rimonabant; management went out of its way to dispel the characterization of rimonabant as a lifestyle drug. In fact, the CEO went so far as to say that "it is not for American big bottoms" but for visceral obesity. Harsh! Given the poor/nonexistent reimbursement for "lifestyle" therapies and the clinical data supporting the considerable metabolic benefits of the drug, we don't really blame them for harping. Too, we think the company has actually sought patients that have multiple cardiometabolic risk issues, because these seem to be the patients, at least a subset of them, that benefit most from rimonabant, at least according to doctors to whom we've spoken who have participated in trials to date. Financially, Sanofi's diabetes performance was strong. For 2006, diabetes was listed as one of their four major growth areas, and the market - insulin - was noted as growing at 15% annually. Lantus sales were 451 million euros ($587 million) in 4Q, up 36%, and 1.67 billion euros ($2.2 billion) for the year, up 37%. 4Q sales rose 20% in Europe and 43% in the US; for 2006, sales rose 27% in Europe and 40% in the US. Management said key changes in sales rep call activity in 4Q led to the much higher Lantus growth; Sanofi's sales reps were shifted away from Allegra and toward

Lantus and Ambien. The company also said Sanofi will continue to maintain a sales force in primary care, citing as one reason the increased importance of general practitioners in writing insulin prescriptions. Notably, the company said that the introduction of Januvia has cut only into Byetta's market share and not that of Lantus. We agree Sanofi probably doesn't have to worry that much about Januvia stealing share from insulin, but we do think it will contribute over time to a longer delay in the move to insulin for type 2 patients – never an easy area. Notably, Sanofi's pipeline for metabolic disorders is filling up. It currently has two pre-clinical, one phase 1, two phase 2a, and four phase 2b molecules, all in addition to rimonabant, which is approved in Europe. The four phase 2b molecules are: AVE1625 (CB1 antagonist), AVE0010 (GLP-1 agonist)**,** AVE5530 (cholesterol absorption inhibitor), and AVE2268 (SGLT-2 inhibitor). The latter three are planned for submission in 2009/2010. The phase 2b for the SGLT-2 inhibitor will report in 4Q07 with phase 3 expected to begin in 1H08. We were surprised to hear virtually nothing about AVE0010 and so much about the SGLT-2 inhibitor – actually, we spoke to some doctors at ADA Postgrad who were not as excited about the SGLT-2 class due to their experience from decades ago, when many patients experienced glycosuria from uncontrolled hyperglycemia. We heard that glycosuria causes urinary tract infections in both men and women, and the polydipsia (thirst) and polyuria (frequent urination, especially at night) were nothing to smile about either. One doctor commented that only a younger generation of researchers with no experience with glycosuria would think it was a good idea to make a drug that caused the condition! *Overall, we think this earnings call marked a shift in tone at Aventis regarding diabetes. Rimonabant, of course, is the crux of Sanofi's cardiometabolic risk positioning, but even Lantus has shifted from a late stage diabetes management tool to a means of preventing a cardiovascular event.* To that end, management described ORIGIN as much anticipated (2010). The prevention trial for rimonabant is CRESCENDO, expected to report in five years. Management discussed how treatment goals for cardiometabolic are becoming more aggressive. Though this concept isn't especially new for intensively managed patients, the buzz about prevention "opportunity" is both new and interesting. Lastly, management announced that Sanofi will hold an R&D meeting this year on September 17 – that is also the first day of EASD.

- **Avanir 4Q06—Little new in very short earnings call**: In Avanir's year-end call on February 9, CEO Eric Brand gave an update on Zenvia, a drug in development for diabetic neuropathy. Last quarter, management said that Zenvia for diabetic neuropathy is in phase 3 and that they will look for opportunities to partner it when phase 3 data come out in mid-2007. There was no new information in this call.

- **GlaxoSmithKline 4Q06—Avandia sales take an upswing in wake of ADOPT, company sends letter to doctors about increased fracture risk, OTC orlistat approved**: GSK reported Feb 8 that full-year 2006 sales for the Avandia franchise well exceeded $3 billion globally, up 25%, with sales of over $2 billion in the US, up 24%. Management cited positive physician reception of ADOPT results for part of the strength. For 4Q06, global Avandia franchise sales totaled £406 million ($798 million*, up 7% from the previous quarter and up a whopping 21% from 4Q05), with £292 million in the US ($574 million, up 10% from the previous quarter and up 25% from 4Q05). That was a great US result in particular. Global 2006 Avandia franchise sales were £1.645 billion ($3.23 billion, up 25% from 2005), with £1.194 billion in the US ($2.35 billion, up 24% from 2005). After the publication of ADOPT data in December, which management characterized as very positive, GSK noted an immediate upswing in TRx's for Avandia. Since only three weeks of that would have been included in 4Q numbers, we think we can assume that 1Q07 must be going quite well for Avandia, despite Januvia, though this may change after a February 22 letter from the company to all US doctors warning that Avandia may be associated with increased risk of fractures in older women.

* We calculated the US dollar numbers assuming the current exchange ratio of 1.965 dollars to a pound, but as the dollar has been depreciating in recent months, the actual US dollar amounts were likely lower.

GSK said Januvia is having no negative impact, which we find surprising. This is likely a little overstated in our view, but based on these numbers we would agree that Januvia's impact hasn't been significant yet. This is in line with our thought that TZDs aren't going to die due to DPP-4 inhibitors, despite the issues surrounding the class – weight gain, edema, association with congestive heart failure, and now the increased fractures. All that said, their mechanism of working against insulin resistance is unique in our view – we will be looking at PTP1B inhibitors in an upcoming issue as this new class also addresses insulin resistance. Alinea Pharma is at top of the heap of companies exploring this class. Back on TZDs – we do believe TZDs will benefit from the addition to the Byetta label (add on to TZD therapy), and we expect combo Byetta-TZD use to increase despite the relatively high cost of this combo. On the Avandia growth front, management noted that Avandamet use is on the rise especially in Europe; in particular, they said that physician reception of ADOPT data has been very positive, with Avandamet benefiting the most – this is in line with our interpretation that ADOPT was more favorable for combo therapy than any single drug. CEO JP Garnier said that going forward, he expects that sales of Avandia as a stand-alone product will be a modest part of the overall franchise. We had hoped to hear an update on the regulatory plans for a pre-diabetes indication for Avandia stemming from the DREAM trial, but disappointingly, there was no news. In other matters, the FDA finally approved Alli, GSK's over-the-counter (OTC) orlistat on Feb 6. Management spent some time talking about GSK's strategy for launch, which the company said will be similar to the strategy it used to market Nicorette – emphasizing patient responsibility. On February 21, Roche also sold GSK exclusive rights to sell Alli in countries outside of the US and Japan. In GSK's pipeline is Avandia for Alzheimer's, which Garner called "a bit of a dream," but the fact that he mentioned it at all makes us think there might well be positive movement (see our August 2006 issue for more on Avandia being used for Alzheimer's). Expected in 2007 are go/no-go decisions on whether to pursue phase 3 for their SGLT2 inhibitor (with Kissei, in phase 2b) and GLP1 receptor agonist (with Human Genome Sciences) – management did not give details on these. In the late stage pipeline are phase 3 line-extension studies for Avandamet XR, Avandia + statin, and rosiglitazone XR.

- **Roche 4Q06—BG growth remains sluggish as Roche works on its pharma diabetes pipeline**: In Roche's year end earnings call on Feb 7, management reported 6% growth in Diabetes Care for 4Q06 and 3% growth for the full year 2006. Blood glucose monitoring growth for 2006 was 3% while insulin delivery growth was a more robust 11%. Management pointed out that Roche's diabetes trend has been up overall for the last few quarters, with growth at -1% in Q405, -5% in Q106, +6% in Q206, +5% in Q306, and +6% in Q406. It also noted that the Accu-Chek portfolio was renewed in 2006, with the introduction of the Accu-Chek Spirit pump in the US in November 2006 contributing to insulin delivery growth. (Since it wasn't on the market at all last year, all the new revenue is incremental.) Clearly, blood glucose monitoring continues to be challenging, as it is for most of the other players; we believe Byetta has had a role in slowing testing frequency and that managed care continues to pressure prices. On the pharma side, management highlighted R1583, Roche's GLP-1, on a slide of Roche's overall pharma pipeline but gave no new information except to note that phase 2 trials were to begin in early 2007. It said that important data will be reported in 2007 on R1440, its glucokinase activator (GKA) for diabetes. We note (see above) that Novo recently licensed its GKA to TransTech Pharma. Additionally, Roche continues to work on its CETP inhibitor R1658 (JTT-705), for which phase 2 safety data are expected to be available in mid-2007. Roche will decide then whether to continue with phase 3 studies, with filing expected in 2010 if the company does continue. Management said it continues to remain encouraged by the data on this molecule. Also in phase 2 is R1439, Roche's PPAR-α/γ agonist, which went into phase 2 testing in 4Q06. Molecules R1579 and R1511 are in ongoing phase 1 studies. Orlistat (Xenical) was not mentioned during the presentation, but surprisingly to us, the Roche press release noted that sales grew steadily in 2006 despite the launch of a competitor in some markets (rimonabant).

- **Alkermes 4Q06—More color on AIR insulin and Byetta LAR partnerships**: Alkermes offered more color than usual on its partnered programs in its Feb 7 year-end call, as the company was very bullish on LAR and AIR. The January 8 news of an expanded agreement with Lilly was mentioned – as a reminder, Alkermes will now be the exclusive commercial manufacturer of AIR Insulin powder. It will sell commercial product to Lilly on a cost-plus basis as well as earn a favorable low-end double-digit royalty on net AIR Insulin sales. The agreement also provides for additional investment by Lilly, expected at more than $30 million, for the construction of a second manufacturing line, which will expand Alkermes' manufacturing capacity three-fold. Financially, Alkermes' R&D revenues were $19.5 million this quarter, up from $10 million this quarter last year, from AIR Insulin and LAR partnerships, as well as from a non-diabetes related Cephalon partnership. Management said AIR was in a comprehensive development program, with many activities ongoing to prepare for commercialization. In 2006, the program gained clinical trial material for studies involving about 4,000 patients in over 20 countries. Stability batches that will be used for Amylin's phase 3 trial were initiated as well as expansion to a second manufacturing shift. In phase 3, there are seven clinical trials, which include AIR with and without orals and with and without basal insulin. A 2007 milestone will be the publication of AIR Insulin patient training data in a peer-reviewed journal. Management called Byetta LAR, partnered with Amylin and Lilly, "possibly the next standard of care." A 2007 milestone will be completion of enrollment in the pivotal 300-patient phase 3 study this quarter, with top line study results expected in 2H07. Process development scale-up work is ongoing; scale-up to the intermediate batch size is complete and this material is being used in the current study. Management called the construction of Amylin's commercial manufacturing facility a high priority for the alliance and said that they've announced that the commercial manufacturing process would be finalized in 2H08.

- **Polymedica 4Q06—Solid patient growth and impressive reorder rates**: Polymedica, which distributes diabetes products using a direct-to-consumer model reported fiscal 3Q07 results on Feb 6. Diabetes revenue grew 5% from 2Q and 10% from this quarter last year – down from 22% year-over-year growth last quarter. Diabetes revenue for the year-to-date grew 42% from the prior year. This is better growth than might have been expected, although it represents a decrease compared to past quarters. CFO Keith Jones said the revenue increase was due to patient growth, which was 1.3% this quarter from last and 7.3% from a year ago – sequential growth slowed compared to last quarter's 2.9% growth. Jones expects similar patient addition in the future. Diabetes reorder rates increased to 91.3% from 89.7% in 2Q – this was impressive, we think, but Jones said it may be difficult to maintain this level in subsequent quarters. He said that in the March quarter (4Q), diabetes revenue should be flat or decrease slightly from the September quarter (2Q), but should pick up again by June (1Q08). He expects gross margins to increase next quarter into 58%. He also said that since acquiring NDP in 2005, Polymedica has developed the insulin pump business and is starting to make "real progress" in the area. We understand the company would like more pumpers because they test more frequently, but we're not sure how they are defining real success. Overall, management characterized Polymedica's Liberty brand as a unique direct-to-consumer model. Polymedica will spend about $60 million this year in direct advertising, which sounds not so different from a year ago. Non-TV ads will go up; magazine advertising hasn't done as well. Recently, it has expanded services into pharmacy from solely diabetes. The November agreement with Medco was termed the next important step for the Liberty program and, over time, management believes it will eliminate a great deal of execution risk. CEO Patrick Ryan said the March implementation for the Medco agreement has been daunting, but they are still on track for March, having worked cooperatively "in the spirit of partnership." Ryan also said that Polymedica was exploring co-branded insurance products. COO Steve Farrell gave an eagerly awaited competitive bidding update. The final ruling should be released soon, and Farrell expected CMS to begin implementation by the end of calendar 2007. He did not expect surprises and he expects diabetes test strips to be included in at least some MSAs (metropolitan statistical areas) but only a small number. He also did not expect the ruling to have any

significant financial impact on Polymedica this year. It would likely affect reimbursement for only about 5 to 7% of the customer base in the beginning. It may affect more, and have more financial impact, in the longer term, late 2007 to about 2009, when it may roll out to the next 70 MSAs. The long-term effects generally are hard to estimate, according to Farrell, but it's been suggested that larger players like Liberty will gain market share at lower reimbursement rates. Polymedica reiterated its stance that competitive bidding is the wrong way to solve problems in diabetes. It runs against what the company feels are the winning strategies - more testing for current patients, testing for prevention, etc. Farrell said he believes that legislative relief from competitive bidding is a possibility, but emphasized "possibility."

