DIABETESCLOSEUP

Science Throws a Curveball – or Two... February 2008 • No. 77

From the Editor

Progress in diabetes, it seems, rarely moves in a linear fashion. If last month was a step forward, this month was two separate steps backward. Let's review them in order:

First, the New England Journal of Medicine *reported that intensive insulin therapy in the ICU may be bad for patients because of increased hypoglycemia. The trial, which compared intensive and conventional insulin therapy in the ICU, was halted due to a potentially dangerous increase in hypoglycemia in patients receiving intensive insulin regimens. Second, preliminary results of the ACCORD trial were disclosed – which, in our view, have left patients and providers with difficult questions about optimal care. In this 10,000-patient study, the intensive treatment arm was halted due to increased mortality in the conventional treatment arm. Both of these studies are reviewed in depth in this month's newsletter.*

In both of these trials, it seems that science has thrown the diabetes community a curveball. These findings raise doubts about the most important assumptions in diabetes care, and offer the message that intensive glucose control is inherently dangerous for diabetes patients.

However, I would suggest that we need to take a deep breath and not rush to make judgment. We need to remember that these studies examined specific populations whose medical outcomes cannot be applied to all patients with diabetes – a fact that unfortunately is often overlooked by sensational media reports. Tight glycemic control has been shown before to prevent complications and cardiovascular disease, but not necessarily to improve the outcomes of diseases already present at baseline. Patients included in the ICU study had sepsis at baseline (sepsis occurs in up to 20% of ICU patients according to Alberti et al., 2002, Critical Care Medicine), while patients in the ACCORD trial had a history of cardiovascular disease (CVD) or were at especially high risk for CVD.

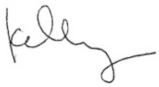
Let's not forget the broader purpose of diabetes care. Ideally, treatment for diabetes would trick the body into thinking it did not have diabetes while at the same time remaining simple enough for patients to (almost) forget they had diabetes. Lately, we've developed a view that in diabetes management – drugs or devices – given the level of self-care required to do well and given dour physician economics, it's not just about first-in-class or best-in-class; we're asking, with every new product we hear about – could it be simplest in class, or at least, relatively easy to teach and learn? Physiologically, the goal of treatment is for glucose levels to stay out of the hypoglycemic and hyperglycemic range and A1c – the overall grade score of glucose control – to fall in the range of 4%-6%. A lower A1c is probably in and of itself a good thing. The question remains, is there a point beyond which getting to a low A1c poses more risk than benefit? Is that point different for certain populations, such as patients with CVD? Would that suggest that we need to work doubly hard to avoid cardiovascular disease in the first place? If so, what is the best way of doing that? Reducing A1c? Reducing post-prandial hyperglycemia? Taking cardioprotective drugs? Then, of course, there are other questions. How did patients in ACCORD reach the low A1cs? What role did hypoglycemia play in the half of patients in the intensive arm that died due to sudden death? What about the drugs that increase risk for other adverse effects? What role did weight play? Are drugs that don't cause hypoglycemia or weight gain more helpful than we had imagined? What do the SMBG data look like for patients in each arm of the trial, and especially the

patients that died? More practically, what did baseline cardiovascular risk look like? Was there part of each group that had continuous monitoring? Should there have been? While we understand that patients needed to be contacted immediately once the death data were known, we continue to believe that too little information was released with ACCORD and that the publication should have gone out with the original announcement – the downside for patients of not knowing where to turn is too great.

Until these questions are answered, we should remain calm, which, of course, isn't that easy for an anxious patient or provider.

So, yes, science has thrown us a curveball, but that doesn't mean we bail out. We just have to lay back, readjust our sights, and study the pitch until it's in our zone again.

Optimistically,



Kelly L. Close

Major Headlines

In This Issue

Blogwatch

See below for blogs since our last monthly newsletter. You can view all of our blogs and subscribe to the RSS blog feed online at www.closeconcerns.typepad.com/close_concerns_weblog/

- **February 13:** ACCORDing to Dr. Shimon and Jill Crandall - Breath of Fresh Air
- **February 11:** Januvia May Have Some Company in the DPP-4 Inhibitor Arena in the US (it already does in the EU!)
- **February 6:** ACCORD - Take a deep breath
- **February 3:** Where are the candidates on diabetes and obesity?
- **January 31:** ADA expo on Saturday Feb 2nd in SF!!!
- **January 21:** A win for GLP-1, a blow for inhaled mealtime insulin

There are more blogs from us on Revolution Health at www.revolutionhealth.com/blogs/kellyclose

- **February 4:** (A part of) a possible solution to the healthcare crisis?
- **January 30:** Body size - choices and lack thereof
- **January 24:** Waist circumference - one way around the problem

Coming soon in DCU...

We're getting ready for what looks to be an amazing conference season (did the last season end?), and we will be writing about *a slew of exciting* meetings. First off, looks like Washington is the city to be in near-term, with Avalere Health's reimbursement summit in March and the NIH diabetes meeting later in the spring. See our conference section inside on page 37 for more on these, where we also discuss AACE in Orlando and ADA in San Francisco – you've got until February 23 to register "early bird" for San Francisco – do it! – you can spend the extra funds on a ferry ride or some of our incredible cuisine! Very near term, Mark Yarchoan is headed to Prague on Monday … read about this meeting, the First International Conference on Advanced Technologies & Treatments for Diabetes (ATTD) in our major preview and plan to meet him there for a Pilsner!

1. Quotable Quotes in Diabetes

"My initial reaction is that this is a very complex study and the results are inexplicable with respect to the underlying biological mechanisms responsible for the increased risk."

—Dr. John Lachine, principal investigator of the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, discussing the unexpected results from ACCORD. Our full coverage of the ACCORD trial is on page 16.

"Here we're sitting in a vacuum. We have the media scaring patients, but we don't have the data."

—Dr. Jay Skyler, hoping that patients will not generalize the findings of ACCORD and overreact before publication of the full data.

"When we think about what we do clinically, we think about the last trial we saw, but we often forget all the myriad of data that have been published going back decades."

—Dr. Irl Hirsch, urging the diabetes community not to over-interpret the data from ACCORD in light of the many previous studies, such as the DCCT and UKPDS, that demonstrated benefits to tight glycemic control.

"Do you know what's wrong with injections? It's doctor phobia, not patient phobia. I have never in my life had a patient that refuses to use injections."

—Dr. Ralph A. DeFronzo encouraging the use of Byetta at the American Diabetes Association's 55th Annual Advanced Postgraduate Course.

"If I were Hillary Clinton now, I'd be going for the diabetes vote. You know, you've got 30 to 40 million votes out there."

—Dr. Paul Zimmet, discussing how different countries are tackling the diabetes epidemic during his interview with Diabetes Close Up. The full interview appears on page 23.

"...I mean, it's intuitively stupid that most of the treatments we have for type 2 diabetes result in weight gain, including insulin, when the important thing you need to do is lose weight in type 2 diabetes..."

- Dr. Paul Zimmet

"If a patient is on Avandia or Actos and doing well, scare tactics should not prompt you to stop therapy. Only data can do this. We need to weigh the evidence in publications, not in the evening news."

—Dr. Robert Ratner, defending the TZDs and particularly Avandia at the American Diabetes Association's 55th Annual Advanced Postgraduate Course.

"It is disturbing to me that one out of three patients is started on sulfonylureas, and these drugs have no protective effects on beta-cells. Yes, you might drop the A1c, briefly. But in no time, the A1c will start to creep up, and by the time you notice, there will be no beta cells left."

—Dr. Ralph A. DeFronzo, speaking against the use of sulfonylureas at the American Diabetes Association's 55th Annual Advanced Postgraduate Course.

"I had never treated anyone with a multiple personality disorder before, but the one thing that was clear to me is that all of her personalities still had diabetes."

—Dr. Irl Hirsch, discussing the treatment of very difficult ("brittle") diabetes patients by presenting a variety of unique case studies at the American Diabetes Association's 55th Annual Advanced Postgraduate Course.

2. diaTribe FingerSticks

-by Daniel A. Belkin

3. DCU Company Watch

- **Medtronic—CGM now annualizing at $60 million "even without widespread coverage":** During the Medtronic F3Q08 earnings call on February 19, Medtronic Diabetes reported revenue of $258 million for its fiscal third quarter, up 14% year over year and up 5% sequentially. By our calculations, pump growth likely grew ~10% - even though this was a little below some analyst estimates, we felt this was a very good results given the very tough "up 24%" comparison in F3Q07. Growth was attributed to new insulin pump adoption and strong uptake of CGM along with solid US growth. Medtronic's CGM is now annualizing at an incredible $60 million; Hawkins noted that this comes "even without widespread reimbursement coverage." Medtronic's partnerships with J&J (US focus) and Bayer (international focus) blood glucose monitoring are showing early momentum, which also certainly bodes well for the BGM franchise. The blood glucose meter co-developed with Bayer was launched last week with initial shipments in Germany, and the Medtronic/LifeScan meter is expected later this spring. We believe this deal will bolster Medtronic Diabetes' weakest link – the absence of a partner with a robust, reliable blood-glucose monitor to provide wireless data transmission capability between monitors and Paradigm pumps. At the same time, we think DexCom's deals with J&J and Insulet will certainly make both Animas and Insulet more competitive with Medtronic, assuming they do a good job on the joint CGM/pump devices and continue on their "patient friendly" paths. No shortage of excitement here!