- **Mannkind 4Q06—Clinical development on track, partner still lacking**: In the Mannkind call, we learned that studies continue, they raised money, and partnership discussions are ongoing but undecided. We assume the big issue with partnership is a gap between what Mannkind wants at this stage and what a partner is willing to give. Mannkind continues to express its belief that TI (its Technosphere Insulin System) isn't a pulmonary insulin so much as it is a new class of super fast-acting insulins. We would consider this a breakthrough product if everything the company says comes true, but we remain skeptical (perhaps if only because we find ourselves wanting it too much!) and have begun a series of conversations with insulin experts about it to learn more. The company continues to describe TI as offering better results than analogs (we think it was very smart of them to do a comparison with analogs), with better PPG control, fewer hypoglycemic events, and no weight gain. The practical reality of this would mean that if TI works as advertised, no carb counting or blood glucose monitoring would be required or there would be no "gap" between the timing of eating and taking insulin - this would be nirvana for most any patient. As well, we still continue to be cautious about any insulin delivered via the lung for safety reasons. However, as noted, the idea of a super fast-acting insulin is compelling (and probably true to some degree – it's just a matter of how many of Mannkind's claims have merit and that's what we want to uncover). Notably, Mannkind is the one inhaled insulin program that intrigues doctors, even many of the ones who are negative on inhaled insulin. We think the ongoing focus on post-prandial is very smart, and we note that they do have a very talented advisory board. Back on numbers – for the quarter, total operating expenses in Q4 for Mannkind were $71.8 million, compared with $35 million in 4Q05. They were $233.8 million for the full year, compared with $118.1 million in 2005. Net loss for Q4 was $71.3 million or $1.30 per share, compared with a net loss of $33.3 million or $0.66 per share in 4Q05. In 2006 Mannkind also raised $500 million for a manufacturing plant in Danbury, CT. Obviously, enormous funds are being poured into this program. As a reminder, market cap for Mannkind is ~$800 million. Investors asked about a variety of issues, including comparisons with Exubera, financial details, partnership, development timeline details, safety studies, the phase 3 studies, and dosing. We remain a little concerned about the dosing – 15 units and 30 units will be the two doses, which seem awfully large increments even when divided by five (absorption is only ~20% so the effective doses are more like 3 units and 6 units). Four key phase 3 trials are currently ongoing: 102, 103, 009, and 030. The lead study is 102, comparing premixed with TI in 650 type 2 patients. Study 103 compares TI bolus with rapid-acting analog bolus, both used with basal in type 2 diabetics. This study, as well as being a much more relevant comparison than against regular insulin, is also easier to enroll. Study 009 assesses TI in combination with metformin, which is not a required FDA phase 3 trial, but we agree with the company that this is important in establishing TI as early-line treatment - a company less well-funded would not be pursuing this study at this point. Study 030 is a two-year pulmonary safety study in type 1 and 2, which completed enrollment in September 2006 with 2,050 patients. An NDA filing is expected in 2008 with filing in Europe a quarter afterwards. There are preclinical studies ongoing for the next Technosphere product. Al Mann said the company has treated over 2,000 patients in trials to date.

- **Pfizer—Stepping into GLP-1 field with BioRexis acquisition**: Pfizer announced Feb 1 that it has acquired BioRexis, a private biopharmaceutical company that owns a technology for the delivery of long-acting protein drugs. The technology uses human transferrin – blood plasma based – to permit sustained duration of action. (We admit to being a little leery of any human plasma-based drug delivery mechanism but admittedly, we don't really know anything about the BioRex technology to judge.) Its method involves genetically fusing protein drugs onto human transferrin, a natural protein with a half-life of 14-17 days. Presumably, the fusion protein would have the same half-life as normal transferrin. BioRexis was using this technology to develop a long-acting GLP-1 agonist – we find the theoretical concept behind the technology sound. The main technical challenge is creating a fusion protein that retains both the GLP-1 receptor-binding capacity of the original protein agonist and the long plasma half-life of the transferrin scaffold protein – it sounds like BioRexis has done this. The company presented promising efficacy data on appetite reduction and weight loss in rats at a conference in March of 2006 – it will be interesting to see if this can be replicated in humans, and what the glucose-lowering efficacy will be. Overall, we like seeing Pfizer's interest in diabetes confirmed with this acquisition. Pfizer did not disclose the acquisition price, but from public announcements we found that about $38 million has been raised from venture capitalists, so we are guessing that Pfizer may have paid 3-5 times this number – again, a big-time guess on our part.

- **Tomen America/Nippon Kayaku—GlycoMark test for postprandial glucose available**: Tomen America, a Japan-based international distribution company, announced Feb 1 that the GlycoMark test is now available to US doctors through LabCorp, a clinical laboratory company. Developed by Nippon Kayaku, GlycoMark measures serum levels of 1,5-anhydroglucitol (1,5-AG), a simple sugar excreted through the kidney with a structure very similar to glucose. Blood concentrations of 1,5-AG are usually quite stable, but during periods of acute hyperglycemia, the kidney becomes overwhelmed with reabsorbing glucose, and more 1,5-AG is excreted into the urine. Thus, according to Tomen America, low 1,5-AG levels are a sensitive measure of hyperglycemic excursions, more sensitive than A1c or fructosamine. We think this test is intriguing and has good potential considering the increasing interest in monitoring and controlling glycemic variability – for now, it will be most useful in clinical trials rather than practice.

- **AstraZeneca 4Q06—Saxagliptin phase 3 results to be presented at ADA, dapagliflozin phase 3 decision to be made late 2007**: In AZ's Feb 1 call, CEO David Brennan said that AstraZeneca's pipeline progress in 2006 was mixed. On one hand, the company lost tesaglitazar (Galida), a PPAR agonist that was in phase 3. We note that this was due to elevated levels of creatinine, which indicated kidney damage. BMS and Merck had already abandoned their muraglitazar. On the other hand, AZ had a number of significant business transactions in 2006, including the very recently announced partnership with BMS to develop two compounds to treat diabetes. Brennan said that "in line with our stated focus on diabetes," (! can you so never imagine this phrase five years ago?) they have agreed to co-develop and co-market saxagliptin and dapagliflozin with BMS. Saxagliptin is a once daily, oral DPP-4 inhibitor, with a number of phase 3 studies ongoing in both monotherapy and combination therapy. Data from these studies will be presented at June's ADA, and an NDA submission is planned for 1H08. Dapagliflozin is an orally active SGLT-2 inhibitor. Phase 2b is expected in 2007, and a phase 3 decision will be made "later this year." In Q&A, management said vaguely that there is "some evidence" that saxagliptin will be differentiated from other DPP-4 inhibitors, but it will take time to see.

- **Neurometrix 4Q06—Marketing DigiScope to doctors for detecting retinopathy**: In its year end call on Feb 1, management talked about Neurometrix's Q4 announcement of an exclusive agreement with EyeTel to market, brand, sell, and service DigiScope, an FDA-cleared diagnostic device that PCPs and endos can use for early detection of diabetic retinopathy (DR). Management said that it has recently launched the sales effort and predicted that the market opportunity in the US is $700 million.

So far, EyeTel has generated ~$11,000 in revenue per account, including a $3,000-4,000 installation fee, $150 per month in rental, and $45 per scan. This produces 20% to 25% operating margins for Neurometrix, which management said was consistent with goals. Neurometrix's main product is the NC-Stat for nerve conduction testing. Management was pleased that that NC-Stat was used to perform 60% of all testing for diabetic peripheral neuropathy and lower back and leg pain in 4Q, up from 55% in 4Q05. A new product for detecting neuropathy, called Advance, will launch in 2007.

- **Metabasis/Daiichi Sankyo—Phase 2 enrollment complete for novel type 2 drug CS-917**: Daiichi Sankyo announced Feb 1 that it has finished enrolling a three-month, 392-patient proof-of-concept phase 2b study for CS-917, a novel molecule for treating type 2 diabetes that works by inhibiting fructose-1, 6-bisphosphatase (FBPase), an enzyme in the liver gluconeogenesis pathway. CS-917 reduces blood glucose levels by decreasing liver glucose production – we note this means that it is likely more effective for fasting glucose than controlling postprandial excursions. Metabasis licensed the molecule and development rights to Daiichi Sankyo in 1997 but retains co-promotion rights in North America. The phase 2b trial will look at two doses of the drug (which is administered twice daily) and will be followed by phase 3 testing if successful. We think this is an interesting drug because it has an entirely novel mechanism, but success will depend on efficacy and tolerability coming out of this trial – there are already cheap, effective oral drugs for reducing fasting glucose (i.e. metformin), but there is always room for improvement in tolerability.

- **GW Pharma—Preparing for phase 1 trials of CB1 antagonist for obesity**: GW Pharma, a publicly-held UK-based company, announced in its year-end earnings call on Jan 30 that it intends to begin human clinical trials on a cannabis-derived molecule for the treatment of obesity – the mechanism would be similar to that of rimonabant. No word on when trials will begin. GW's lead drug candidate is Sativex, a whole-plant cannabis extract delivered by an oral spray. Sativex is under clinical development for a number of indications, including diabetic neuropathy, for which it is in phase 2 trials. Sativex is approved in Canada for neuropathic pain associated with multiple sclerosis. Sativex Oromucosal Spray is a cannabis-derived medicine that targets the cannabinoid receptors in the body. It is licensed to Bayer in the UK and to Almirall elsewhere in Europe, though it is not yet approved for any indication in Europe.

- **GlucoLight—Founder Ray Krauss discusses in-hospital noninvasive continuous monitor**: GlucoLight is developing a continuous (as in two readings per minute), noninvasive glucose monitor for the hospital market, which Krauss estimated at $500 million. Because hospitals can support larger, more expensive, more difficult-to-use devices, the in-hospital product could be completed with a $12 to $15 million investment - impressive. The device consists of a disposable patch and a sensor. After a two-hour settling, calibration with a single drop of blood starts readings, which Krauss said was a significant differentiating feature from competitors. Additional calibration points are needed with significant changes in blood glucose. The device stays well calibrated for at least two days. It is estimated to cost $5,000-$10,000 for the monitor and about $20 per disposable. The device is noninvasive, but does not use spectroscopy as is often assumed. GlucoLight has identified a patented area of physiology that accurately reflects BG levels, even with significant numbers of interferents. Krauss said that early and preliminary data show comparable to superior accuracy with regard to conventional CGM devices like Medtronic's and DexCom's. Krauss hopes that the pivotal trial, which is not yet planned, will show that the device is accurate enough to base therapy on. GlucoLight looks to ask the FDA to start the pivotal trial in early 2008. Krauss, whose experience is in the hospital market, maintains that continuous is the most important feature for an in-hospital device. Nurses test blood glucose as frequently as every 20 minutes in the CCU and ICU. Noninvasive is also important, since at the end of 48 hours, nurses test as frequently, but dwelling lines are no longer in the patient.

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

2. Galvus Interruptus: FDA demands more data from Novartis

Both the medical and financial communities were surprised on February 26 when Novartis did not receive FDA approval for Galvus (and perhaps because we talk to both groups we were doubly surprised). According to Novartis, the agency says it wants "additional data, including a clinical study in patients with renal impairment." Whether the required study is a 12-week trial or a 26-week trial, it is unlikely that Galvus will be on the market before 2008.

While this would be a positive for Merck, for it would mean no near-term competition for Januvia, the only approved DPP-4 inhibitor, questions about Galvus's safety may also cloud the class a bit. The FDA would like to see patients with serious renal problems studied as a separate population – this seems reasonable. Merck did a small (25 patient) short-term (12-week) study in this population and reported no safety concerns. However, Januvia's label does guide physicians to reduce dosage in patients with moderate to severe renal impairement (or End Stage Renal Disease). In November 2006, Novartis reported that in one pre-clinical study, Galvus triggered skin lesions in one species of primate. While no skin lesions have been reported in the human trials involving approximately 5,500 patients treated with Galvus, it is not clear how a build up of an 'inactive' metabolite in the kidney could be related to skin lesions, and it is possible that the FDA has asked for further data exploring the possibility of a link. One thing we learned at ADA Postgrad in New York last weekend (Feb 22-24) was that Novartis apparently did its monkey studies in a different strain of monkey than had Merck and at a higher dosage, so if some association were found there could be a suggestion of a class effect.

At this point there are more questions than answers, and until Novartis meets with the FDA to discuss Galvus, it will not even be clear what Novartis needs to do to gain approval. In the meantime, it is clear that Merck will have the DPP-4 market to itself for awhile and will likely be able to launch Janumet (Januvia plus metformin combination) before Galvus is available – we expect this to become available this spring if no class problems emerge with the DPP-4 inhibitor class.

We have been asked whether the FDA has been "fair" to Novartis, or is effectively holding Novartis to a higher standard than what Merck faced. In turn, we asked Dr. Wendell Cheatham (Medstar, long experience with FDA, former Takeda exec, etc.) his opinion. Dr. Cheatham stated that there are many reasons why the Galvus development package could have been different enough from the Januvia development package to justify further FDA requirements for studies. He added that it is not unusual for approval requirements to increase in the time between one approval and application for another. While cautioning that he is not privy to all the data submitted by either Merck or Novartis, Dr. Cheatham observed that the side effect profile of the various DPP-4 agents in development have been different enough to suggest that one agent is not just a "carbon copy" of another. Therefore, treating each new drug application independently would appear to be appropriate.

Significantly, Dr. Cheatham is not worried that requirements for Galvus will raise concerns at this time about Januvia. Januvia already has dose adjustment labeling for renal impairment, and the FDA would likely have already required further adjustment, or new labeling, if the Galvus data indicated a problem. This observation leads to a major conclusion of ours, which is that at this point we see no reason to be worried about the DPP-4 class, or even about Galvus – we know that GALIANT and other trials are ongoing. If there were serious fears, we imagine these Galvus trials would be on hold. We believe the medical community has much less reason to be concerned than the financial community, which of course cannot ignore the implications of delay for an important drug launch.

Having said this, we believe there is still much to learn about the DPP-4s, both individually and as a class. The method of action is not well understood and the long-term side effects are still unknown. Early experience with Januvia safety has been a very pleasant surprise and, while efficacy may ultimately limit their use in treatment, if DPP-4s make it easier to introduce patients to therapy and keep them compliant,

the benefits of this class will be substantial.