- **Biodel—Fiscal Q1 reported as expected – looking forward to data later this year:** During the Biodel F1Q08 earnings call on February 14, CEO Dr. Sol Steiner provided an update on the status of VIAject and its clinical trials – all is ongoing as expected. As a reminder, VIAject is a super-rapid acting injectable mealtime insulin. Dr. Steiner confirmed that both of the pivotal phase 3 clinical studies are fully enrolled, with results expected at the end of July 2008. Notably, he also said that the dropout rate in the clinical trial was less than had been anticipated, though no specific numbers were provided. Biodel aims to file an NDA for VIAject before the end of the year, an ambitious but attainable goal in our view. Biodel reported a net loss of $11 million ($0.55 per share) for the quarter ending December 31, 2007, as compared to a net loss of $3.7 million ($0.31 per share) for the comparable period last year. On February 12, Biodel completed an offering of 3,260,000 shares of common stock at $15.50 per share, offering net proceeds of $47 million – this nicely bolsters the $73 million in cash on hand at the end of December. Dr. Steiner briefly mentioned that Biodel plans to build and finish a facility to prepare for the commercialization of all six presentations of VIAject (i.e., syringe and vial for U-25 and U-100, two adult pens, and two pediatric pens).

- **Transition Therapeutics—Chasing new partnerships:** During Transition's February 13 earnings call, management indicated that the company is actively looking for new partnerships after its partnership agreement with Novo Nordisk was terminated in November 2007. Transition is developing synthetic gastrin (TT-223), a drug that may improve beta-cell function and regeneration alone or in combination with other anti-diabetic drugs. The company is also studying TT-223 in combination with epidermal growth factor (EGF) to promote beta-cell preservation and regeneration. Animal as well as the phase 2a data for this combination, released in June of 2007 were promising, but questions remain about the safety of EGF for long-term use (potential for increased cancer risk). Management said that it would be important to find a partner that is actively developing a GLP-1, with the goal of eventually marketing a combination GLP-1/gastrin drug. This seems like a promising combination in our view, as both drugs could help to preserve beta cells. Management indicated that a partnership was likely before the end of the year – this caught our attention. Transition plans to commence a phase 2 trial evaluating TT-223 in type 2 diabetes patients receiving metformin with or without TZDs in the first half of calendar 2008, with other phase 2 trials to follow.

- **Sirtris—Characterizing SIRT1 activators as frontline therapy option:** Sirtris CEO Dr. Christoph Westphal provided a broad overview of the company and reviewed recent clinical data at the BIO CEO & Investor Conference on February 12. Dr. Westphal repeatedly described SIRT1 activation as a possible frontline therapy for diabetes or pre-diabetes. So far, preclinical and early human data have indicated that SRT-501 or related new chemical entities (NCEs) are convenient, safe, have high tolerability, don't cause weight gain or hypoglycemia, reduce inflammation, and are effective at lowering blood glucose as well as reducing insulin resistance. Early data, of course, but our interest is high. Of the oral drugs, only metformin currently has this profile – and for many, metformin actually isn't that tolerable due to the GI effects (which can be managed although 40 percent of ADOPT trial participants experienced GI problems nonetheless, high for a relatively recently diagnosed population).

  In contrast to previous presentations, Dr. Westphal seemed to express more enthusiasm for the company's preclinical new chemical entities and less for its lead compound, SRT-501 (resveratrol), which is currently being studied in phase 2 as an add-on to metformin. We believe that SRT-501 is largely a proof-of-concept drug and may be put aside after phase 2 when the more potent NCEs enter clinical testing – on that note, we are interested in knowing what endpoints the company believes should be met for SRT-501 to move forward out of phase 2. Dr. Westphal

indicated during Q&A that it is unlikely that SRT-501 will be used in monotherapy for diabetes, but that it could be an effective drug when used in combination with metformin. We remain intrigued with the SIRT1 activator class and believe it has potential to become significant in the future – in particular, we are very interested in whether NCEs really could become first-line therapy. We continue to believe that simplicity and tolerability, as well as efficacy, are some of the key parameters that govern physicians' choice of first-line therapy.

- **Sanofi-Aventis—Lantus is on fire, and the diabetes pipeline stirs – going for a type 2 rimonabant label in US, not just weight reduction:** The 4Q07 earnings presentation on February 12 was a very interesting one for Sanofi-Aventis, which reported very strong sales for Lantus and gave a terrific pipeline update. Yes, Lantus continues to be on a roll, ringing in sales of 552 million euro (~$800 million) for 4Q, an increase of a whopping 31% from a year earlier and about 6% from a quarter earlier. Notably, sales have already risen over 10% from its first 500 million euro quarter in 2Q07, just six months earlier! Annual sales of Lantus were 2,031 million euro ($2.8 billion), up 29%. A $3 billion drug, growing at 30%!

  Sanofi continues to benefit from Lantus' reputation as an "easier" insulin therapy and no slowdown looks to be in sight. Lantus is Sanofi's third-largest product and by far it's fastest growing across all geographies, including Europe (up 21% in 2007), the US (up 30%), and elsewhere (up 52%). We note that the US result was also especially impressive since 4Q growth in 2006 had been 40%, a challenging comparison. Pierre Chancel, Senior Vice President, Global Marketing, discussed the company's goals and ambitions for Lantus, saying that Lantus has driven patients to switch from premixed insulins and NPH, and has increased insulin usage as an add-on to oral agents. Avandia's problems have clearly benefited Lantus, though it's impossible to pinpoint the precise degree. He also said that the ADA and EASD have recognized that basal insulin is the "most effective" way to treat to A1c target, and this may drive the use of basal insulin as a second line therapy after metformin – that was interesting, as we had not heard that characterization but clearly basal insulin is a key part of the ADA/EASD algorithm. Sanofi management expressed hope that Lantus will soon become the number one anti-diabetic drug worldwide; it was second in worldwide sales to Actos in 2007, which logged sales of just over $3 billion. Since Lantus grew 30% and Actos grew 21%, we believe Lantus has a good chance of achieving that goal in 2008 … but what a race!

  In contrast to Lantus, Apidra has had an extremely rough go breaking into the rapid acting analog arena, currently dominated by Humalog and Novolog. No data about Apidra were provided during Sanofi's earnings call, and indeed, it has received scant attention in earnings calls since its US approval nearly four years ago. We're guessing that sales were below $100 million for the year since the last drug listed in Sanofi's press release achieved around this level in sales. The Apidra result is, in our view, an indication that growth in the rapid-acting insulin market is difficult to achieve. Long-acting analogs (Sanofi's Lantus and Novo Nordisk's Levemir) sold $3.3 billion in 2007, up from $2.3 billion in 2007, representing growth of roughly 40% for the category. This compares to $2.9 billion for rapid-acting analogs in 2007 (Lilly's Humalog and Novo's Novolog), up from $2.4 billion in 2006, or growth of 20% for this category. In 2006, short-acting analogs actually sold *more* than long acting analogs by about $100 million, but this changed dramatically in 2007, when long-acting analogs became the bigger market by about $400 million. While a $2.9 billion market growing at 20% is very robust, a $3.3 billion market growing at 40% is truly stunning. Sanofi dominates the long-acting market with over 85% global market share allowing it to take risks elsewhere in its diabetes business.

  On *that* front, the biggest news in R&D is that Sanofi will begin phase 3 for AVE0010 this quarter with a 78-week (1.5 year), 3,000-patient program that examines a once daily 20 µg subcutaneous

GLP-1 injection in monotherapy and as an add-on to metformin, SFUs, and insulin (notably not Januvia or TZDs). The phase 2 program tested dosages of 5, 10, 20, and 30 µg, with results suggesting that the GI side effect rate was too high at the 30 µg dose. A comparison vs. Byetta is planned and we would imagine that AVE0010 will not be shown to be more efficacious, but will likely show what Sanofi may describe as better "simplicity" – fewer GI side effects (quoted at 20% on the call), which might be appealing to primary care doctors in particular, along with the once-daily use. Filing for AVE0010 is expected in 2010 with launch in 2011 – so we assume launch will be two years behind Novo Nordisk's liraglutide and one to two years behind Amylin/Lilly's once-weekly exenatide – thus the Byetta trial may not have that much relevance anyway, although we love seeing head-t0-head data so we don't have to say "Of course, this is a difficult comparison without head-to-head data." AVE0010 is an immediate release formulation; a controlled release formulation that would be given once weekly is in phase 1.