—by Kelly Close

3. Interview with Dr. Zachary Bloomgarden - Galvus, rimonabant, CGM, and more

I sat down recently with Dr. Zach Bloomgarden, who is noted not only for his huge clinical practice (more than 1,000 patients) on New York's Upper East Side but also for his many articles on diabetes (nearly 250). Since 1994, he has also written over 150 columns, "Perspectives on the News," for Diabetes Care. Dr. Bloomgarden studied mathematics at Princeton University and received his medical degree from Albert Einstein College of Medicine, followed by postdoctoral training at Montefiore Hospital in the Bronx and a fellowship at Vanderbilt University Hospital, in Nashville, Tenn. He is currently a Clinical Professor of Medicine at Mount Sinai School of Medicine. He spoke to us about the latest controversy with Galvus, the importance of rimonabant, the potential of continuous glucose monitoring, and much more.

Kelly Close: Dr. Bloomgarden thanks so much for taking time to talk with us.

Dr. Bloomgarden: Oh, it's my pleasure.

Kelly: We wanted to dive right in and ask you about your experience with some of the latest therapies for patients with type 2 diabetes. We've heard a lot about how Byetta patients will go through a cycle of success, where they see some weight loss and they become more encouraged and they experience drops in A1c, which in *turn* makes them more motivated about eating well and exercising. Do you see that with your patients?

Dr. Bloomgarden: I think that's an interesting way of conceptualizing it. Weight is such an important issue for people with diabetes that those people who lose weight with Byetta find it tremendously empowering to continue with the treatment. There may be other benefits as well in stimulating endogenous insulin. It's interesting that Byetta has been mainly used by endocrinologists off-label. Rather than treating people on monotherapy with sulfonylureas or metformin or on the combination of the two, most endocrinologists use metformin in persons who are already on insulin. There are quite a few advantages to administering Byetta to that group. They do get the benefit of weight loss, counteracting the weight gain, which we recognize as an adverse effect of insulin therapy. They have less hypoglycemia than they encounter using rapid-acting insulin. This sets off a positively reinforcing cycle of therapeutic success. Another benefit is the lack of need for time-consuming titration as required with insulin. By allowing endogenous insulin to drive postprandial insulin excursions, it becomes easier to achieve a stable level of glycemia.

Kelly: It's interesting because this kind of behavior was the whole point of the Diabetes Prevention Trial in many ways, no? That makes us wonder about the power of giving patients sort of a "jump-start" with Byetta might be – obviously, we know no one would recommend putting Byetta in the water, on the other hand, isn't the whole problem with diet and exercise that it's hard to convince people to continue working on better diet, better exercise?

Dr. Bloomgarden: To an extent. Recall, though, that weight loss and exercise particularly increase insulin sensitivity, while Byetta has an entirely different set of actions in increasing insulin secretion.

Kelly: How about Januvia – can you give us any broad thoughts on the drug and what you think will happen with patients over the longer term with this therapy? Are you seeing A1c drops?

Dr. Bloomgarden: Yes, with some, although not all patients show dramatic improvement.

Kelly: And the approvable letter for Galvus?

Dr. Bloomgarden: From my perspective, there are three possible explanations (not mutually exclusive):

1. Novartis erred in their studies. This seems not to be the case. They have presented a rather extensive set of studies, and many have been published. The file you sent me gave a nice and very detailed overview – your readers might be interested in seeing it, and should ask you for it!

2. The FDA is unfairly singling Novartis out. Importantly, it is not clear to me that there is a requirement for all medicines with renal excretion or with a metabolite having renal excretion be studied in persons with renal insufficiency, as long as the drug is labeled as not being studied in this group. It would be interesting to see how many of the new drugs approved over the past five years had such studies. If none, then again it seems unfair.

3. The class actually is not safe and neither drug should have been approved.

Kelly: And if you were a betting man …?

Dr. Bloomgarden: I favor alternative 2, that the FDA unfairly has put a burden on this agent. I think the opinion piece by David Nathan is incorrect in its suggestion that the gliptins are of lower efficacy than other drugs and reflects his failure to realize that they were studied at considerably lower baseline A1c levels than the other agents to which he compares them. I think that it is perfectly possible that there are unknown side effects but that the existing safety data is reassuring and that he expresses an alarmist position in the second set of criticisms of his piece. I also think that the FDA recently approved another in a new class of diabetes treatments, inhaled insulin, and I find it bizarre that the same issue of the NEJM with Nathan's piece also had an extremely positive article on Exubera, despite the very real evidence of pulmonary toxicity with this agent.

Kelly: Whew. Switching gears, can you tell us what sort of patients benefit the most from Januvia and how do you feel about the drug so far?

Dr. Bloomgarden: Everything looks like Januvia ought to be a really good drug for diabetes. It gives the same benefits as Byetta with glucose-dependent insulin secretion, and with no need for titration. There's one dose for everybody, and it's not associated with weight gain, although not giving weight loss in the way seen with Byetta. I have found that there's some heterogeneity in patient response to Januvia, so that some patients have very good responses to Januvia and other patients with type 2 diabetes really don't show quite good a response. I think probably we're going to have to learn a little bit more how to use it and how to distinguish those who will succeed from those who will not.

Kelly: That's really interesting… so how do you decide if you put patients on Januvia versus Byetta?

Dr. Bloomgarden: Not everyone is interested in having injected medication. For someone on oral agents we can look at Januvia as a medicine that's very appropriate early on in the diagnosis of diabetes, because insulin deficiency occurs from the very beginning of the diagnosis of diabetes, and because in fact the loss of prandial insulin is much more strongly a feature of early diabetes than is the loss of basal insulin. Thus, the benefit of this agent would be particularly great early in type 2 diabetes – and this describes a huge segment of the diabetic population. An important initial approach to therapy, then, is to start with metformin and then add Januvia, and, perhaps, metformin and Januvia should be started together. One would anticipate such an approach to be associated with very low likelihood of hypoglycemia, little need for dosage adjustment on the part of the physician, and long duration of benefit: a very easy way of treating diabetes.

Kelly: Dr. Bloomgarden, in terms of advantages of incretins, it would be great to get your view on the glycemic-dependent nature of the drugs. Do your patients on Byetta and Januvia monitor their blood glucose less frequently than they did before going on this therapy, because there is less hypoglycemia? Do you think patients on incretins, which are glycemic dependent, should monitor less often? Or, do most take the drugs with SFUs or insulin so they need to monitor anyway?

Dr. Bloomgarden: No, monitoring the blood glucose should also be seen as something that's empowering, and that helps the person with diabetes to understand how the diabetes is doing, rather than viewing it as a burden and kind of a horrible thing that people have to put up with. I just don't see how you can manage diabetes in *anyone*, whether on oral agents or insulin or combinations, without home glucose monitoring, and for that reason, although it's probably true that home blood sugar testing is less required with Byetta than with a basal-bolus insulin regimen, I find it helpful to encourage patients to do it.

Kelly: Do you think that Januvia would eventually become useful in very early diabetes, such as for diabetes prevention?

Dr. Bloomgarden: Well, we don't really know what we're doing with diabetes prevention. The Diabetes Prevention Project was a magnificent and complicated study that in truth generated as many or more questions than it did answers. Metformin was far less effective than the lifestyle intervention in reducing the progression from prediabetes to diabetes – a rather amazing finding. In a similar study, the Finish Diabetes Prevention Program, the lifestyle intervention actually continued to benefit several years after the study was formally ended – offering quite an advantage over pharmacotherapy. In the Finish DPP, there was ongoing benefit of the lifestyle intervention, as reported in a recent *Lancet* article, for years after the study ended. In the DPP, the benefit of metformin lasted precisely as long as the people took the drug, and when the drug was stopped, the rate of diabetes development returned to whatever it would have been previously. Furthermore, metformin is associated with side effects.

Another important concept is that in a certain sense prevention of diabetes is unimportant. What we're really interested in is the prevention of complications of diabetes. The blood sugar, particularly in a study like the DPP, is simply a number on a continuum. If, arbitrarily, the blood sugar is 201 rather than 199, a box is checked and we say "diabetes." But nothing really has happened, unless we can show that the rate of heart disease, of neuropathy, of renal disease, and so on, has decreased.

Kelly: Is your perspective related to the fact that there are no long-term outcomes studies about diabetes prevention right now?

Dr. Bloomgarden: Right, there are no outcomes studies that actually show that we have accomplished anything. That's not entirely fair, as there is indirect data from the TRIPOD study showing reduction in carotid intra-medial thickness. That may be evidence of reduced atherosclerosis, but it can be analyzed in multiple different ways. I'd love to say that I think that thiazolidinediones prevent heart disease, but the fact is that both the DREAM study and the ADOPT study don't exactly tell us that. In fact, there was a little bit of a suggestion of more heart disease in both of those studies with rosiglitazone, one in the setting of diabetes prevention and the other in the setting of early treatment. It becomes quite a dilemma to say we should administer thiazolidinediones or we should administer metformin or we should administer a DPP-4 inhibitor to somebody with pre-diabetes unless we know what we're getting into. It's perfectly possible to design a study which will show that it does do some good, but it would require thousands of people studied for a far longer period than the period of the DPP or the period of the ADOPT study.

Kelly: Which long-term outcomes trials that are going on right now that would help answer this question?

Dr. Bloomgarden: NAVIGATOR is a study of valsartan and nateglinide, and it's a two-by-two factorial design in people with increased risk of developing diabetes. It might be particularly likely to give us useful information in that it's studying a population that was recruited to a large extent with existing cardiovascular disease. That's really the way to go – to recruit persons at high risk for whom there's likelihood of seeing a difference in outcomes. In contrast, in the DREAM study, actual event rates were rather low, perhaps only one quarter of the event rates as seen in the HOPE study. I am sure that power calculations were done on the DREAM study, and that they showed that the study had little

chance of showing an outcomes difference. For such a difference to be seen, one must recruit high-risk persons and measure both cardiovascular outcomes and development of diabetes. I do look at the blood sugar as just an intermediary, a biochemical number. If, then, one gives a glucose-lowering drug and measures the blood sugars in a glucose tolerance test for several years, and finds that the glucose numbers are lower in the people who received the glucose-lowering drug, one has learned little. Were the metformin arm of the DPP and the rosiglitazone arm of the DREAM study then exercises in reinventing the wheel? Given those considerations, I'm much more a lifestyle modification advocate than I am a drug advocate when it comes to prediabetes. Now it may be that obesity therapy is sort of lifestyle in a pill and that maybe is the way to go.

Kelly: Can you give us your thoughts on pharmacotherapy for obesity?

Dr. Bloomgarden: Rimonabant might be very important. I think there's a lot to worry about with depression and anxiety as potential side effects, but as far as the blood sugar benefit, in the RIO-Diabetes study, which appeared several months ago in *Lancet*, there was tremendous benefit of rimonabant in people with relatively early diabetes, three quarters on metformin, one quarter on sulfonylureas. Their mean A1c was 7.2%, and they had a 0.6% fall in A1c with rimonabant. That's huge. There appear to be rather complicated political reasons making it difficult for the FDA to approve rimonabant as a diabetes drug, but it appears hypocritical. A large diabetes prevention study with persons at risk of developing cardiovascular endpoints, might or might not win – but that would be where the money is. If you can show fewer heart attacks, strokes, and so on in people treated with rimonabant, defined in a certain fashion by baseline risk, then you've got an incredibly important drug to fight the epidemic of what Paul Zimmet termed diabesity.

Kelly: This is one of many areas that to us have the potential to become either mightily promising or mightily troubling. In your view, are any other obesity drugs in the pipeline that might be especially promising?

Dr. Bloomgarden: Symlin and leptin may be interesting – but we are waiting for once weekly preparations before we can begin to think about advocating these injected medications for obesity treatment. (Editor's note: Although there are not necessarily any planned once-weekly trials, Dr. Bloomgarden said that is what he would like to see.)

Kelly: The next area we wanted to jump to was your opinion on continuous glucose monitoring and your views on the outlook for the technology.

Dr. Bloomgarden: The number of people who need CGM is high, but we're going to need to demonstrate benefit. The price undoubtedly is a little inflated. That will be forced down a bit. The devices don't have to be changed every three days. A lot of my patients reuse the same device for another three days. Hopefully, rather than costing $10 a day it will come down to $4 a day and will be covered to some extent. That will make a big difference. Also, we need much better data analysis programs.

Kelly: What are the other major improvements you think need to be done, besides the data analysis?

Dr. Bloomgarden: I think it's ready. I think the technology is basically here. Those of my patients who are using it are absolutely getting less hypoglycemia. When the blood sugar really goes up and down all the time, testing finger sticks 20 times a day is not as good as getting a readout 1,400 times a day. In a day to day sense, people with type 1 diabetes need CGM and of course CGM works best in, and is really designed for, pumpers. We're getting closer to a closed loop, with part of the loop being the patient himself. A closed loop not requiring patient intervention will hopefully come, and will be just marvelous for type 1s.

Kelly: How close do you think we are to the closed loop?

Dr. Bloomgarden: That's a huge question and it may be the technology is not really sturdy enough to support independent decision making. We'll just have to see.

Kelly: With CGM there is a lag time between interstitial fluid and blood glucose, although the importance and the time of that lag has been controversial –for you, how much of an issue is this?

Dr. Bloomgarden: That's an issue. It's not quite ideal, and patients will need to learn how to deal with CM as a trend-gathering device rather than as an absolute readout device. We're not going to have intravascular glucose access on an outpatient basis for a really long time. Now that will come in hospitals, and so CGM in ICUs will allow us to test the hypothesis that true euglycemia in the intensive-care setting makes a difference, but that's a slightly different topic, another use of the technology – a very important use but in a different area.

Kelly: That's very interesting because of course Dr. van den Berghe's data suggests keeping patients under intensive insulin management in the ICU is very beneficial to outcomes.