Elsewhere in the pipeline, a phase 3 monotherapy study should begin on AVE2268, Sanofi's SGLT2 inhibitor, in the second half of 2008, assuming success in the phase 2b trial - results expected by June. Rimonabant's 5,700-person diabetes trial is 60% enrolled; combination rimonabant and insulin data will be shown at ADA.

Sanofi hasn't given up hope for US approval and, in fact, say they will file for a type 2 diabetes treatment label in 2009 - we had previously assumed filing would be for weight management only. Combo use of Lantus and rimonabant might be encouraged, similar to longer-term combo use of AVE0010 and rimonabant This reminds us of the old days with Lantus and Amaryl, before the latter went generic. The massive (17,000-person) rimonabant CRESCENDO trial is over 80% enrolled. We VERY much look forward to data on rimonabant's use in atherosclerosis (STRADIVARIUS), which will be shown at ACC in late March in Chicago and data on rimonabant and dyslipidemia, which will be shown in late April in Instanbul, Turkey, at the European Atherosclerosis Society.

- **Alkermes—Bullish, of course, on exenatide once-weekly efficacy:** During the Alkermes earnings call on February 7, CEO David Broecker characterized exenatide once weekly phase 3 data as the "best ever seen for any diabetes medication." These days, as noted, we think about new therapies and technologies and ask the following questions: 1) How good is it? 2) How safe is it? 3) How easy is it to teach? 4) How easy is it to learn? 5) How many follow up phone calls is the doctor or diabetes educator or PCP likely to get – how big is the hassle factor, in other words. When we apply this methodology to exenatide once weekly: 1) It's good – 1.9% A1c drop from 8.5% baseline, with 75% reaching 7% or less and 50% reaching 6.5% or less. Check. 2) Safety, well, there is good 3.5-year data on exenatide and the compound gets extra credit of course because it mimics a natural hormone. Plus, there is less risk of hypoglycemia with GLP-1 (no risk in monotherapy) than with insulin. More data would be better, but seems like until we hear otherwise, this is a check. 3) How easy is it to teach? Not as easy as a once daily pill, but easier than insulin because the dosing isn't variable and again, the risk of hypoglycemia is low. Check. 4) How easy is it to learn? We don't know because we don't have information here yet. So we're on the sidelines on this one. 5) How many follow-up phone calls will providers get? We're on the sidelines here too. On the face of it, a once-weekly shot sounds very easy… as long as there are no big issues about mixing, as long as the shot is relatively straightforward and not too painful, and as long as injection site reactions aren't an issue. But if that's all clean, we can't imagine very many calls will be made, and that would be a hearty check as well.

  Notably, on inhaled insulin, Broecker said that although Pfizer and Novo Nordisk have dropped inhaled insulin, Alkermes continues to believe that eventually most diabetes patients will require insulin. We still don't know, of course, the extent to which exenatide once-weekly may have the

potential to prevent or delay insulin use in patients, although clearly once beta cells have died, insulin use of some sort is required. A key question is how long GLP-1 could delay this need for insulin – clearly millions of patients today are failing oral therapies and not taking insulin. We believe that many diabetes complications result from patients *not* taking insulin at all or doing so incorrectly (i.e. they are on Lantus only when they could benefit from mealtime plus long acting analogs). Broecker emphasized that patients want a convenient and simple delivery system for insulin, and he stressed that the advantage of AIR insulin is that it fits in the palm of the hand. AIR insulin certainly seems easier than Exubera, a major plus, and partner Lilly would seem much more experienced in insulin initiation than was Pfizer. Issues like lung function testing will be out of the hands of Lilly/Alkermes. For other elements, like ease of use, the Lilly/Alkermes product is clearly heaps better.

- **GSK—TZDs alive and well, including Avandia – big expectations for GLP-1 albiglutide:** During the 4Q07 earnings call on February 7, management discussed the major factors that influenced the company's performance in 2007, and their potential impact in 2008. This was a very good, interesting, strategic call – we wish more calls were like this; sort of introspective, quite informative and insightful. We continue overall to be struck at the power of the TZD class and believe the prospects for "safer" TZDs look intriguing right now. Why? Well, look at Avandia's numbers. In 4Q07, global Avandia sales were £231 million ($472 million), down 43% from £406 million in 4Q06 (a little up from third quarter, about 3%). Check it out! Global sales were still half a billion dollars for a drug that was dragged through the MUD in the US! This drug has some staying power – especially when you consider that its counterpart Actos had nearly a billion dollars in 4Q global sales! For 2007 global Avandia sales were £1.22 billion ($3.03 billion), down 26% from £1.65 billion in 2006. Yes, that's a big drop, *but* the big news for us with the 2007 report was that the TZDs are still very much alive, having logged nearly $1.5 billion in sales in the fourth quarter through Takeda (about 2/3 of that total) and GSK (about 1/3) and even more notably, over $1.0 billion was in the US.

  GSK seems committed to reviving Avandia sales, although it's hard to say if the company will be successful. Interestingly, CEO JP Garnier referred to the ACCORD results as "exoneration" for Avandia because they suggest that treating type 2 diabetes increases cardiovascular events regardless of what drug is used. We think the results are still too new to interpret as specifically as this (that's another way of saying that we didn't think the ACCORD study group exonerated Avandia at all – but it's true they didn't make the situation worse and they did imply that in their statistical analysis Avandia was *not* an independent factor related to the higher rate of deaths in the intensive arm). We note that it may be difficult for GSK to convince physicians to prescribe Avandia in new cases when there is an alternative available on the market that is perceived as safer and potentially more efficacious - particularly if Takeda's marketing about Actos' lipid benefit is effective. We look forward to more data on drugs addressing insulin resistance – it will be important to see if there are links between efficacy and weight gain or whether truly "next gen" TZDs can be created that don't prompt weight gain but do reduce insulin resistance – by our reckoning, that would be an amazing new oral drug and so we're watching closely.

  Mr. Garnier harshly criticized Dr. Steven Nissen's methods and public dissemination and noted that 52% of Avandia patients who were discontinued on the drug were not put back on another diabetes treatment, which is clearly alarming from a public health perspective. (We've requested back up on this data as we haven't seen it elsewhere.)

  Total Alli sales in 2007 were £150 million – pretty amazing for an OTC drug that is half the strength of the Rx version – we wonder about the extent to which the lower dose means fewer side effects. Regardless, we were certainly impressed with the marketing. Fourth quarter 2007 Alli

sales were £40 million, up from £34 million in 3Q07 and £76 million in 2Q07. Our major question is whether consumers are using Alli for long-term weight loss or just buying it and trying it. We never underestimate the interest in losing weight from the American public.

On the pipeline front, Mr. Garnier stated that GSK's GLP-1 (albiglutide) is a very competitive offering in efficacy, safety, and convenience. He added that, "If we come up after Byetta and the others, we want the best offering." We note, however, that as far as accruing long-term safety data goes, products entering the market later will be playing catch-up to earlier drugs like exenatide and liraglutide.

- **Novartis—EU finally approves DPP-4 inhibitor Galvus, first competition to Januvia:** On January 31, the EU approved Novartis's DPP-4 inhibitor Galvus, ending months of setbacks and paving the way for Galvus' launch in Europe. Galvus' approval was expected after Novartis worked with the European authorities to change the drug's dosing information in December of 2007. Under the reworked dosing, Galvus will be available for use only with a sulfonylurea at a 50 mg once-daily dose and with metformin or a thiazolidinedione at a 50 mg twice-daily dose. The 100 mg once-daily dose will not be available due to concerns about liver damage – this is a negative since we think the 100 mg once-daily dose would probably have been the most popular, but the key thing is the drug is becoming available! The second approved DPP-4 inhibitor in Europe, Galvus will struggle to compete with Merck's Januvia, we believe, because all patients using Galvus will need to have regular liver screening – something that is not a requirement for Januvia. In the US, discussions are continuing with the FDA on steps needed for approval, but at this point resubmission is not expected before 2010.

- **Orexigen—FDA raises concerns about epilepsy drugs and, indirectly, Empatic:** On January 31, the FDA released a warning linking drugs for epilepsy to a doubling of risk of suicidal thoughts and behavior. The meta-analysis included approximately 200 clinical trials with 43,892 patients and found 4 suicides and 105 reports of suicidal symptoms among the 27,863 patients who were given the drugs and no suicides and 35 reports of suicidal symptoms among the 16,029 patients treated with placebos (0.43% vs. 0.22% risk, respectively). Although epilepsy and diabetes are relatively unrelated areas of medicine, Orexigen's phase 2 obesity candidate Empatic lies at the intersection of both fields. Empatic is a combination of bupropion (an amphetamine), and zonisamide (a sulfonamide anticonvulsant used for the treatment of epilepsy and one of the drugs that is implicated in the FDA's warning). Zonisamide has also been associated with other central nervous system side effects. The drug's package label notes frequent association with tremor, convulsion, abnormal gait, hyperesthesia (increased sensations), and loss of muscle coordination in movement. We don't yet know the dose of zonisamide that will be contained in Empatic. Zonisamide is typically used in dosages from 100 mg to 400 mg per day; the highest dosage Empatic group used 360 mg of zonisamide daily. In its presentations, Orexigen management argued that the since respective components of its drug candidates are FDA approved, naturally the combined product will also be approved; however, we question this assumption. Even though obesity carries a high degree of morbidity and mortality, the FDA's risk tolerance for obesity is very low (as compared to epilepsy). Given the current FDA environment, the safety bar that all drugs need to pass is also higher than in the past.

- **AZ/BMS—Saxagliptin on track for mid-2008 filing; endocannabinoid in development dropped:** In back-to-back earnings calls on January 31, AstraZeneca and Bristol-Myers Squibb confirmed that the DPP-4 inhibitor saxagliptin, in joint development by both companies, was on track for NDA submission in mid 2008 and EU market authorization application (MAA) in 2H09. Target indications for the NDA include monotherapy, add-on combination therapy, and initial combination therapy with metformin – that must be a big filing!

Clearly combination therapy is the goal, which makes sense since we know DPP-4 inhibitor use in monotherapy isn't that powerful. That notwithstanding, given the pressures on time with patients, some in the medical establishment seem more than fine with a 0.5% A1c drop using a simple, single drug. AstraZeneca management specified that results from exposure studies that included dosing up to 40x the top clinical dose revealed no signs of skin lesions. Management also added that the company was voluntarily performing a chronic study in renal failure patients, emphasizing that this trial did not form a part of the critical path for NDA submission though it would no doubt prove useful for marketing purposes. Interestingly, during the BMS earnings call, management was asked whether their conversations with the FDA gave them complete confidence (does this exist?!) that the FDA would not require these renal studies for the mid 2008 NDA submission given the FDA's recent cautionary posture with Novartis' Galvus. Management stated they couldn't comment on the data that Novartis was looking at. They said they hadn't seen any safety issues with saxagliptin from their clinical data, adding that the FDA had not (yet) asked for any additional data to supplement what they plan to deliver. We look forward to new safety and efficacy data for saxagliptin to be presented at ADA in June 2008 and at EASD in September 2008.

Regarding dapagliflozin, an SGLT2 inhibitor also being jointly developed by AstraZeneca and Bristol-Myers Squibb, both companies indicated that phase 2b data will be presented at ADA 2008 along with publication of phase 2a and phase 2b data. AstraZeneca's pipeline document shows estimated NDA and MAA filings in 2010.

AstraZeneca has discontinued research on compound AZD3988 labeled for treatment of diabetes/obesity. In response to a question asking for commentary on the CB1 antagonist program, management was tight-lipped, stating its preference to wait until phase 2 results were available before divulging more information. We aren't necessarily surprised about this given all the CNS concerns that have come to light with this class of medication.

- **Novo Nordisk—Another stellar year especially for Levemir; liraglutide moves into phase 3 for obesity**: On January 31, Novo Nordisk reported another strong year driven by sales growth in insulin analogs and North American sales, though quarterly growth was more challenging this time around – just 5% vs. double digits the other three quarters. Diabetes care sales in 4Q06 totaled 7,987 million DKK ($1.6 billion), up about 5% year over year. Sales reached a milestone $6.0 billion for the full year, up 9% (14% in local currencies). Sales of modern insulins (NN's parlance for insulin analogs) grew by 20% (35% in local currencies) in 2007. Global sales of NovoRapid, NovoMix, and Levemir in 2007 were 6.7 billion DKK (~$1.3 billion, +20%), 4.7 billion DKK (~$930 million, +24%), and 2.6 billion DKK (~$520 million, +84). This was terrific growth for Levemir – we're not sure if that was an artifact of outstanding growth for long acting analogs generally (Lantus grew 30% from a $2-billion plus base exiting 2006) or whether there are new strategies in place for Levemir but either way, great to see for Novo Nordisk, especially as Novolog growth was slowing (relatively speaking) exiting 2007, though from an impressive high base.

  While overall, Novo Nordisk's diabetes care sales in 2007 were very strong, fourth quarter sales growth slowed because modern insulin growth wasn't as high and human insulin growth reversed (human insulins fell 11% in the fourth quarter, compared to declines of 2-6% in Q1, Q2, and Q3). For 2008, management set sales growth expectations at around 7% (10% in local currencies), and underlying profit growth of at least 20% in local currencies, not including non-recurring costs relating to AERx. This makes sense and seems appropriate – growth is slowing but profitability prospects are improved due to AERx.

On an impressive note, Novo Nordisk also reported the results of two liraglutide phase 3 clinical trials that took place in Japan. In a 24-week monotherapy study, patients in the liraglutide arm saw a reduction of 2% A1c starting from a relatively high baseline of 9.0%, a statistically superior result over the active comparator, a sulfonylurea. During Q&A, management said that the sulfonylurea active comparator caused an average 1.5% A1c drop – we know, of course, that SFUs typically crash and burn – excellent results like this don't turn our head because they are rarely durable, as shown in ADOPT. Subjects treated with liraglutide lost an average of 2 kg, starting from a baseline weight of 65 kg; this is roughly comparable to early weight loss with Byetta – the key will be to see if weight loss is progressive. We aren't sure of the baseline weight. Notably, nausea was experienced in less than 10% of liraglutide patients.

In the second Japanese trial, liraglutide was associated with a 1.5% A1c reduction from a baseline of 8.5% over 24 weeks when used in combo with an SFU. Impressively, about 70% of subjects in the latter trial reached an A1c of 7.0%. Liraglutide appeared to be well tolerated overall, with nausea reported by about 5% of liraglutide patients and constipation and diarrhea reported in 10% of liraglutide patients. It is difficult to directly compare the results of the liraglutide phase 3 data to the exenatide once-weekly phase 3 study showing a drop of 1.9% A1c from a baseline of 8.5%, given the different starting A1cs and the different patient populations – notably, we heard Dr. Alan Garber comment during the Novo Nordisk symposium on ADA Postgrad that Japanese patients respond particularly well to incretin therapies. In our view, liraglutide's efficacy is likely to fall somewhere between that of Byetta and exenatide once weekly, though we hesitate to compare the clinical trial results directly (since we can't, and it will depend on which of three doses of liraglutide). We eagerly await more clinical data to make this comparison (head-to-head would be best). On another impressive note, submission plans in Japan are just a quarter behind the US and EU – liraglutide should be filed in the third quarter of this year, which would put it first in market there.

On the pipeline front, two insulin analogs have moved into phase 2: NN5401 and NN1250. We believe that NN1250 is an improved basal insulin (next generation Levemir?) and that NN5401 is a new mix. NN9535, the company's once-weekly GLP-1, remains in phase 1. We would venture that NN344 may have been dropped – no word about this has been given in two quarters now though it was on the pipeline chart through mid-2007. No further details were given on inhaled forms of basal insulin and GLP-1; we understand these are new compounds and won't be tested in humans for one to two years.

On an exciting note, Novo Nordisk announced plans to initiate phase 3 clinical testing of liraglutide for the treatment of obesity and perhaps pre-diabetes before the end of 2008. It has planned trials with about 4,500 participants, with plans to provide one-year data from the obesity trial and three-year data from the pre-diabetes trial to the FDA. We assume "conversion" from various states (pre-diabetic to non-pre-diabetic, pre-diabetic to diabetic, etc.) as well as cardiovascular events will be some of the major outcomes. This is exciting from a public health perspective, as alternatives for obesity treatment are clearly needed. In a prior clinical trial comparing liraglutide with orlistat, more than 75% of patients treated with the highest dose of liraglutide achieved 5% weight loss and 25% of patients lost 10% of their weight. An important question from our view is what dose that was and what side effect profile emerged.

- **Takeda—Benefiting from Avandia's troubles, Takeda moves into driver's seat on TZDs – pipeline looks powerful:** On January 31, Takeda reported strong sales of Actos and announced new diabetes compounds in early stage development. Global Actos sales rose 23% to $3 billion versus a year ago, due to strong growth in US sales and Avandia's problems. We were surprised during the Avandia controversy to learn that Takeda's marketing for Actos (with

partner Lilly in the US) has not historically emphasized its lipid profile advantages compared to Avandia. However, a change on this front may be contributing to Actos' strength: 2007 US sales of Actos were $2.2 billion, up 21%, reflecting, as noted, market share gains from the Avandia controversy. Europe, Japan, and Asia (excluding Japan) saw year over year increases of Actos sales of 7%, 6%, and 1%, respectively – clearly the propensity of the US to pay for more expensive drugs is reflected in a much higher growth rates there. Global quarterly sales of Actos increased by 14% to just under $1 billion (105.5 billion yen) compared to Q407. This included a quarterly increase of 11% in the US to 83.5 billion yen ($781 million). In the EU, Actos sales increased by an impressive 51% - this is from a low base, increasing from6.2 to 9.3 billion yen ($58 million to $87 million), but clearly a great performance.