Dr. Bloomgarden: Right. I'm a believer. I think, on balance, data really do suggest that it's true. I think the problem is you need to have an incredibly organized nursing support staff to do it because the ICU nurses treat the patients' blood sugar, not the physicians. And so you have to have a usable algorithm, and it's not easy to measure the blood sugar in the ICU, because patients have arterial sampling lines and nurses have to glove up and take out blood and then discard some and then you get some more blood and then you test it. Each blood glucose measurement done properly in the ICU is, then, very expensive, and complicated, and a huge nursing burden. When we have intravascular CGM, it will be like continuous blood pressure and continuous EKG measurement, available to every person in every ICU in the United States, and extremely useful in terms of therapeutic decision-making.

Kelly: Do you think it would be useful outside of the ICU, in other hospital wards? We have been very struck, for example, by Dr. Tony Furnary's data showing the importance of tight glycemic control in critical care.

Dr. Bloomgarden: It'll be a little more complicated to do it … we'll just have to see. First we'll have to do it in ICUs and there's a tremendous amount yet to be done in ICUs.

Kelly: Thank you so much for all your work in diabetes and for sharing your thoughts with our readers today.

--Jenny Jin, Dan Belkin, and Kelly Close

4. Conference Reports

- **ADA Postgrad, February 23-25, New York, NY**
  We always find this meeting particularly useful for understanding what clinicians are thinking because so many of the attendees come for the CME, and may not go to many other meetings throughout the year. Many of the lectures were very pedagogical and the workshops very clinic-focused and user-friendly. Below we present our learnings and perceptions of how certain classes of therapies are evolving.

  Don't worry about Byetta – it'll still be huge. We've seen a lot of concern from analysts over the past few months about a slowing of prescription growth for Byetta due to the entry of DPP-4 inhibitors to the market, but from what we heard at this meeting, Byetta is still a growing behemoth. Prescription growth may be slowing, but we suspect now that this has a lot to do with the level of sampling that Amylin and Lilly are doing – we heard several HCPs talk about how their refrigerators are just stuffed with Byetta samples. This year's meeting also made a nice contrast to last year, where there were still a lot of clinicians who hadn't heard much about the drug. We did hear Dr. Robert Ratner of Medstar make the interesting point that the two-year data for Byetta suggest that while A1c drops are maintained and weight loss is progressive over time, patients aren't actually able to discontinue their other oral antihyperglycemics, which suggests to him that there may not ultimately

be any β-cell regeneration. Of course, this may be because the patients are just too advanced for that – which is why he said he would like to see Byetta being tested in earlier patients.

Outlook for DPP-4 inhibitors is more of a mixed bag, but everyone agrees that Januvia is huge. It's not a question in our view of whether Januvia will be a blockbuster – it's only a question of how many billions it will bring in. It sounds like a surprising majority of type 2 patients, when given a choice between Byetta and Januvia, would choose the latter even over the potential to lose weight simply because they don't want to go on injections. We heard concern, however, about the fact that DPP-4 has at least 62 other natural substrates in the body, which means that inhibiting it may be a disaster waiting to happen. We think the clinical profile has been very clean so far – Januvia is at least highly specific to DPP-4 with little cross-reactivity for the other DPPs. Galvus, while also specific, seems to be a little *less* so, according to Dr. Ratner. Regarding the monkey skin lesions – it remains unclear what exactly these are, but we heard that it may actually be a class effect because BMS has seen similar results with saxagliptin, and Merck's analogous trials were done in a different species of monkey at lower doses… at this point it is unclear whether this is one of the issues prompting the approvable letter, but if it is, it will be interesting to see whether it goes onto Galvus' label, and whether Januvia's label will be affected.

Lots of interest in incretins in prediabetes. There's continuing interest in seeing Byetta tested for prediabetes, but the general expectation among experts is that Amylin is waiting for LAR to do that. Expert opinion also suggests that DPP-4 inhibitors should work best in early diabetes (before loss of endogenous GLP-1 secretion and deterioration of β-cells) and we heard more than one doctor say that using these drugs as early as prediabetes would make sense. We note that absolute safety and tolerability is very important for a prediabetes label – a diabetes drug may not need to have perfect tolerability, but a preventive drug likely will. In that vein, incretin mimetics are generally viewed as a safer long-term therapy than DPP-4 inhibitors, and we agree that there's *less* likelihood of adverse effects cropping up when administering a single peptide as opposed to inhibiting an enzyme that affects dozens of peptides. On the other hand, incretin mimetics really aren't natural endogenous hormones, even if they resemble GLP-1, and there is still risk of immunogenecity. We think Byetta is good and LAR will be safe, but some caution with any new therapy – even exenatide – should not be abandoned.

Symlin is difficult to use but patients who use it love it. There weren't any talks explicitly on pramlintide at this conference, but the doctors who have prescribed it say that their patients love it. It isn't easy to prescribe, they say, but the weight loss is better than with Byetta. Dr. Jack Leahy noted that patients who don't respond as well to exenatide often actually do very well on pramlintide and lose a lot more weight. We (and others) have wondered all along why Amylin has chosen not to develop exenatide for weight loss and it's probably a multitude of reasons – they're waiting for LAR, they own all of Symlin and only half of Byetta, etc. – but efficacy is also another good reason.

Negativity on TZDs and hopes for cleaner insulin sensitizers. TZDs didn't receive as much attention at this meeting – incretins occupied the limelight, along with Dr. Sidney Wolfe, who got much more attention and applause than we had expected. We chatted a bit about PTPIb's with a thought leader, and what the potential was ther3 for a new type of insulin sensitizer that works without weight gain. Insulin resistance is a huge problem in type 2 patients and actually contributes, we think, to the difficulty of getting type 2 patients to A1c goal, sometimes even after they're put on insulin therapy. Having something with a cleaner side effect profile would really help patients. DPP-4 inhibitors have offered clinicians a safer alternative to sulfonylureas – a safer alternative to TZDs would be a wonderful next advance.

Direct-to-consumer (DTC) advertising is growing in importance. One really interesting point that we were reminded of at this meeting is just how much diabetes is a primary care disease. There simply aren't enough endocrinologists to treat the vast numbers of patients with diabetes and unfortunately, PCPs' prescribing patterns tend to have little to do with practice guidelines and a lot to do with whatever they're familiar and comfortable with. Newer therapies take much longer to penetrate primary care markets than specialist markets, which is why DTC will become more important. Endos don't really pay attention to it, but PCPs do and patients do, and they are the major players in diabetes care – which at its best is very patient-centric and patient-driven. The big DTC campaign that we'll be watching is Pfizer's Exubera, which is supposed to begin in the second half of 2007.

The ADA/EASD algorithm for type 2 is controversial. We were surprised, when this algorithm was published in August 2006, that it didn't include any of the newer therapies. Many of the HCPs we talked to at Postgrad suggested that more evidence is needed before they can be included, but many also said that exenatide should have been part of the practice guidelines. We also heard the algorithm's suggestion that patients being initiated to insulin go on basal insulin first questioned on multiple fronts – by doctors who think prandial insulin is the way to go and by doctors who think exenatide should be tried first.

Cliché as it sounds, earlier, more aggressive therapy is catching on with clinicians. The mantra of earlier, more aggressive therapy has been carried by pharma for quite some time now, but we sensed that HCPs are really getting on the wagon now as well. We expect to see much more utilization of pharmacotherapy in the coming years for several reasons: 1) patients are taking more drugs because of the use of combo therapy, 2) patients are taking drugs longer because they're starting earlier, and 3) there are more patients because of better diagnosis and also a growing incidence of disease. Interestingly, one of the consequences of this may actually be *later* insulin therapy, as we got the sense that at least endocrinologists are really trying Byetta before initiating patients on insulin. It's an open question whether the durability of effect for incretin mimetics is going to be better than for existing drugs, but if so, the lag time to insulin will only increase more.

Universal caution on inhaled insulin – from specialists, at least. We've written before about the hassle factor with Exubera, and what we heard at this meeting underscored the real importance of this issue. One clinician who has done a lot of inhaled insulin trials told us that the Pfizer data on patient satisfaction and preference for inhaled insulin are actually totally meaningless because the patients who go on these trials are self-selected, so of *course* they like the stuff. Meanwhile, HCPs are universally worried about long-term safety. On the flip side, in some ways Pfizer's launch to endos is something of a futile cause and the failure of Exubera to take off in the specialty market may not reflect what will happen in the primary care market. After all, endos don't have the same reservations about initiating insulin therapy as PCPs do, and the patients who see them are more likely to accept injections as well. Most endos also don't have the necessary spirometry equipment in their offices to perform PFTs – though we note that the PFT tests will not exactly be convenient for PCPs either.

Rimonabant was not mentioned much. We did hear Dr. Ratner point out that the weight loss with Byetta is not as good as with rimonabant. However, it's also progressive weight loss with Byetta as opposed to a fixed drop and weight maintenance with rimonabant.

CGM and pumps got little attention. On the issue of pumps, we point out that many HCPs haven't even yet heard of Insulet, even though the company has filed to go public – we look for fast days ahead. On CGM, we're looking forward to the next generation of device and for Abbott's device to be approved. With CGM, as with SMBG a few decades ago, it will really take a lot of money and work from industry to convince payers that this is a worthwhile new technology and for DexCom to go at it

alone means that reimbursement has been very difficult so far, though we do hear a few anecdotes here and there of private insurers paying for it in isolated cases.

- **EuDTT, February 4-6, 2007, Montpellier, France –**
  Below we present our conference highlights from the 1st European and Diabetes Technology and Transplantation Meeting. Overall, we felt the meeting was fairly positive in tone, but little new has happened over the past year (and certainly since the DT&T meeting in November 2006 in Atlanta). Continuous glucose monitoring is maturing slowly, and there was a general sense that we should not wait for huge improvements in accuracy (which is limited by possibly unavoidable physiological lag times anyway) but should use the technology to improve patient care now. Reimbursement remains a sore subject and challenges in outcomes testing remain – we lack good trials to prove to payors that this technology is worthwhile. Islet transplantation, non-invasive monitoring, and inhaled insulin were lesser topics at this meeting but also received their share of the attention. Overall, an interesting meeting with good speakers – we particularly enjoyed the discussion group on CGM, even if more industry reps seemed to be present than doctors!

  Continuous glucose monitoring (CGM) is slowly maturing. There are new technologies and strong results from the more established manufacturers. To paraphrase Dr. Aaron Kowalski of the JDRF, it's not a question of if CGMS will greatly change patients' lives, but when. We respectfully still say it's "if" due to product quality and reliability issues and the absence of reimbursement and the power of managed care, but we certainly look to Dr. Kowalski the area is poised for success.

  The notion that 'perfection is the enemy of the good' was a big catchphrase here – there was general agreement that patients should have easier access to technology, such as CGMS, if it can safely improve their lives. In other words, the standard for regulators should be patient outcomes rather than statistical indications of accuracy. Most of the participants in the CGM discussion group we attended agreed that while accuracy isn't perfect, it's good enough already to be of clinical use to patients. We agree and note that outcomes studies are in the works but haven't been seen yet with the newest technologies.

  Reimbursement for CGM (and even insulin pumps) remains difficult across the globe. US payors seem to be looking for the following: (1) Decreases in A1c – not excursions or anything else. A1c is the gold standard. (2) Reductions in severe hypoglycemic episodes. A reduction in days out of work also counts. (3) Durability of effect. The insurers need to believe people will actually use CGM when they aren't in a trial.

  We are clearly not going to see a fully closed-loop artificial pancreas (AP) any time soon, but in early work, the hybrid (semi-closed loop) algorithms seem quite promising. (This is where patients 'announce' meals, so the algorithm doesn't get caught out by rapid blood glucose changes). The experiments are in controlled situations and *in silico*, so we should be skeptical - but the hybrid algorithms actually do better than a majority of patients would do themselves. We expect that this technology will still take a while to reach the market, and as always reimbursement is a major question, but there is an exciting base of science.

  Results from advanced modeling techniques for AP algorithms were presented at this conference. It's good to see more sophistication in algorithms. There are still, however, some significant issues with inter- and intra-patient variability.

We didn't find the islet cell transplantation talks of wide interest, except to note the discussion around how exenatide might one day be instrumental in islet cell transplants, depending on whether β-cell preservation is being seen. This is still quite speculative.

Non-invasive monitoring remains an area of skepticism. We weren't that impressed with the technology. Despite over >5,000 patients issued and dozens of companies in the field, we've yet to see a reliable, convenient device emerge and don't expect one for some time.

We attended a single talk on inhaled insulin, which was somewhat more positive than we expected. The speaker concluded that inhaled is valuable for type 2 diabetes and is comparable to subcutaneous injections. Anecdotal evidence from doctors we've spoken to indicate otherwise – huge issues with convenience and dosing with Exubera remain, as well as the perpetual worry about long-term outcomes and safety.

—Conference reporting by Daniel Belkin, Jenny Jin, John Close, and Kelly Close

5. FDA releases new draft of recommendations for obesity drug development

On February 14, the FDA placed a long-awaited new draft of its recommendations for developing obesity drugs on its website, entitled "*Guidance for Industry Developing Products for Weight Management*." This draft is an updated version of a report that was first completed in September 1996, and it incorporates suggestions that have been made since the FDA invited public commentary in January 2004. This latest draft is also open to public commentary and includes three new sections: 1) guidance for pediatric obesity, 2) guidance for drug-induced obesity, and 3) guidance for combination weight-loss drugs. The introduction of the draft ends with a note that the guidances are only suggested or recommended, not required, for drug approval. Below we provide our main takeaways followed by a full-length assessment of the FDA draft.