And wow, R&D looks like it's had some successes. Takeda announced that two new diabetes drugs entered human phase 1 testing: TAK -379 (an insulin sensitizer) and TAK-100 (a DPP-4 inhibitor). Alogliptin, the company's lead DPP-4 inhibitor, has been filed in the US and remains in phase 3 in the EU and phase 2 in Japan. SYR-472, a second generation PPAR (insulin sensitizer), is in phase 2 in the US and Europe and phase 1 in Japan. Takeda also has two early stage drugs in development for diabetic neuropathy – TAK-428 and TAK-582, both in phase 2.

- **GSK—Avandia briefly enters the limelight, again – Dr. Steven Haffner leaked data:** A peer reviewer for *The New England Journal of Medicine (NEJM)* leaked a copy of Dr. Nissen's meta-analysis of Avandia to GlaxoSmithKline weeks ahead of publication, according to a statement released on January 30 by Senator Charles E. Grassley, a Republican on the Finance Committee. The leak was widely reported in the mainstream media. By receiving advanced notice of the article's publication, GSK was undoubtedly better prepared to respond to Dr. Nissen's meta-analysis with critiques of its methodology and by publishing an interim analysis of the RECORD trial that failed to find a statistically significant association between Avandia and risk of myocardial infarction. The peer reviewer who leaked the material, Dr. Steven Haffner of the University of Texas Health Science Center at San Antonio, was presumably a consultant for GSK. While we aren't concerned in any way about the leak relative to sales implications, this surprising and disappointing news may further increase scrutiny by Congress into dealings between doctors and drug companies. The leak also threatens to undermine the perceived objectiveness of the journal peer-review process.

- **Merck—Januvia franchise now annualizing at over $1.0 billion:** Merck's 4Q07 results released on January 30 showed very strong results for the Januvia franchise of $296 million for the quarter (up from $42 million a year ago and $204 million in 3Q07) - $252 million for Januvia (up 500% from a year ago and up 37% from $184 million in 3Q07) and $44 million for Janumet (up 131% from 3Q07). These results were spectacular, considering this was only Januvia's fourth full quarter on the market. To be annualizing over $1.0 billion at this stage of launch is remarkable in our view and reflects the demand for simple therapies. Merck is clearly winning on questions surrounding "How easy is the drug to teach? To learn? How many phone calls does it prompt?" If the drug can continue to avoid safety issues, we expect it to continue as a runaway success, even with the expected introduction of other drugs in the DPP-4 space in 2008/2009 (Takeda's alogliptin and BMS/AZ's saxagliptin). Although the Januvia franchise did exceptionally well overall, we would have expected Janumet to be a bit higher - while we know endos don't like to start two drugs at once, we think PCPs are less focused on the downside here.

  The international launch of Januvia has been strong, to say the least - Januvia is now approved in 69 countries and launched in over 40, while Janumet is approved in seven. Reimbursement continues to be strong for the drug, and concerns that the drug would be too expensive to be

approved have been proven incorrect. We are surprised at the reimbursement strength and give Merck a great deal of credit on this front.

- **Roche—Diabetes care franchise back on upswing:** On January 29 in a call lead by CEO Dr. Franz Humer, Roche Diabetes Care reported sales of 3.216 billion Swiss Franc (CHF) (~$2.95 billion US dollars). This reflects sales growth of 11% (5% in local currency) over 3.02 billion CHF reported in 2006. This bodes well for the blood-glucose monitoring climate.

  Management appeared quite confident of phase 3 progression of several of their early-stage pipeline drug candidates. The company apparently aims for a best in class profile for their GLP-1 candidate, R1583 (Ipsen). Phase 3 trials are anticipated to begin in 2H08 – management made it sound like the decision was made but they also reserved just enough judgment not to push it into phase 3 in case of a surprise. The high hurdle of significant weight loss set as part of the target profile with Roche's DPP-4 inhibitor candidate, R1579, could mean one of two things: Roche may indeed find market success by creating a differentiated product which would be in high demand, or they may not decide to go through with phase 3 trials if they are unable to substantiate these weight loss claims from their study data. We're surprised by how much weight loss is discussed, given that it has not been seen in phase 2 trials. In our view, Roche maintains one of the most robust, comprehensive phase 2 pipeline in the diabetes industry – it includes GLP-1s, DPP-4 inhibitors, PPARs, a CETP, and an obesity drug, all at least in phase 2, some with imminent phase 3 plans.

  Back on the device side, planned product launches for 2008 include the Accu-Chek Inform II, Accu-Chek Aviva Nano and the Accu-Chek Active. As we understand it, the Accu-Chek Inform II will be the first wireless-enabled hospital blood glucose meter. This should be interesting – there's been a lot of hand waving about advanced systems entering the hospital over the last few years, as the tight glycemic control arguments are so strong in at least the surgical ICU – but most products are still in development, and so sales of this product should benefit from some already-increased adoption of tight glycemic control protocols in hospital settings.

  Although management did not explicitly touch on Xenical (orlistat), we saw from slides that the prescription-strength weight loss drug was down 10% (worldwide) in local currency sales from 2006 and hit about $550 million for the year. Sales for the drug continue to fall though again, for a challenging (side effects) drug that is barely marketed to be bringing in half a billion in sales speaks to us more about the power of the obesity market than anything. As noted earlier, in the US, Alli, the OTC version marketed by GSK, has been strong early on stemming from a good DTC campaign. Roche receives royalty from GSK as licensor of the drug.

- **Amylin—Rocking along:** During its 4Q07 earnings call on January 28, Amylin reported $195 million in net product sales, a 10% increase over 3Q07 and a 29% increase over last year in the same period. Byetta sales were $176 million, up ~9% from the third quarter and 28% from 4Q06, benefiting partially from wholesaler inventory levels. Full year sales for Byetta were up 24% from 2006 at $636 million. Symlin made up the remaining $18.4 million, up 15% from 3Q07 and 35% from 3Q06. Symlin's strong full year sales of $65.5 million were up a solid 50% from the year ended December 2006. We may see more impressive quarterly Symlin numbers in 1Q08 following the launch of the new Symlin injection pens which have added convenience and fixed-dosing that could appeal to prescribers. (We wrote about the new pen in our "Test Drive" column for diaTribe – see www.diatribe.us/issues/8/test-drive.php). Management was pleased to point out that within one month of launch, the new Symlin pen was enjoying 60% open access from payors. For us, the power of post-prandial glucose reduction is big – as is more time in

euglycemia overall. It's a challenging drug to learn, for sure, but we think growth will continue slowly but steadily.

Exenatide once weekly continues to push forward, but there was no news about whether a bioequivalency study would be required by the FDA. The filing date "by mid 2009" seems conservative, but we assume this is just to cover the chance that new data would be needed. Other big news from Amylin includes a doubling in enrollment of the once-weekly exenatide superiority trial vs. metformin, pioglitazone (Actos) or sitagliptin (Januvia) as a stand-alone therapy. We believe the superiority trials represent a positive sign of confidence by Amylin and we look forward to the results mainly because we think currently *doctors* are holding patients back from Byetta more than anything else. Even though it isn't that hard to teach, the perception seems to be that it is – Kelly's primary care doctor in San Francisco, for example, flatly says "*injections are off the table in my practice, as is anything new – SFUs and metformin are all any type 2 needs*." Unbelievably, this is a noted UCSF trained doctor who is an amazing, very highly regarded PCP. Clearly, even very welcome new options are slow to change behavior.

Amylin also reported plans to make a pramlintide/metreleptin combination injection in 2008. In phase 2, the combination of these hormones was shown to cause 12.7% body weight reduction (an average reduction of 25 lbs) and 70% reduction in excess body weight over a 24- week period. Dr. Alain D. Baron, Senior VP, Research, made an interesting comparison to a recent *JAMA* study, which showed that laparoscopic adjustable gastric banding brought about 60% loss in excess body weight after a two-year period, to provide more perspective on how impressive Amylin's pramlintide/metreleptin results were. He added that the company was performing a six month, multi-arm, dose ranging study of 600 patients to be completed in a year. He stressed the need for such studies given payors' repeated requests for both clinical and health economic outcome benefits before they agree to reimburse an obesity therapy.

Abbott—Strong BGM data in 2007, up 10%: On January 23, Abbott reported 2007 global blood glucose monitoring sales of $1.25 billion, up 10% versus a year ago, a very respectable result versus 2006, when worldwide sales rose just 6.5%. Abbott Diabetes Care global sales had a strong result overall, bolstered by international results offsetting US weakness. Revenue of $334 million rose 15% versus a year earlier, reflecting international sales of $200 million (a first for this milestone), up 29% (17% operationally), while US sales were flat versus a year earlier (a year ago, US sales fell 2% in the last quarter). The recent strong suit at Abbott Diabetes Care is clearly international - management mentioned an expanded commercial presence in India and China, where sales rose 70%. This is in contrast to international sales a year ago, which were up just ~5% (flat operationally). US sales will be critical to bolster in the quarters ahead - we continue to believe incretins have affected the blood glucose market negatively at least to some extent though we assume Abbott feels this less than other players since type 2 adults not on insulin are probably not one of their strongest segments.