Main Takeaways

- *Drugs for treating medication-induced obesity must be carefully tested for drug-drug interactions, and labels will only be granted for the treatment of weight gain caused by specific drugs, not by drug classes. Biologics/proteins must be evaluated for immunogenic potential and CNS-acting drugs for neuropsychiatric function and abuse potential.*
- *The FDA will evaluate single fixed-dose combination drugs if phase 2 trials show at least an additive effect compared to monotherapy with each. Phase 3 trials of combination drugs will be evaluated on the same basis as single drugs.*
- *The pediatric guidelines are fairly progressive in acknowledging the potential utility of pharmacotherapy in obese children. They differ from adult guidelines in that efficacy is measured by BMI change rather than weight change – a surprising endpoint, in our view, as pediatric obesity might better be assessed by BMI percentile.*
- *Primary efficacy endpoints for obesity drug trials have not changed. The FDA believes that secondary endpoints should include changes in blood pressure and pulse, lipoprotein lipids, fasting glucose and insulin, A1c (in type 2 diabetes patients), waist circumference, the proportion of patients who are on concomitant medications, and quality of life.*
- *In terms of stand-alone indications for weight-related diseases, the FDA requires that a drug has a weight-independent effect in order to get a separate indication. Encouraging, we think, is the fact that the guidelines allow for the potential that a drug might receive a separate indication for either the treatment or prevention of weight-related disease such as type 2 diabetes.*
- *The FDA believes that a potential drug for metabolic syndrome should normalize or improve all of the components of metabolic syndrome independently of weight loss – this seems like a fairly stringent requirement to us. The guidelines indicate that the FDA still does not consider the syndrome a disease entity. On balance, we believe this makes it more rather than less difficult for*

companies to get a label that even refers to IGT or IFG, and we also believe that this makes Sanofi's job with rimonabant even tougher.

Definition of medical weight loss

- **Medical weight loss is defined as "a long-term reduction in fat mass with a goal of reduced morbidity and mortality**." Notably, this definition includes improvements in biomarkers as well as weight – blood pressure, lipids, and A1c are cited. We believe this reflects the thinking that obesity products ("weight management products" is the actual phrase used throughout the document) have to actually improve outcomes, not just reduce weight. Blood pressure, lipids, and A1c are all surrogate measures of outcomes risk. The FDA notes that weight loss and maintenance must be shown over at least one year.

Background on adult and pediatric obesity and weight loss

- **Obesity is defined as "a chronic relapsing health risk"** – not a disease. The report notes that its causes include genetic, environmental, and behavioral factors, which does not absolve patients of blame but is broad enough not to point to any one cause in particular. A table classifies people by BMI as underweight (BMI under 18.5), normal weight (18.5 to 25), overweight (25 to 30), and obese (over 30). While obesity is stratified into class 1 (30 to 35), class 2 (35 to 40), and class 3 (over 40), the overall focus of these guidelines implies that the main target population for weight loss drugs is overweight and class 1 obese individuals. We aren't sure whether the FDA believes patients with higher BMI would use surgical options (clearly only a minority have to date, just over 200,000) or whether they are just focused on the groups that would start to take the weight management remedies – we suspect the latter. We think more extreme obese patients would still take weight loss drugs, but they are probably more likely to discontinue because the drugs don't work well enough. The guidelines note that waist circumference is a good measure of visceral fat.
- **Five percent weight loss remains the recommended goal**. This amount of weight loss has been shown to improve metabolic and cardiovascular risk factors, though no randomized controlled trials have proven yet that weight loss ultimately reduces outcomes such as cancer, CVD, and mortality. The guidelines emphasize that only patients who fail lifestyle modification, and for whom the benefits of weight loss would outweigh the potential risks of pharmacotherapy, should be considered. The suggested patient population remains unchanged: people with BMI $\geq$30 or with BMI $\geq$27 who have accompanying comorbidities.
- **Pediatric populations are also discussed**. The American Academy of Pediatrics defines obesity as BMI $\geq 95^{th}$ percentile for a child's age and sex. For patients aged 2 to 7 years, they recommend lifestyle modification if BMI is $\geq 95^{th}$ percentile and there is an accompanying comorbidity. For patients aged 7 years or older, the requirement is less stringent: BMI $\geq 95^{th}$ percentile or BMI $\geq 85^{th}$ percentile with comorbidities. As with adult patients, pharmacotherapy is only suggested after failure of lifestyle modification.

Recommendations for clinical trials

- **Phase 1 and 2 trials** should include patients with a broad range of BMIs (27 to 35) and drug doses – all the way from no effect to maximum tolerated dose. These studies should show efficacy differences between all active doses and placebo. The FDA suggests that companies decide early on if the drug will be fixed-dose or titrated.
- **Phase 3 trials** must include sensible lifestyle modification programs and assess the drug in a variety of patients (in terms of demographics and race), including at least a subpopulation of patients with BMI >40. They should include at least 3,000 patients on active drug and 1,500 patients on placebo for at least one year. Phase 3 trials should also include trials devoted to type 2 patients, which the FDA acknowledges as a more difficult population for weight loss.

- **Primary endpoints** remain unchanged from before: the difference in mean percent weight loss between drug and placebo, and the difference in the proportion of subjects who lose at least 5% of body weight between drug and placebo.
- **Secondary endpoints** that should be included are changes in: blood pressure and pulse, lipoprotein lipids, fasting glucose and insulin, A1c (in type 2 patients), and waist circumference. The authors note that waist circumference is not an adequate proxy for visceral fat – CT or MRI scans are needed. Other suggested endpoints include the proportion of patients who are on concomitant medications and quality of life. The FDA expects that weight loss drugs will improve blood pressure, lipids, glycemia, and other parameters because these would be indirect effects of weight loss.
- **Safety assessments** should include measurements of body composition in a "representative sample" of clinical trial subjects to make sure drugs are causing fat-specific weight loss. Certain drugs will warrant specific safety assessments: 5HT receptor system drugs must be assessed for valvulopathy, and CNS-acting drugs should be assessed for neuropsychiatric effects and abuse potential. All protein drugs (biologics) must be assessed for immunogenic potential.
- **Patient withdrawal** is common in weight-loss trials, which is why the guidelines urge companies to perform intent-to-treat (ITT) analyses of their trial data. Patients who withdraw from trials should still be assessed at what would have been the end of their trial period. Graphical presentations of data are required.

Metabolic syndrome

- **The guidelines clearly indicate that the FDA does not recognize metabolic syndrome as a disease entity because no single cause has been isolated for the syndrome.** Nonetheless, the high prevalence of the syndrome in adult Americans (~25%) is noted, and the guidelines implicitly acknowledge the need for products to treat the syndrome. The document notes that products to treat individual factors in the metabolic syndrome are available, but "ideally, a therapeutic product intended to treat metabolic syndrome should *normalize* or improve *all* components of the syndrome, independent of weight loss." The guidelines also say that a potential product for metabolic syndrome would ultimately have to be shown to prevent type 2 diabetes and to reduce cardiovascular outcomes. To us, this was perhaps not surprising, but it does certainly indicate that getting a label showing a drug reduces metabolic syndrome will be very difficult indeed. Note that the phrase "cardiometabolic health" was not mentioned in these guidelines.
- **We think the emphasis on a benefit *independent* of weight loss is interesting – this description sounds like an extremely high bar to meet, not because all of the components of the metabolic syndrome must be addressed, but because they must be improved independently of weight effects.** We're not sure many physiological systems directly affect *all* of the components of the syndrome. It's also probably not necessarily obvious to show how much of the improvements observed with a drug are indirect effects of weight loss or direct effects. Sanofi has said that rimonabant's metabolic effects are roughly half independent of weight loss, which we assume is probably not really good enough. Although Sanofi is clearly committed to an extensive clinical program, in light of its phase 3 RIO trials, SERENADE trial for a possible diabetes stand-alone indication, and CRESCENDO trial program for showing long-term outcomes, we don't think it would be able to obtain an MS label for quite some time.

Combination drugs:

- **Two or more products in single fixed-dose combinations are permissible only if the combination has an additive (or more) effect.** The guidelines indicate that phase 2 trials for such a combination product would have to compare the efficacy of the combination with the efficacy of each drug alone. Once additive effects are established, phase 3 trials may just compare

the combination with placebo. The final product would be evaluated by the same standards as single drugs (above).

Drugs for medication-induced weight gain

- **Clinical studies**: This is for patients who gain weight on psychotropic, anticonvulsant, and other drugs. Potential patients would have to have documented weight gains of >5% within the first six months after starting a drug known to cause weight gain. The guidelines call for careful drug-drug interaction studies and explicitly warn against the use of serotonin receptor agonists in patients who are already taking proserotonergic agents for psychiatric disorders because of the risk of serotonin syndrome.
- **Labeling limitation**s: Any approvals would be limited to specific drugs – i.e. if X is approved to treat weight gain caused by Y, it cannot be given to patients who gain weight on Z even if Y and Z are from the same drug class. We imagine that this would limit the potential benefits of filing for medication-induced weight gain indications. However, many psychotropic drugs are so widely used (Lilly's Zyprexa, for example) that even an indication for use with just that particular drug could open a huge potential market.

Product labeling and stand-alone indications for co-morbidities

- **Secondary endpoints**: The final label for a weight management product may not include all of the secondary endpoints included in clinical trials. Whether specific secondary endpoints are included in the label will depend on the degree to which they improve in the clinical trials.
- **Stand-alone indications:** If a company wants to file for a separate indication for the prevention or treatment of a weight-related comorbidity such as diabetes, dyslipidemia, or hypertension, the drug must be shown to have a weight-independent effect on that co-morbidity. This sounds very sensible to us – a drug must have a direct effect on a disease if it's going to be indicated for that disease – and we think it's encouraging that the FDA recognizes the possibility of drugs for the treatment and *prevention* of weight-related diseases. Overall, we believe this makes it much tougher for rimonabant to get a label for diabetes.

Pediatric patients

- **Patient populations**: The guidelines say that drugs should only be evaluated in pediatric patients after phase 3 trials in adults have been performed. Pediatric trials should include only children with BMI $\geq 95^{th}$ percentile for a child's age and sex and should be at least one year long. The guidelines recommend that initial trials be limited to adolescents (aged 12 to 16 years) and patients with accompanying comorbidities (type 2 diabetes, dyslipidemia, or hypertension). No explicit guidelines for sample sizes are given.
- **Efficacy endpoints**: For children, efficacy endpoints should be based on change in BMI rather than weight. We're somewhat surprised to see this – we thought that efficacy would be based on change in age-adjusted BMI percentile, since appropriate BMI ranges for children change as they grow.

—Jenny Jin and Kelly Close

6. Bill Clinton to speak at the first Global Changing Diabetes Leadership Forum

If there was ever a disease that needed global leadership, it's diabetes.

Twenty years from now, according to IDF statistics released in Cape Town in late 2006, 380 million people are expected to have diabetes, 300 million of whom will be in developing countries. What is stunning about that number is that 20 years ago, an estimated 35 million worldwide had the disease.

By our count, that's an increase of almost 1,000% in just two generations. We won't say that the sky is falling, but we do believe that Chicken Little is on red alert.

We were pleased that the UN in December passed a resolution on diabetes that marked the first time a non-infectious disease has been recognized in that fashion. Acknowledging the crisis is a good first step.

Now Bill Clinton steps to the plate as the keynote speaker next month for the Global Changing Diabetes Leadership Forum. The event, in New York on March 13, is hosted by Novo Nordisk; according to a company spokesman, the forum's goal is "to chart a course" for the future of diabetes care and the management of the epidemic. About 150 attendees are expected, with representatives from healthcare institutions, governments, academic institutions, and patient associations. They include many of the usual suspects, but also acclaimed author Malcolm Gladwell.

Diabetes has indeed reached the Tipping Point.

Professor Arthur Miller of Harvard Law School will chair a panel of other high-profile international thought leaders:

- Professor Martin Silink, president of the IDF;
- Dr. Herbert Pardes, president and CEO of the New York-Presbyterian Hospital and Healthcare System;
- Dr. Francine Kaufman, director of the Comprehensive Childhood Diabetes Center at the Children's Hospital Los Angeles;
- Dr. V. Mohan, president of the Madras Diabetes Research Foundation in India;
- Professor Elizabeth Teisberg, of the Darden School of Business at the University of Virginia;
- Professor David Matthews, of the Oxford Centre for Diabetes, Endocrinology, and Metabolism;
- Dr. Julio Frenk, former Mexican Minister of Health;
- Guy Barnett, an Australian Liberal Senator;
- Lars Rebien Sørenson, CEO of Novo Nordisk.

What interests us is whether Bill Clinton is simply giving a speech to earn another generous fee, or whether he takes a real interest in the problem and is willing to exert his considerable influence – political, financial, moral – to improve the lives of diabetic patients. And who knows? He may learn a few things at the forum, so the next time he bumps into his wife, he could educate her as well and raise the glycemic index of the presidential campaign.

—by Daniel Belkin and James Hirsch

7. Know Your Numbers, Outlive Your Diabetes - New Book on Diabetes Gives Patients a Nice Framework for Their Care

Some years ago, as part of a routine physical exam, my endocrinologist instructed me to provide a 24-hour urine sample. I don't recall that he told me why, but I assumed it was important. Then a funny thing happened – no one told me the results. So after about two months, I called the office and asked one of the assistants.

To my surprise, we had a problem.

The test showed trace amounts of albumin in my urine. I had no idea what that meant, and the assistant didn't say much, except to note that I needed to speak with the doctor. (Thanks.) Fortunately, my brother is a diabetologist, so I promptly called him; and he explained that microalbumin is a protein, and its presence in urine indicates early damage to the kidneys. No need to panic, he said: if caught early and treated, the problem can be reversed.

I went on an ACE inhibitor, moved to a new city, got a new endo. Subsequent urine tests revealed no microalbumin, and my current doctor believes the original result was a false positive. (Improved testing has also eliminated the need for 24-hour urine samples.)

The episode is a reminder why patients will benefit from a new book, "Know Your Numbers, Outlive Your Diabetes," which provides a wonderful framework for tracking your care. It describes five essential tests that patients need to take on an ongoing basis – what the exams measure, what the numbers mean, and what to do if the results indicate a problem.