The high point of the earnings call was hearing that a US Navigator launch would be later this quarter - we would assume hearing that on the call would mean that the product is approved in the US since Abbott has had problems with disclosures before. It would be good for the industry to have another product out although CGM is not yet a thriving market due to lack of reimbursement and product problems with early generations (which have made significant progress). They will face a steep curve catching up with Medtronic and DexCom, who have been the only two players in the CGM field for over a year. We expect that once approved, the company will move forward rapidly with generational developments.

- **Daiichi Sankyo—FDA approves type 2 diabetes indication for WelChol:** On January 18, Daiichi Sankyo announced that the FDA has approved a type 2 diabetes indication for WelChol as an add-on to one or more anti-diabetic drugs including metformin, sulfonylureas, and insulin. WelChol is a bile acid sequestrant that was approved in 2000 in the US for the reduction of elevated low-density lipoprotein (LDL) cholesterol as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (a.k.a. statin). WelChol is currently the only drug approved for both the reduction of blood glucose and low-density lipoprotein (LDL) cholesterol.

  Given that about 40% of people with type 2 diabetes also have high LDL cholesterol, a drug that addresses both conditions should be welcomed. However, WelChol is less effective at controlling diabetes than other diabetes medications – it only lowered A1c by about 0.5% from an 8.3% baseline in recent studies. It is also less effective at lowering LDL cholesterol than statins. Furthermore, WelChol often causes gastrointestinal side effects and although the fact that it's a combo drug is good, patients must take six tablets once a day or three tables twice a day, a bit of a hassle. For these reasons, we don't expect WelChol to have a major impact on the diabetes landscape. The new indication is likely to increase WelChol's use as an adjunct to statins for patients who also want to achieve improved glycemic control, and it also probably represents the first of many combination therapies addressing glycemia and lipids.

- **BD—Studying the feasibility of Intra-Dermal Insulin Injections:** While searching through the clinical trials database, we noticed an ongoing clinical trial by Becton, Dickinson and Company. The company is conducting a feasibility study comparing the effect of intradermal and subcutaneous insulin administration on blood glucose levels after a standard meal. The study's hypothesis is that intra-dermal insulin will have a more rapid onset and provide a better glucose profile than subcutaneous injection. The researchers will use both regular insulin (Humulin) and insulin lispro (Humalog) in the study, and all subjects enrolled are type 1s. We wonder if the results will call into question the status quo, and we look forward to hearing about the results. Details about the study may be found on the Clinical Trials website at: http://www.clinicaltrials.gov/ct2/show/NCT00553488.

- **Pfizer Animal Health—Raising awareness about obesity – in dogs:** Every January begins with fresh New Year's Resolutions about gym memberships, trimming weight, and running marathons. In 2008, dog owners are making similar pledges for their beloved canines. We are experiencing an obesity epidemic of grand proportions – in dogs. Recent studies indicate that 25 to 40% of the approximately 17 million dogs in the US are overweight or obese, and their owners are often not aware that Rover is rotund. To right this egregious wrong, Pfizer Animal Health has sponsored a month-long program called The National Canine Weight Check to help dog owners determine if their pet is overweight and to raise awareness about the health implications of canine obesity. Dog owners may obtain information about the program and sign up for a free weight check at www.StopCanineObesity.com. We hope that the program will be successful at reducing obesity in dogs so that if nothing else, perhaps it will prompt dog owners to join their pets in the weight loss effort!

—By Kaku Armah, Kelly Close, Jenny Jin, and Mark Yarchoan

4. In the News: ACCORD Results Raise Concerns About Intensive Treatment

The intensive treatment arm of the 10,000-patient Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was halted 18 months ahead of its expected completion date. The move, by the Data

Safety and Monitoring Boar (DSMB), occurred after the board found that the intensive treatment arm had 25% more deaths than the standard treatment arm. The intensive treatment group had a median A1c of 6.4% as compared to a median 7.5% for the standard treatment group. Of the ~10,000 study participants, 257 had died in the intensive treatment group, compared with 203 who were receiving standard treatment (a difference of 54 deaths). According to those close to the trial, the hazard ratios and p value were very convincing[1]. Notably, although patients in the intensively treated group had a lower number of cardiovascular events, a higher percentage of these events were fatal.

The researchers of ACCORD said that they have not identified any specific cause for the higher mortality rate in the intensive treatment arm, emphasizing that there is no evidence that the higher rate is due to increased hypoglycemia or to any specific drug or combination of drugs including Avandia. Because patients were treated with individualized treatment algorithms and the numbers on particular drugs or drug combinations are relatively small, it may be difficult to implicate any specific cause for the increased mortality. We are concerned that the results will cause some patients and healthcare providers to move away from (or stop moving toward) tight glycemic control. On that front, we were pleased to see that the American Diabetes Association (ADA) has put out press releases strongly cautioning people with diabetes not to over-interpret the findings from the ACCORD trial. We are extremely concerned that media coverage of the story will prompt type 2 patients to generalize the results and overreact, even though the researchers of the study have indicated that this was a very specific population.

So what do we make of the ACCORD findings? A lower A1c, similar to people without diabetes, is almost certainly not inherently dangerous, so something about the way that A1cs were lowered was likely responsible. The results are very surprising in our view, as they appear to conflict on the surface with numerous previous trials such as the DCCT or the UKPDS, showing that more intensive control is associated with improved outcomes. Most recently, we heard that preliminary results from the 11,000-patient Action in Diabetes and Vascular disease; preterAx and diamicroN-MR Controlled Evaluation study (ADVANCE) "provide no evidence that intensive treatment to lower blood glucose (sugar) increases risk of death" according to a press statement released by the University of Sydney's George Institute for International Health that is running the study. ADVANCE has a study population that appears, at least on the surface, to be very similar to ACCORD, suggesting that the ACCORD results may not be generalizable even to patients with diabetes who have high baseline cardiovascular disease risk.

One theory put forth by Dr. Irl Hirsch is that the increased mortality observed was an early effect of intensive control in people who already had complications, akin to what happened early in the DCCT in people who already had retinopathy (in the DCCT, retinopathy worsened overall for patients in the intensive treatment group at first, but as the study progressed retinopathy decreased in the intensive arm and increased in the standard treatment arm). In other words, intensive glucose control may prevent complications but it may also worsen complications that are present at baseline. If this theory is correct, it would suggest that we should be treating intensively BEFORE the onset of cardiovascular disease. A key question will be the percentage of patients in ADVANCE and ACCORD who had baseline cardiovascular disease, and whether specific baseline cardiovascular disease histories (pervious MI, stroke, etc.) predisposed patients to increased mortality.

Other theories that have been proposed are that undocumented hypoglycemia, weight gain, or increased glycemic variability may have played a role in the ACCORD results. Of course, it is premature to speculate before the full publication of the ACCORD and ADVANCE results, and we look forward to analyzing the full dataset of both studies.

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[1] Simply using the endpoints of the study, we calculate that the difference is statistically significant (P value of ~0.01 using a simple 2X2 chi-squared test).

- **ACCORD is a ~10,000 patient trial that compares cardiovascular outcomes in patients with type 2 diabetes and high cardiovascular disease risk receiving diabetes therapy targeting an A1c of < 6.0% compared therapy targeting an A1c of 7.0% to 7.9%** Patients were to be treated and followed for 4 to 8 years (approximate mean of 5.6 years) at 77 clinical sites within the United States and Canada. Occurrence of a major cardiovascular disease event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, was the primary outcome. Other cardiovascular outcomes, total mortality, microvascular outcomes, health-related quality of life, and cost-effectiveness served as secondary endpoints. The study had an expected completion date of June 2009, with the primary results to be announced in early 2010. At the time of the interim report, the mean A1c achieved by the intensive group was 6.4%, compared to 7.5% in the standard treatment group. A stable A1c was generally achieved by subjects after 6-9 months of treatment and was maintained throughout the study.

- **The trial was halted 18 months ahead of its expected completion date by the Data Safety and Monitoring Board, which found that intensive treatment increased mortality by 25%.** Of the 10,251 study participants, 257 patients in the intensive treatment group died, compared with 203 who received standard treatment, a difference of 54 deaths. This corresponds to a mortality rate of 11 per 1,000 patient life years and 14 per 1,000 patient life years over the course of four years for the standard and intensive treatment groups, respectively. Notably, 10% fewer heart attacks occurred in the intensively treated group, though a higher percentage of these heart attacks were fatal.

- **These results are very surprising in our view, given that they conflict with the common presumption that patients with physiological A1c will be healthier - we stress, however, that these results specifically apply to the high risk population examined in this study and almost certainly do not reflect the results of intensive treatment of most patients with type 2 diabetes.** Given that having blood glucose levels that resemble those of a person without diabetes should reduce risk for cardiovascular events and death, we expect that it is the means by which the intensively treated patients achieved a lower A1c that is responsible for the increased mortality observed in this group. Another possibility is that A1cs were reduced too quickly in the intensive treatment arm of the study. Patients with uncontrolled hyperglycemia may adapt to the high levels of glucose and have problems when glucose control is rapidly improved, much in the way that alcoholics adapt to alcohol and may experience dangerous withdrawal when the alcohol is stopped. Thus, although these results seem to conflict, at least on the surface, with the results from the UKPDS (2000) and EDIC (2005), these studies examined different populations and different endpoints, so direct comparisons are not possible. UKPDS convincingly showed that tighter glycemic control reduced microvascular risk in patients with type 2 and EDIC showed conclusively that tighter glycemic control in type 1 patients reduced macrovascular risk. ACCORD seems to show that, at least in a population with advanced diabetes, reducing blood glucose very quickly and very aggressively (to levels around 6%) may present additional risks.

- **Statistical analysis:** The researchers did not reveal the P value of the association between intensive control and increased mortality in the study. Our understanding is that this would be normally calculated using a Kaplan-Meier curve using data throughout the study. Simply using the endpoints of the study (257 deaths vs. 203 deaths) and assuming that ~ 5,100 patients were enrolled in each treatment arm, we calculate a P value of ~0.01 (2X2 Chi-square test) – a statistically significant value (i.e., less than 0.05%). This means that there is only about a 1% chance that the observed difference in mortality was due to random chance. We look forward to seeing the more meaningful and powerful statistical calculation that will be shown when the

results of the study are published in a peer reviewed journal. We believe this must have been hard for the researchers – they had to give results as soon as the DSMB ruled, but they have not had time to perform a complete analysis of the available data.

- **To date, the researchers overseeing the study have been unable to identify any specific cause for the higher mortality rate observed in the intensive treatment arm.** The researchers noted that no evidence currently links the higher mortality to increased hypoglycemia nor does any evidence suggest that specific drugs or drug combinations, including Avandia, predispose to higher mortality. The drugs that were used in both treatment arms included metformin, thiazolidinediones (primarily Avandia), insulins, sulfonylureas, exenatide, and acarbose. Given the large number of potential drug combinations used in this study, we believe that the lack of a statistically significant association to particular treatments may be due to a lack of statistical power rather than a true absence of association.

- **The study researchers dismissed the notion that Avandia was responsible for the increased cardiovascular risk in the intensive treatment arm.** They indicated that an analysis had found no link between Avandia and an increased risk of death. Unfortunately, they did not disclose the percentage of patients in the intensive and standard treatment arms who were using Avandia. In all likelihood, a higher percentage of patients in the intensively treated group were using Avandia, possibly at higher doses, than in the standard treatment group. Possibly, the early analyses weren't done using drug doses but rather using the binary question of whether or not Avandia was used. Furthermore, it is likely in our view that the Avandia analysis was conducted within group (ie. Avandia/no Avandia within the intensive treatment arm, and Avandia/no Avandia in the standard treatment arm) – if this was the case, it would be difficult to show statistical significance between Avandia and increased mortality because the number of deaths for each group would be relatively small. Again, we look forward to clarification when the full dataset is published.

- **As the study researchers noted at the time of the announcement, this trial examined a very specific population of patients, and the results should not be generalized to all diabetes patients.** Shortly after the ACCORD announcement, an interim announced was made from the ADVANCE trial, which, similar to ACCORD is examining cardiovascular outcomes in intensively managed patients with type 2 diabetes. To date, ADVANCE has seen no evidence for increased cardiovascular disease risk in its intensive treatment arm, further indicating that the ACCORD results are population specific. In support of this notion, Dr. John Buse indicated that the ACCORD study population was representative of about 10% of patients with diabetes. We believe that because the study patients were not representative of all type 2 patients given the study group's high risk profile, type 2s overall should not overreact to the results. Facts: 1) Patients in the trial had diabetes for at least 10 years and had a high baseline risk of cardiovascular disease. 2) The baseline A1c going into the trial was 8.2%. 3) Patients entering the trial had either known cardiovascular disease or two risk factors - high blood pressure, high cholesterol, obesity, or smoking. 4) They were 62 years old on average. We understand this is the profile for a high-risk patient – but in reality, it's going to be hard for the average type 2 patient or his or her PCP to say definitely that that they aren't at high risk. For us, the question isn't about entry criteria for the trial, it's about characterizing the group of patients that died. But from the information given, patients might assume they are high risk if they have the profile of those entering the trial. Relying on doctors to clarify the results of this trial for their patients is insufficient, given that most doctors will not know how to assess their patients' risk given the information disclosed to date. Until more concrete guidelines are provided based on the profile of

patients who died in this study, patients and doctors will be left anxious, and without clear direction.

- **Notably, the study researchers stressed that both arms of the trial were better controlled at the 4-year mark than the average type 2 patient in the US.** That was a silver lining in the trial that was easy to skip over – given that all patients achieved an A1c of 7.5% or less, the outcomes overall were much better than would have been expected. We think part of the reason for this was the testing patterns – all patients were testing more frequently. Specifically, patients in the intensive treatment arm were testing blood glucose 3-5 times a day and in the conventional arm about 1-2 times per day. We know that the average testing frequency in the US is about 1.5-1.7 times per day, but that this is not representative of the average patient with type 2 diabetes, some of whom don't test at all.

- **We believe the results of ACCORD should not be generalized** to 1) newly diagnosed type 2 patients; 2) patients with type 2 who do not have multiple cardiovascular risk factors; and 3) those with type 1. How type 2 patients (or their payors) will determine whether they are at high risk of cardiovascular disease isn't altogether clear.

- **We are very concerned that the results of this study will cause some patients and healthcare providers to avoid tight glycemic control.** We are worried that at the margin, where a healthcare provider might have put a patient on more aggressive medication, that providers will now say, "*Oh, 8%, oh, that's okay. Never know, do we*?" We believe that if someone sees Gina Kolata's *New York Times* article implying that ACCORD undermines previous trials showing the benefit of tight glycemic control, patients at the margin won't be reaching for their blood glucose monitor or pill bottle or pen or syringe before they eat.

- **ADA provided excellent guidance to patients.** While we were disappointed by various media accounts, we were pleased to see that both the ADA and the American Association of Clinical Endocrinologists (AACE) have put out press releases strongly cautioning patients not to be alarmed and over-interpret the findings from the ACCORD trial. Dr. Richard Kahn, Chief Scientific & Medical Officer at the ADA, wrote, *"[The] ADA continues to reinforce that good control of blood glucose is important in the management of diabetes and its complications and reminds people with diabetes not to alter their course of treatment without first consulting with their health care team*." We would say the next step is just to make sure that healthcare teams out there, particularly those in primary care, have good guidance.

- **We hope to see subsection analyses of the data soon.** In particular, we would like to know if A1c measurements were associated with mortality, or if a difference could only be observed between the two treatment groups. Similarly, we would like to see a sectional analysis of each of the drugs frequently used in the study (metformin, sulfonylureas, TZDs, incretins, and insulin) as well as drug doses. Of these drugs, Avandia, high insulin doses, and sulfonylureas have all been suggested by some researchers to raise cardiovascular risk, and we would like to see if the data supports any of these associations. We'd also like to see data on weight in the two groups, especially in those patients who died, to better understand the role excess weight may have played. Unfortunately, given the diverse treatments used in these groups, pinpointing any particular drug therapy or drug combination may be difficult, if not impossible. While the study researchers have already said that there are no associations, we would like to see at least aggregated data on doses of various medications used.

- **We anticipate that further information from the ADVANCE trial will help distinguish the population at risk during intensive diabetes therapy.** ADVANCE is not showing the same increased mortality observed in ACCORD, despite what appear to be, at least

on the surface, similar study populations and treatment protocols. We don't yet know what the baseline level of cardiovascular disease was in the ACCORD trial, but it may be higher than the 32% reported in ADVANCE, potentially explaining the divergent outcomes. ADVANCE also relies heavily on SFUs to initiate intensive therapy; without knowing more about the therapy actually used in ACCORD, we cannot yet evaluate whether we may be seeing some treatment advantage from SFUs in high-risk patients. ACCORD had a slightly lower target A1c (6.0% versus 6.5%), though without knowing the A1c levels of the patients who died in the ACCORD trial, the importance of this difference cannot be evaluated. Clearly numerous explanations could account for the differences between ACCORD and ADVANCE, but the main point is that the ACCORD findings are not generalizable even to a similar population of patients, suggesting that the actually number of people who are placed at risk by intensive diabetes therapy is likely to be smaller than the population that would have met the ACCORD enrollment criteria.