The book is co-written by Dr. Richard Jackson, Director of Outreach at the Joslin Clinic and Senior Investigator in the Research Division at the Center, and Amy Tenderich, a journalist who, after developing type 1 diabetes in 2003, launched a successful diabetes blog (www.DiabetesMine.com). Part of the book's strength is the blending of authoritative medical information with the real-world experience of living with the disease. The authors, for example, emphasize the need for patients to be realistic in their care – eschewing the Platonic ideal of glycemic perfection that some authors advocate.

Breaking new ground in a diabetes book isn't easy. As the epidemic has spiraled, dozens of "how-to" books have been published in recent years – how to maintain normal blood sugars, how to eat properly, how to care for your eyes, your feet, and your heart; how to exercise or, for that matter, how *not to exercise* and still maintain good control.

"Know Your Numbers, Outlive Your Diabetes" is also a how-to book. In straightforward prose, the last two-thirds cover the usual bases (exercise, food, medications, hypos, complications, travel tips, etc.). It's a good primer for newcomers to diabetes and a solid, if overly long, refresher for diabetic veterans. But the book's real value is its first 100 pages, in which the authors isolate the five key areas, or "health factors," that patients need to monitor to ensure a long and full life. My guess is that most patients know about some if not all of these areas, but the book lays them out in a clear, accessible fashion. You should know your numbers for these five areas:

- A1c, which measures average blood sugar levels over a three-month period.
- Blood pressure, which predicts cardiovascular risk and should be taken at least every six months.
- Lipids, which refer to different types of fat in your blood and have been linked to increased risk of heart disease and stroke; should be tested annually.
- Microalbumin, which, as noted, refers to protein in the urine and is a sign of kidney damage; should be tested annually.
- Eye exams, which screen for retinopathy, or changes on the retina; should be tested annually.

Dr. Jackson and Tenderich recommend creating a "Diabetes Health Account," in which you add or subtract "money" based on your scores. But the real value of the chart, at least initially, is not what the numbers say but simply that you know what they are. I have to admit that while I have my blood pressure taken once a quarter and my lipids tested once a year, I have no idea what my actual results are. I trust that my doctor would tell me if they were too high, but not every patient, myself included, should be that trusting.

The good news is that if any of these tests reveal problems, patients can do something about it – *as long as the problem is caught early enough*. In this sense, the authors not only create a coherent framework for your health but also deliver a message of empowerment. The burden falls to the patient to act and act now.

The book is actually written for patients with type 2 diabetes, though most of the material is relevant to all types of diabetes, and type 1 patients will appreciate the overview of insulins, pens, and pumps. The text also might have been better shorter and less repetitive…but these are quibbles.

I'm not exactly sure how you "outlive your diabetes," as the title says. I suspect that my diabetes will end on the day that I end. But I salute the authors' intentions: they don't want your diabetes to cut your life short. Knowing your numbers – and having this book – will help you do that.

—by James S. Hirsch

8. In the News

This column highlights items in the news that caught our eye. In this issue, read about why the JDRF will support big pharma and how pop campaigns are encouraging Americans to be healthy.

- ***Wall Street Journal* cites "blockbuster-itis" for why charities like the JDRF are funding for-profits:** A *WSJ* article on January 26 features the JDRF as a nonprofit that turned to funding for-profits out of frustration with the rate of translational research. Academic scientists who have traditionally received funding are making discoveries that larger pharmaceuticals and biotech companies simply are not picking up. The author cites "blockbuster-itis" as a reason – companies want to develop compounds that are surefire, quick (in drug-development terms), billion-dollar drugs – and that disqualifies many academic breakthroughs. Very high-profit drugs will likely not come from diseases with relatively small populations – Parkinson's disease, Spinal Muscular Atrophy, and type 1 diabetes (which the author writes is a group of "'only' 1.7 million people in the U.S."). However, investments from the JDRF and other nonprofits are sometimes enough to make development worthwhile. JDRF board member Michael White tells the *WSJ* that the organization knows donors may not have had this in mind but that it's time to take treatments to market. We're curious to know what happens if JDRF's investments return large profits for them; we assume it will just mean more to reinvest, perhaps a necessary way to keep certain compounds moving forward. The JDRF has funding agreements with MacroGenics, Sangamo BioSciences, Transition Therapeutics, and TolerRx. ["Why Nonprofits Fund For-Profit Companies Doing Drug Research" – January 26, 2007 – Sharon Begley]
- **Shrek encourages children to "get up and play, an hour a day."** The U.S. Department of Health and Human Services unveiled a campaign against obesity on February 1 using Shrek, the big green ogre, and his on-screen friends to encourage children to be active. HHS estimates that 18% of American children are overweight, and the CDC estimates that the number has more than tripled since 1980. DreamWorks, the studio that produces *Shrek*, told the *Wall Street Journal* that Shrek's imperfections make him a good spokesperson – "If Shrek can do this, anyone can." Ironically, DreamWorks partners PepsiCo and McDonald's are helping to support the campaign against obesity. Omnicom Group's GSD&M created the campaign *pro bono*, and ads will run in donated space. [see the ad at www.HealthierUS.gov; *WSJ* – "Shrek, a Massive Beast, Stars in Campaign Against Obesity" – February 1, 2007 – Merissa Marr]
- **Novo Nordisk launches DiVabetic campaign, which kicks off in New York City:** We attended this event, held on February 22 at the grand Gotham Hall in New York City. Four hundred guests – mostly women with type 2 diabetes – showed up for a night meant to combine diabetes education with self-celebration. Guests talked one-on-one with diabetes educators at a series of booths, focusing on setting goals, eating healthy, and exercising, while taking advantage of makeovers, massages, and hors d'oeuvres (healthy ones, with carb counts listed!). There were two successful pilot events last year and there will be six more events across the country this year. Novo Nordisk funded the entire event and educated guests about some of its products at a small booth. We felt that guests responded very positively and welcome novel ways to encourage awareness, adherence, and prevention. [www.divabetic.org]

—by Daniel Belkin

9. Reviewing the Diabetes Literature – Dr. David Nathan's damning Januvia *NEJM* editorial

Below is our list of the most important articles on diabetes and obesity that have been published since our last DCU, along with our quick review of one of the more interesting editorials published this month, by Dr. David Nathan in the *New England Journal of Medicine*. Our team is always looking for the most relevant articles on new diabetes research, and below we've compiled papers from journals such as *Clinical Diabetes, Diabetes Care, Diabetes, JAMA, Nature, NEJM, Lancet, PNAS,* and more.

- *Ann Int Med - Ann Int Med - Intensive intraoperative insulin therapy vs. conventional glucose management during cardiac surgery - Gandhi et al*: The authors randomly assigned 400 cardiac surgical patients to tight glycemic control during surgery or usual care. All patients received tight glycemic control after surgery, in the cardiac ICU. The two groups had the same overall rate of adverse events, but the intensive treatment group had more strokes (8 vs. 1) and deaths (4 vs. 0). The authors conclude that tight intraoperative control offered no advantage and may cause harm.
- *Ann Int Med - Does tight blood glucose control during cardiac surgery improve patient outcome - Van den Berghe*: Dr. Van den Berghe's editorial is a reality check on the negative results of the Gandhi et al paper. She emphasizes that all of the patients in this trial had intensive glycemic control after the operation, so the only difference between the two groups was whether intensive control was started before or after the surgery. She points out a few other flaws in the study and concludes larger studies are needed to understand the effect on intensive control during story. In the meantime, this doesn't change the strong evidence (including her own studies) that intensive control in the ICU after surgery does improve outcomes.
- *Arch Ped Adol Med - Serum lipids and glucose control: The SEARCH for Diabetes in Youth Study - Pettiti et al*: This study looked for an association between serum lipid concentrations and glucose control in youth with diabetes and found strong associations for both type 1 and type 2 diabetes. As expected, the link was stronger for type 2 - these kids probably have other components of the metabolic syndrome and are obese - but the fact that there is also an association in type 1 shows that dyslipidemia should also be a concern for type 1 patients who don't have good glucose control.
- *Clin Diabetes - Diabetes: Magnitude and mechanisms - Fowler:* As diabetes continues to become an increasingly important part of any medical practice, *Clinical Diabetes* has begun a new feature (called "Diabetes: A foundation") in which it will devote an article in every issue over the next three years to reviewing the basics of diabetes care for doctors in internships and residencies. The articles will provide practical information for use in the clinic. This first article is a review of the scope of diabetes and the specific features of different types of diabetes: type 1, type 2, gestational, and a few of the less common ones.
- [***]*Diabetes Care - Point/Counterpoint: Pulmonary inhalation of insulin: another "brick in the wall"* vs. *No time to inhale: arguments against inhaled insulin in 2007 - Cefalu/Nathan*: This is a debate on whether inhaled insulin is an efficacious and worthwhile tool in the treatment of diabetes. In Point, Dr. William Cefalu argues that the convenience of inhaled insulin will lead to improved control through better compliance. In Counterpoint, Dr. David Nathan counters that inhaled insulin results in substandard glycemic control, which makes him worry that patients will further sacrifice glycemic control for the sake of convenience. While we agree with both doctors, we think that any technology that improves the overall glycemia of the population has the potential to reduce complications and long-term costs, and that inhaled insulin may have a place in diabetes treatment as the technology improves and as the long-term safety data emerges.
- [***]*Diabetes Care - Point/Counterpoint: Consider all proven therapies within a comprehensive approach* vs. *The power of lifestyle management - Gerstein/Tuomilehto*: This is a debate on whether

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

pharmacotherapy should be used to prevent diabetes. In Point, Dr. Hertzel Gerstein argues that any treatment that works should be used, beginning with lifestyle interventions and, when those fail, pharmacotherapy. In Counterpoint, Dr. Jaakko Tuomilehto counters that lifestyle intervention is more effective, safer, has longer-lasting effects, and is more economical than drugs. While we agree that a healthy lifestyle prevents diabetes most effectively, the reality is that most people do not successfully change their lifestyles. We think ruling out drugs because they aren't as effective or cost-effective as lifestyle would be a mistake – in the long run, both will be needed to stem the epidemic.

- ***Diabetes Care - An assessment of eligibility for inhaled insulin (Exubera): The Fremantle Diabetes Study - Davis, Davis*: This study is bad news for Exubera – it suggests several ways Exubera is inferior to subcutaneous insulin. The data show that about one third or more of diabetes patients are ineligible for the product at screening. Eligibility for Exubera also decreases over time within a given group of type 2 patients – in this study it is due to longer duration of diabetes, though we assume that Exubera use itself would also decrease eligibility over time because it causes small decreases in pulmonary function. This means that Exubera loses to subcutaneous in many ways: fewer people are eligible to start with, efficacy declines over time, and the longer you have diabetes the less likely you are to be eligible for Exubera (which offsets your greater likelihood of needing insulin over time).
- ***Diabetes Care - Effect of adjunctive pramlintide treatment on treatment satisfaction - Marrero et al*: This study corroborates the idea that Symlin lowers insulin doses, improves glycemic variability, and provides visible day-to-day improvement, creating higher patient satisfaction and providing a possible next step for patients who are already intensively managed. In this study, the pramlintide group required less insulin, primarily at mealtime, to stay at target. Those on Symlin lost weight and lowered their postprandial glucose levels. Despite nausea-like symptoms, 97 of the 130 pramlintide participants stayed on for a study extension. The majority reported that side effects would not discourage them from long-term use. Pramlintide participants reported better blood glucose predictability, flexibility, weight control, and appetite control. Although this was an end-of-study survey without a survey at the start to reflect baseline, we feel that it should contribute to increasing physician support for pramlintide.
- *Diabetes Care - Clinical implications of the DREAM Study - Davidson*: In this commentary, Dr. Mayer Davidson points out that TZDs would be most effectively used to treat people with prediabetes. The biggest challenge, he believes, is identifying these people: oral glucose tolerance tests are inconvenient and fasting plasma glucose tests are unreliable. Instead, he suggests that an A1c level between 6% and 7% be considered diagnostic of prediabetes and that people with such A1c levels are the best population to treat. This is certainly an interesting idea – Dr. Davidson clearly supports using pharmacotherapy for diabetes prevention and this is a practical suggestion for implementing it.
- *Diabetes Care - Comparison of vildagliptin and rosiglitazone monotherapy - Rosenstock et al*: This 24-week phase 3 study showed that vildagliptin is non-inferior to rosiglitazone in monotherapy in 697 drug-naïve type 2 patients. From baseline A1c of 8.7%, vildagliptin 50 mg twice daily lowered A1c by 1.1% while rosiglitazone 8 mg once daily lowered A1c by 1.3%. Patients on vildagliptin saw no weight change (-0.3 kg) while patients on rosiglitazone gained weight (+1.6 kg). One case of mild hypoglycemia was observed in each group. We don't see this trial as very helpful because vildagliptin was given twice daily, which is not how it will be marketed from what we understand. Novartis may use this trial to argue that DPP-4 inhibitors are preferable to TZDs as first-line therapy. However, metformin is currently the ADA-recommended first-line therapy of choice and vildagliptin failed non-inferiority compared to metformin. On the flip side, Merck hasn't published a phase 3 comparison between sitagliptin and a TZD yet (the trial is currently in progress), so this trial represents data on vildagliptin that is not yet available on sitagliptin.

- ***Diabetes Care - The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes - Monnier et al*: In this study, Dr. Louis Monnier and colleagues stratified 130 type 2 patients into five groups by A1c value (group 1 had lowest A1c and group 5 had highest). They found that differences in daytime postprandial glucose were most significant between the groups 1 and 2, differences in early morning / dawn phenomenon glucose were biggest between groups 2 and 3, and differences in nighttime fasting glucose were largest between groups 3 and 4. Assuming that A1c value in these patients was a proxy for the progression of diabetes, this implies that postprandial glycemic control is lost before fasting control. We thought one of the striking findings of the study is how well A1c level correlates with duration of diabetes – this speaks to just how difficult it is for patients to stay well controlled over time.
- *Diabetes Care - Prevalence of hyper- and hypoglycemia among inpatients with diabetes - Wexler et al*: This observational study of 999 patients in 44 hospitals found that "marked, persistent" hyperglycemia is very common in the hospital and is often treated using only sliding-scale regimens, which we understand are an inadequate and often inaccurate method of dosing insulin. Fortunately, the survey also found that severe hypoglycemia is rare - most likely because hospitals prefer running patients high in order to avoid the risk of hypoglycemia. We see this study as clear evidence of the need for intensive insulin management in hospitals.
- *Diabetes Care - Progression from newly acquired IFG to type 2 diabetes - Nichols, Hillier, Brown*: This study followed 5,452 HMO patients who had at least two elevated fasting glucose measurements (100-125 mg/dl) between 1994 and 2003. In this study, 8.1% of all patients with fasting glucose between 100 and 109 mg/dl and 24.3% of all patients with fasting glucose between 110 and 125 mg/dl developed diabetes. Mean progression time to diabetes for the former was 41.4 months, or a rate of 1.34% per year. Mean progression time for the latter was 29.0 months, or 5.56% per year. We think this was a well-designed study, the first to offer a quantitative estimate of the progression rate from IFG to diabetes in a managed care patient population.
- *Diabetes Care - The BIGTT Test: A novel test for {beta}-cell function, insulin sensitivity, and glucose tolerance - Hansen et al*: This paper describes a new model for calculating insulin sensitivity and acute insulin response that requires only data on a patient's sex, BMI, plasma glucose, and serum insulin levels during an oral glucose tolerance test (OGTT). The authors report that based on validation testing with 258 individuals, their model is accurate and can be used for large scale studies.
- *Diabetes Care - Glucose measurement: Confounding issues in setting targets for inpatient management - Dungan et al*: This long, thoughtful paper discusses the many issues that confound glucose measurements in the hospital setting, making it difficult to set targets for glycemic control. The authors note that work by Dr. Van den Berghe and others has established the need for intensive glucose control, but currently the limited accuracy of point-of-care testing devices and the time delay associated with central lab testing means that "accurate, well-validated blood sensors, particularly those that provide continuous readings" are badly needed. We couldn't agree more. We think that hospitals, and particularly ICUs, are an important area where CGM could do much good.
- *Diabetes Care - Pharmacotherapy of childhood obesity: An evidence-based, conceptual approach - Freemark*: In this paper, Dr. Michael Freemark summarizes the risks and benefits of using orlistat, sibutramine, metformin, and rimonabant in childhood obesity and provides a model for selecting patients for pharmacotherapy, including which drugs to use and when. Dr. Freemark concludes that to date, sibutramine has shown the greatest efficacy in children. The evidence is not yet clear whether rimonabant will be safe for children. We're encouraged to see him note that in the future, other medications may be used for obese children as well, including "incretin mimetics, melanocortin 4 receptor agonists, ghrelin antagonists, etc."
- *Diabetes Care - Is metformin safe in patients with mild renal insufficiency? - Kazory*: In this short communication, the authors present a case study of a man with mild renal insufficiency who

developed metformin-associated lactic acidosis (MALA). They opine that metformin should not be given to anyone with abnormal serum creatinine (a measure of kidney function) because renal function can worsen quickly even in patients with mild disease. We thought this was an interesting observation – if this suggestion were put into effect, more patients would be unable to take metformin and would have to go on sulfonylureas or Januvia, which are currently the only oral antihyperglycemics indicated for patients with renal disease. In light of the FDA approvable letter requesting more information on renal function, it will be interesting to see whether Galvus also gets a label indication for renal disease.

- ***Diabetes Educator - The physiology of incretin hormones and the basis for DPP-4 inhibitors - McKennon, Campbell*: This is the most positive review paper on DPP-4 inhibitors we've seen to date; it cites all of the advantages and none of the long-term safety concerns associated with this class. While the authors briefly discuss Byetta, DPP-4 inhibitors are the clear stars of this paper and described as a completely novel approach to the treatment of type 2 diabetes. The authors favor vildagliptin, they say, because it has greater potency than sitagliptin. We don't think there's evidence to justify this position, but it's interesting and reflects, we think, Novartis's more comprehensive publication strategy. If there is a difference in efficacy, it must be small as neither drug has huge efficacy to begin with.
- ***Diabetic Medicine - Incretins and other peptides in the treatment of diabetes - Todd, Bloom*: This review is very positive on incretin mimetics. DPP-4 inhibitors are also viewed positively, but with more caution regarding their long-term safety. We found the authors' review of exenatide and liraglutide very helpful in comparing the two. Exenatide is currently limited by its short duration of action; the twice-daily version does not provide 24/7 action. We look forward to LAR to fix this. In the meantime, liraglutide's longer half-life means it probably does a better job of lowering both fasting and postprandial glucose and causes less nausea (which is linked to ups and downs in exenatide's action). Data on whether liraglutide delays gastric emptying remain mixed. The authors believe that DPP-4 inhibitors, if eventually proven safe, will be more useful in early type 2 and less in advanced patients.
- ***Diabetes Obes Metab - A triumph for physiology driving drug discovery: the potential impact of DPP-4 inhibitors in type 2 diabetes - Donnelly*: This editorial presents a positive perspective on DPP-4 inhibitors, particularly in early combo therapy. Dr. Donnelly believes they are safe and tolerable, but notes that there is concern about side effects from increasing DPP-4 substrates other than GLP-1 and GIP. He thinks one of the more intriguing aspects of the DPP-4 inhibitor class is its potential in the stabilization and restoration of β-cell function – we would opine that it is also a matter of duration of effect. We've seen fairly convincing evidence that vildagliptin and sitagliptin improve β-cell function, but no one knows at this point how long the effect is going to last – what we need is an ADOPT-like trial with DPP-4 inhibitors to look at duration of effect.
- ***Diabetes Obes Metab - DPP-4 inhibitors: a major new class of oral antidiabetic drug - Idris, Donnelly*: This review explains why the DPP-4 enzymes's many roles in the body have caused doctors to worry about neural and immune side effects from DPP-4 inhibitors. The authors also discuss the current debate over whether DPP-4 inhibitors' effects on glycemia are mediated only through the incretins GLP-1 and GIP or whether other substrates are involved – we think not, but there are some good arguments for why that may be the case. They briefly list the DPP-4 inhibitors in development and discuss their clinical profiles, including effects on insulin secretion and β-cell glucose sensitivity as well as weight neutrality and safety and tolerability.
- *Diabetes Obes Metab - Vildagliptin improves glycaemic control in patients failing TZD monotherapy - Garber et al*: This Novartis study showed that vildagliptin lowers A1c in type 2 patients failing pioglitazone monotherapy. In 463 type 2 diabetes patients with a mean baseline A1c of 8.7%, vildagliptin 50 mg or 100 mg once daily reduced A1c by 0.8% or 1.0% respectively after 24 weeks

with no significant side effects. While this is a significant A1c drop, we note that the baseline A1c value was quite high – it looks like in clinical trials, patients who are closer to the recommended ADA A1c level of 7% usually drop half a point or less on vildagliptin.

- *Diabetes Obes Metab - Efficacy and tolerability of initial combo therapy with vildagliptin and pioglitazone - Rosenstock et al*: This Novartis study showed that vildagliptin and pioglitazone lower A1c more effective in combination than either drug alone in drug-naive type 2 patients. In 607 drug-naive type 2 diabetes patients with a mean baseline A1c of 8.7%, combo therapy with pioglitazone and vildagliptin produces greater A1c reductions than monotherapy with either drug. After 24 weeks, patients on 30 mg pioglitazone, 50/15 mg vildagliptin/pioglitazone combo, 100/30 mg combo, and 100 mg vildagliptin had A1c drops of -1.4%, -1.7%, -1.9% and -1.1% respectively. We note that the 50/15 mg combo produced a greater A1c lowering than higher doses of each drug in monotherapy – this supports the idea that giving lower doses of multiple drugs in combination may be more beneficial than maximal doses of a single drug.
- *Diabetes Obes Metab - Effect of adding sitagliptin to metformin on 24-h glycaemic control and beta-cell function - Brazg et al*: This small Merck study showed that sitagliptin improves several measures of glycemia and β-cell function. In 24 type 2 patients failing on metformin monotherapy, four weeks of sitagliptin reduced 24-hr weighted mean glucose by 32.8 mg/dl, fasting plasma glucose by 20.3 mg/dl, and mean daily SMBG values by 28 mg/dl. Beta-cell function also improved, as measured by glucose and C-peptide concentrations during the 5-hr period after a standard breakfast. This adds to the growing body of evidence that DPP-4 inhibitors improve β-cell function, but we note that the big question of β-cell health or regeneration remains unknown.
- *Diabetes Obes Metab - Efficacy and safety of sitagliptin compared with the sulfonylurea glipizide - Nauck et al*: This Merck study showed non-inferiority of sitagliptin compared to a sulfonylurea. In 1,172 type 2 diabetes patients failing monotherapy on metformin with a mean baseline A1c of 7.5%, sitagliptin was non-inferior at 52 weeks compared to glipizide. A1c changes from baseline were 0.67% in both groups. Hypoglycemia was much rarer with sitagliptin (5%) than glipizide (32%). While the sitagliptin group lost 1.5 kg, the glipizide group gained 1.1 kg. We think that ADOPT proved very strongly that sulfonylureas are not a good choice of oral agent in type 2 diabetes – this study supports the idea that DPP-4 inhibitors have a better side effect profile compared to this class.
- ***JAMA - Measuring progress toward achieving hemoglobin A1c goals in diabetes care: Pass/fail or partial credit - Pogach, Engelgau, Aron*: In this commentary piece, the authors argue against an A1c goal of less than 7% for all patients and want to allow doctors to have looser guidelines "where appropriate." Pay-for-performance itself isn't discussed, but our guess is that they are worried about how this will be measured. We understand it's complicated (the best doctors will have the toughest patients) but the answer should not be to dilute the guidelines, in our view – especially because we think there's a good chance the A1c guidelines need downward pressure anyway (as AACE has done a bit, by recommending 6.5% rather than 7% for A1c goals).
- *Journal of Cerebral Blood Flow & Metabolism - Hyperglycemia in acute ischemic stroke: a vascular perspective – Martini, Kent*: This paper reviews molecular pathways in the vasculature that are affected by hyperglycemia and concludes that the molecular effects of hyperglycemia cause pro-vasoconstrictive, pro-thrombotic and pro-inflammatory activities in the endothelium of the vasculature that promotes stroke – we think this is a good review of the medical link between hyperglycemia and stroke.
- *Nat Med - Extracellular carbonic anhydrase mediates hemorrhagic retinal and cerebral vascular permeability through prekallikrein activation - Gao et al*: In this paper, Dr. Ben-Bo Gao and colleagues report the use of proteomics to identify a potential target for treating diabetic retinopathy. They found that there are higher levels of a form of extracellular carbonic anhydrase (CA-I) in the vitreous gel of the eye in individuals with advanced retinopathy. CA-I increases the vascular

permeability of the retina and promotes kallikrein-mediated innate inflammation mechanisms to contribute to retinal edema and vision loss. We think this is an exciting new application of proteomics and will be interested to see of CA-I becomes confirmed as a valid drug target in the future.

- *Nat Rev Drug Disc - Sitagliptin - Drucker, Easley, Kirkpatrick*: This News & Analysis article concisely summarizes the background behind the discovery of DPP-4 inhibitors in general and sitagliptin in particular. Drs. Daniel Drucker, Chris Easley, and Peter Kirkpatrick then offer their analysis of the role of sitagliptin in type 2 diabetes: they note that many doctors now advocate initiating type 2 patients on two oral drugs in order to preempt the monotherapy failure that invariably happens when patients are started on metformin alone. However, there are no head-to-head studies yet comparing sitagliptin or vildagliptin to other oral agents in combination with metformin, so it is difficult to assess which classes of agents are best used with metformin. We think this would be a fascinating trial for Merck or Novartis to do…
- ***NEJM - Inhaled Insulin for Diabetes Mellitus - McMahon, Arky*: This paper describes a type 2 diabetes patient who needs to begin insulin therapy and then discusses whether he is an appropriate candidate for Exubera. It gives background on inhaled insulin, and then presents the clinical evidence, usage guidelines, adverse effects, and areas of uncertainty associated with Exubera. Finally, the authors return to the case study patient and conclude that he is not suited for Exubera because he needs basal insulin before prandial. They opine that even for patients who need prandial insulin, the cost, limited portability, risk of hypoglycemia, and unknown long-term effects of Exubera should be weighed against the factor of convenience. This resonates with what we've heard from a lot of doctors – physicians seem to be very concerned, ironically, by the lack of convenience associated with Exubera as well as the lack of long term safety data.
- *PNAS - Elimination of insulitis & beta cell regeneration via induction of chimerism in diabetic NOD mice - Zhang et al*: Dr. Chunyang Zhang and colleagues report in this paper an interesting new method of treating early type 1 diabetes in non-obese diabetic mice. The technique is something akin to a short-term bone marrow transplant. As far as we understand, T cells are taken from a donor and engineered so that once transplanted, they will kill the autoimmune T cells of the type 1 recipient patient. Once the patient's autoimmune T cells, which are responsible for β-cell destruction, are gone the patient's beta cells regenerate naturally, curing their 1 diabetes. The transplant is 'short-term' because it only involves transplanting short-lived T cells, not stem cells. As those donated T cells die over time, the recipient's own stem cells replenish them with his or her own T cells.

Below we provide the main takeaways from our lit review on an editorial that Dr. David Nathan of Massachusetts General Hospital wrote in the NEJM that has sparked quite a bit of criticism from industry and some physicians as well. In this article, he states that the FDA has become too eager to approve new drugs for type 2 diabetes and he roundly criticizes the recent approval of Januvia on what he considers to be insufficient efficacy and safety data. While the marked commercial performance of Januvia so far would seem to suggest that physicians don't all share his view… the recent goings-on with Galvus do prompt questions that Dr. Nathan was very smart to raise.

Main takeaways**: In this perspectives article, Dr. David Nathan takes issue with new antidiabetes medications entering the market with high price tags and little efficacy and data. 1) **Specifically he questions whether the FDA was wise to approve Merck's Januvia on so few patients** (467 – although we point out that metformin was approved and widely used based on only 753 patients) treated for such a short period of time (18 weeks), especially when the A1c reduction is modest (0.5-0.9%) and the pill cost is not. 2) **He questions why we need so many drugs** (he cites 30 agents across 9 classes) to treat the epidemic of diabetes. He notes a "limited A1c efficacy" of newer agents (GLP-1s, DPP-4 inhibitors) compared to older ones (insulin, metformin, sulfonylureas) and chides the increased expense of the newer drugs. 3) **His conclusion? The problem isn't a dearth of medication options, it's the clinicians failure to use the ones they

already have. *While we greatly respect what he says and believe that clinician inertia certain plays a role, given the compliance issues with many of the existing medications, we think Januvia does have a place in the pharmacotherapy of type 2 diabetes. 4)* ***We note that while most of the clinicians we spoke to at ADA Postgrad dismissed Dr. Nathan's editorial, it certainly may have had some influence on the FDA's decision to further scrutinize Galvus****. We do agree that there is quite a lot that we don't know about this class – as we have noted often before – which is why the post-marketing surveillance for Januvia will be very important. At the same time, some have said if Dr. Nathan's implied standards were applied, insulin may not even be approved! Debates, debates – where would diabetes be without them?*

Nathan DM. "Finding New Treatments for Diabetes—How Many, How Fast . . . How Good?" NEJM. 1 February 2007. 456(5): d437-440*.*

—by Cindy Glass, Jenny Jin, and Kelly Close

10. Upcoming Conference Previews

- **Diabetes UK, March 14-16, Glasgow, Scotland, http://www.diabetes.org.uk/**

  This is the major annual conference of Diabetes UK, the largest diabetes organization in the UK. About 3,500 health care professionals are expected. The conference is organized into tracks, with scattered general sessions. There is a basic science track, a clinical science track, and several clinical care tracks. We've organized our highlights into categories by topic.

  Diabetes Therapy and Drugs: On Wednesday, March 14, there will be a debate on *Conservative vs. Surgical Management of the Ischemic Foot.* That evening, from 5:15-6:30 pm, several doctors are discussing the *Implications of Recent Clinical Trials*, including DREAM (Dr. Matthews), ADOPT (Dr. Gale), PROactive (Wilding), and lipid trials, particularly microvascular endpoints (Dr. Dodson). On Thursday afternoon, from 2:30-4:00 pm, there will be a very important lecture on *Prescribing New Drugs*. Discussion will include DPP-4 inhibitors, by Dr. Dan Drucker from Toronto, GLP-1 analogs, by Dr. John Buse from North Carolina, and rimonabant, by Dr. Julio Rosenstock from Dallas. Finally, that evening, from 5:15-6:30 pm, will be five (as yet undisclosed) oral presentations on diabetes therapy. We absolutely cannot WAIT!

  Obesity and Cardiometabolic Risk: The opening symposium of Diabetes UK is on *Obesity*. Dr. Sattar will discuss *Prevalence and Pathogenesis*, Dr. Wilding will discuss *Treatment: the role of drugs and surgery* and Dr. Lean will discuss *Implementing Lifestyle Change.* The symposium lasts from 9:00-10:30 am on Wednesday morning. Of three corporate-symposia on Wednesday evening, from 7:00-9:00 pm, we would consider Sanofi's on *Current Affairs and Current Topics* most interesting. This will deal mainly with hot topics in cardiometabolic risk. Last but not least, Thursday afternoon, 4:35-6:05 pm, features a debate on *Which management modality is 'top of the pops' in the prevention of vascular disease in diabetes?* For core treatment, Dr. Packard argues for lipid management, Dr. Cruickshank argues for blood pressure management, and Dr. Matthews for management of insulin resistance and glycemia.

  Beta Cells and Basic Science: We are very much looking forward to the seven oral presentations on *Beta Cells and Islets* on Wednesday from 2:15-4:00 pm. These are as yet undisclosed. There is also a symposium on *Glucose Sensing*, which occurs on Thursday from 2:30-4:00 pm. Discussion will include *Glucose sensing in the control of gene transcription*, *Differential glucose sensing in hepatocytes vs. pancreatic beta cells*, and *Glucose sensing in the brain*. Excellent!

  Clinical Care: Clinical Care will hold the heaviest focus at this Diabetes UK meeting. First, an intriguingly named lecture called *A Rolling Stone* will be given by Dr. Felix Burden for the Arnold Bloom Lecture on Wednesday from 11:05-11:45 am. On Wednesday night is the second of the corporate symposia we'd highlight: Pfizer's *Treating People with Diabetes: does one size fit all?*

from 7:00-9:00 pm. You'll see from the highlighted sessions below, which discuss diabetes care for different populations, that one size probably will not fit all. The following have to do with diabetes treatment in pediatrics, pregnancy, and primary care patients, and all occur at the same time. The first of these sessions has to do with *Pediatric Diabetes (what makes the difference?)*. In a concurrent track, there will be a symposium on *Diabetes in Pregnancy (improving the outcome of diabetic pregnancy)*, which will include discussion on the "planned unplanned pregnancy" and how to improve outcomes in women with type 1. Finally, there will be a session on *Management Options for Type 1 and 2 Diabetes in Primary Care*, which will include Dr. Burden discussing the possibility of having all diabetes care occur in primary care. At the same time as the last three, Thursday morning 8:30-10:00 am, is a discussion of education in a session called *"Supporting Self-Management: Care Planning and Structured Education,"* which will include results from DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed).

Diabetes in hospital inpatients is the topic of a session in the second block, 10:40 am-12:30 pm, on *Inpatient Care*. Dr. MacFarlane will discuss *Inpatient Diabetes ("an increasing problem")*, Dr. James will discuss *Diabetes Inpatient Nursing: impact on adverse prescribing and length of stay*, Dr. McHoy will discuss *Guidelines for diabetes management during endoscopy and colonoscopy procedures*, and Dr. Fisher will discuss *Managing cardiac problems in diabetes*, including data from MINAP. Glycemic standards are becoming stricter and better understood in the in-hospital segment and we're eager to get the intake.

- **ADA Research Symposium: Translating Islet Biology into Diabetes Therapy, March 14-17, Stone Mountain, GA, www.diabetes.org/beta07**

  We always enjoy attending basic science meetings in diabetes, and this ADA research symposium looks like it will be an excellent learning opportunity for making connections between current research in islet cells and potential clinical applications. The meeting includes presentations from 30 thought leaders on the pathogenesis of β-cell dysfunction and how our knowledge in this area should guide clinical practice and may provide ways to prevent or reverse beta cell dysfunction in the future. Below we give a day-by-day overview of some of the talks you won't want to miss.

  March 14: The meeting opens on Wednesday night with a plenary lecture by Dr. Gordon Weir of the Joslin Diabetes Center entitled "*Beta-cells Confronting Diabetes: Opie in 1900 and Onward*" from 8:00-8:45pm. We're interested in what he will say on this topic – as you know, there are two approaches to thinking about the pathophysiology of type 2 diabetes. The first assumes that insulin resistance is the underlying defect that causes metabolic syndrome and eventually diabetes. The second considers β-cell dysfunction to be the major cause of diabetes, since without β-cell failure even the most obese individuals do not get diabetes.

  March 15: The meeting opens in full swing on Thursday, with 16 talks separated into four lecture sessions. We're interested in what Dr. R. Paul Robertson of Pacific Northwest Research Institute will say on the question "*Do Tests of Beta-cell Function in Vivo Correlate with Beta-cell Mass?*" from 11:00-11:30 am, because it is the impossibility of directly measuring β-cell mass in humans that has so far stymied researchers from answering the question of whether newer drugs like exenatide actually increase β-cell mass in humans. After lunch, Dr. Richard Watanabe of USC will discuss "*The Beta-cell, Genetics, and Diabetes*" from 1:45-2:15pm, followed by Dr. Doris Stoffers of the University of Pennsylvania on "*Transcriptional Regulation of Beta-cell Development*" from 2:15-2:45pm and Dr. Susan Bonner-Weir of the Joslin Diabetes Center on "*Islet Neogenesis*" from 2:45-3:15pm. From 4:30-5:00pm, Dr. Steven Kahn will talk about "*Islet Adaptation and Maladaptation to Insulin Resistance*." The day will end with a *Debate on Fatty Acid Effects on Beta-cell Function* with Dr. Guenther Boden of Temple University arguing that "*Fatty Acids Are Good for You*" and Dr. Vincent Poitout arguing that "*Fatty Acids Are Bad for You.*"

March 16: Sessions on Friday begin in the afternoon with Dr. Kathrin Maedler of UCLA discussing "*Pathways to Beta-cell Death*" from 1:00-1:30pm. Dr. Rebecca Hull of the VA Puget Sound Health Care System will then talk about the "*Role of IAPP and Amyloid in Beta-cell Dysfunction*" from 1:30-2:00pm. Later in the afternoon will be a series of three presentations on incretins that we are especially excited to attend. Dr. Jens Holst of the University of Copenhagen will speak on "*Incretin Biology*" at 3:30-4:00pm, followed by Dr. Christopher McIntosh of the University of British Columbia on "*GIP and Glucose Metabolism*" at 4:00-4:30pm and Dr. David D'Alessio of the University of Cincinnati on "*GLP-1 and DPP-IV Inhibitors as Therapeutics*" at 4:30-5:00pm.

March 17: Saturday morning, St. Patrick's Day, will wrap up the meeting with a series of interesting lectures. Dr. Hertzel Gerstein of McMaster University, one of the DREAM trial investigators, will discuss "*TZDs in Diabetes Therapy*" from 9:00-9:30am. Dr. Jack Leahy of the University of Vermont, a powerhouse β-cell researcher, will talk about "*Diabetes Therapy: Direct Drug Effects on Islets vs. Indirect Modulation of Islet Function*" from 9:30-10:00am. From 11:00-11:30am, the always controversial and upbeat Dr. Ralph DeFronzo of the University of Texas will talk about "*Glucagon and the Liver*." Finally, Dr. Claes Wollheim of University Medical Center in Geneva and Dr. Peter Butler of UCLA will close the conference on a forward-looking note with short talks from 11:30am-noon on "*Future Directions in Islet Biology*" and "*Future Directions in Clinical Therapeutics*," respectively.

- **American College of Cardiology, March 24-27, New Orleans, LA, http://acc07.acc.org/**

  Diabetes is intimately tied to cardiovascular disease, so Close Concerns is heading to New Orleans for the Annual Scientific Session of the American College of Cardiology, which also happens to be one of the biggest medical meetings of the year. Though it may not be the focus, diabetes comes up countless times at this meeting, especially in discussions on obesity and the metabolic syndrome, conditions that are closely related. In particular, we will search for clues into therapy for metabolic syndrome, obesity, and pre-diabetes. We are excited to gain insight into diabetes from cardiologists' perspectives. We are also glad to assist the ACC in its effort to help revitalize New Orleans! Please see some meeting highlights below, mostly dealing with obesity and the metabolic syndrome, but also in-patient glycemia, patient adherence, and complications related to diabetes.

  Obesity and the Metabolic Syndrome:

  On Sunday March 25, from 2:00- 4:00 pm, is a series of *Great Debates in Metabolic Syndrome*. Debates include whether a low-carb diet is best for the metabolic syndrome, whether it is a syndrome at all, whether weight-loss medication is in fact the best treatment, and finally, an exciting "State-of-the-Art Lecture" on *Adipose Tissue – The New Endocrine Organ*.

  On Monday will be a track all about obesity. A lunchtime session on *Using Pharmacotherapy to Manage Obesity* will lead into a symposium, from 2:00- 3:30 pm, on the *Management of Obesity for the Cardiologists*. Topics include drug therapy, as well as diet and exercise therapy, for the treatment of obesity, cardiovascular implications of obesity, patient selection for gastric bypass, and ways to maintain weight loss. After the symposium is a "Meet the Experts" panel, from 3:30- 4:30 pm, on *Combination Therapy for Dyslipidemia*.

  On Tuesday, there looks to be another excellent symposium, from 9:00- 10:30 am, on the *Management of Metabolic Syndrome*. This will include discussions on treating blood pressure, lipids, and impaired fasting glucose, and also a talk on preventing diabetes. A Tuesday lunchtime session will discuss *Obesity and the Metabolic Syndrome in the Pediatric Population*.

  Other Diabetes-Related Highlights:

  On Sunday is a 'mini-course' from 2:00- 5:00 pm on *Adherence: A Critical Physician-Patient Interface*. Adherence is a massive issue in diabetes care, and we hope to benefit from talks on *The*

Problem of Adherence, *The Cost of Adherence*, and, curiously, *Pharmacologic Interventions to Improve Adherence*.

On Monday, 10:00- 11:00 am, we're expecting a terrific "Meet the Experts" panel on *Glucose Control in Acutely Ill Cardiac Patients*. In-patient glycemia is growing as an issue as evidence suggests stricter standards in the ICU and CCU.

Also on Monday is a symposium, from 11:00 am – 12:30 pm, on *Biomarkers in Heart Failure*. This will include discussions of inflammatory biomarkers and oxidative stress. Following is a lunchtime discussion of *Disease Management of Heart Failure*. Finally, there is a 4:00- 5:30 pm session on the *Diagnosis and Management of Peripheral Arterial Disease*, which can be a complication of diabetes.

—by Daniel Belkin, Jenny Jin, and Kelly Close