- **We also look forward to data from several other large studies including ORIGIN and VADT that may further elucidate the benefits or dangers of tight glycemic control.** ORIGIN (Outcome Reduction With Initial Glargine Intervention) is a 10,000-patient trial funded by Sanofi-Aventis that is investigating the effect of insulin glargine (Lantus) and omega-3 fatty acids on cardiovascular event risk. The estimated study completion date is October 2009. VADT (the Veterans Affairs Diabetes Trial) is a study of approximately 1,700 United States veterans determining the effects of intensive vs. conventional glucose control on major cardiovascular events with a follow-up of 5-7 years. The study has an estimated completion date of May 2008, and A1c goals of 6.5% vs. ~8% are being compared.

- **In terms of commercial implications for companies in diabetes**, while we by no means see business slowing as a result of ACCORD, we do believe that very tight glycemic control recommendations on the order of moving all patients to 6% would have resulted in robust growth seen across the industry – we no longer expect such momentum and believe that reimbursement pressures could mount as a result of ACCORD.

- **Questions:** 1) How should patients determine whether they are at high risk? 2) What should the average doctor say to patients? What will they say? Educators? PCPs? 3) How will dosing for various drugs change? 4) What were median A1cs for two arms and for those who died, what were average/median A1cs at death? 5) What were the blood pressure and lipid differences? Weight differences? 6) Was glycemic variability measured in any arm? Results? 7) How much larger would the trial have needed to be to study newly diagnosed patients? 8) Could hypoglycemia be the cause of sudden deaths?

Note: Please see our website (www.closeconcerns.com) for an interview with Drs. Jay Skyler and Irl Hirsch, led by biotech expert Mike King and Kelly Close, which discusses the implications of the ACCORD results

—By Kelly Close and Mark Yarchoan

5. In the News II: Direct Annual US Cost of Diabetes Soars to $116 billion in 2007 – Complications the Culprit, Why No Complaints?

It's well known that diabetes costs in the US are spiraling out of control, but the headline this month is that the situation is worse than previously thought. According to new numbers released by the ADA on January 25, annual direct spending on diabetes has risen 26% from $92 billion in 2002 to $116 billion in 2007, and total annual estimated costs including indirect costs have risen by 32%, reaching $174 billion in 2007 from $132 billion in 2002. This is much graver than previously forecast; in 2002, the ADA

predicted that the direct costs of diabetes would total $109 billion in 2010; we've now surpassed that point by $7 billion, and it's only 2008! In our view, the real story is not just that the total costs are going up faster than anticipated, but rather the makeup of these growing costs. Here's a hint: medical costs for diabetes aren't the main cause of the spiral.

- **Let's look at the numbers in a little more detail:** In 2002, medical costs for diabetes (diabetes treatment) made up 25% of the total direct costs. Complications made up 27% of the total, and other "excess" costs made up the balance. And in 2007? Even though policymakers and payors have complained, some bitterly, about the costs of drugs and devices, the percentage of direct spending attributed to direct medical costs for diabetes has actually gone *down*, to 23%. The absolute increase has been from $23 billion to $27 billion, a Compound Annual Growth Rate (CAGR) of just 3%. Said another way, of the $24 billion *more* the US has spent in just five years, only 12% of that stems from more dollars going to drugs and devices.

- **So where has the increase in diabetes spending been? Complications.** The costs of treating complications of diabetes have grown to a massive $58 billion, from $25 billion in 2002. That's a CAGR of 19%! Therefore, as a percentage of the total cost of diabetes, the costs of spending on drugs and devices have gone DOWN and complications have gone UP, rather profoundly. We're spending less to keep diabetes under control, and more to deal with the consequences. The treatment of complications relating to diabetes is now about half of the total US diabetes cost. Here's a brilliant idea for payors: pay a buck and save a buck.

- **We're in far more trouble than we had forecast.** The ADA predicted in the 2002 piece that the US would spend $109 billion in 2010 on direct costs - and, as we saw above, we just finished 2007 and spent $116 billion! If growth keeps at this pace, we'll be at $135 billion in 2010 in direct costs and at $225 billion in 2020, which is over 60% higher than forecast in 2002. We're already spending one in five healthcare dollars on diabetes. We expect that as younger and younger age groups develop type 2 diabetes, there will be an even greater negative impact on national productivity. How bad does it need to be before it's recognized as a crisis and patients receive the tools and therapies they need?

- **These dramatic increases highlight, in our view, the importance of using the right treatments and therapies for patients now**. In our opinion, the fact that the US is now spending one of five healthcare dollars on diabetes reflects far too much spending on hospitalizations and long-term complications and not enough spending on treatments and education on the importance of optimal diabetes management. We believe if more were done to help patients before they progress to truly advanced diabetes, we'd be in much better shape. Let's try giving more people incretins so they'll actually take their medicine, let's try reimbursing the number of blood glucose strips that people really need to treat their diabetes, let's pay for the education needed for patients to correctly connect the dots, let's try intensive insulin in the hospital rather than letting patients languish at blood glucose levels of 150 mg/dL or worse. Let's try making insulin easier - really!

- **Hopefully the ADA report will spark some action from Congress.** The new data were discussed on Capitol Hill during a congressional briefing on January 25. Representatives Diana DeGette (D-CO), Mike Castle (R-DE), Xavier Becerra (D-CA), Zach Space (D-OH), and Mark Kirk (R-IL), leaders from the Congressional Diabetes Caucus, were expected to attend the briefing, joined by leaders from the ADA as well as diabetes researchers, epidemiologists, and statisticians. We look forward to their update.

- **In our view, the total costs of diabetes may be reduced through greater focus on tighter glycemic control, achieved through better diabetes management and**

through more optimized use of diabetes drugs and devices. Last month we reported that for the first time in a long time, the average A1c of people with diagnosed diabetes in the US was dropping and has reached 7.0%. We hope that in time this trend will be reflected in decreased costs from diabetes complications, and that this trend of better glucose control may continue into the future. While clearly, part of the increase can be explained by the constantly growing epidemic, we feel that the costs of treatments are shouldering too much of the blame – here's to spending far more on education and far less, going forward, on complications.

—By Kelly Close and Mark Yarchoan

6. Interview with Australian Diabetes Thought Leader, Director of the International Diabetes Institute, and Endo of Oz, Dr. Paul Zimmet

Dr. Paul Zimmet is the Foundation Director of the International Diabetes Institute and a professor of *Dr. Paul Zimmet is the Foundation Director of the International Diabetes Institute and a professor of* *diabetes at Monash University in Australia. He led a team that carried out the first national diabetes and obesity population study in Australia called AusDiab (published in 2003 in the Med J Aust), and is the author of over 500 peer-reviewed scientific studies and reviews. For his work, he has received numerous awards, including the AM Cohen Award Lecture of the EASD, the Kelly West and Harold Rifkin Medals from the ADA, the Banting Award from Diabetes UK, the Eli Lilly Award of the IDF and the 2007 Novartis Award for Longstanding achievements in diabetes. In an interview with Kelly Close and John Close when they visited Melbourne last December, Dr. Zimmet discussed drugs under development at the Institute for Diabetes Discovery (a company working to develop drugs to treat both the causes – obesity, insulin resistance – and the complications – neuropathy, atherosclerosis – of diabetes; the latter in particular is a sadly underserved field currently). He also talked about the treatment of pre-diabetes and the role of governments across the globe in stemming the diabetes epidemic. Kelly and John went back to Dr. Zimmet last week to get the diabetes expert's opinions on ACCORD and ADVANCE – these thoughts close the interview.*

Kelly Close: Thank you for taking the time to speak with us today. We'll start out by asking about some of the drugs coming out of the International Diabetes Institute.

Dr. Paul Zimmet: Great.

Kelly: One of the ones we wanted to talk about is ISF-402. Is that one of the drugs that came out of the International Diabetes Institute?

Dr. Zimmet: No, but it's a fascinating story. When I finished my physician training in Melbourne in diabetes, it was suggested that I should do a PhD to round me off, and I was sent to the laboratory of a scientist who's very famous, Professor Joseph Bornstein. In 1950, he had developed the first bioassay for insulin, and he was the first person to actually show there were two types of diabetes.

John Close: That's amazing.

Dr. Zimmet: So that happened in Melbourne. He took out virtually every endocrine gland in rats. And then he took extracts of the serum of so-called juvenile [type 1] diabetics, and showed that injecting this serum had no effect on blood sugar in these animals. However, when he took extracts from people with adult-onset [type 2] diabetes and injected it into the rats he was able to lower their blood sugar. So he said, "You know, we've got two types of diabetes." There were many skeptics so he went to London to work with the great Dr. RD Lawrence and they jointly published the results in 1950 in the *British Medical Journal*. And ten years later, Yalow and Berson developed the immunoassay and, of course, they got the

Nobel Prize, but you know, Bornstein's pioneering work, really, has never been recognized properly.

So when I went to work for Bornstein his next idea was that growth hormone had two actions. One was if you give growth hormone injection, the first thing that happens is the blood sugar drops. After a couple of hours, it rises and goes above normal, so it has both an anti-diabetes effect and a diabetes-like effect. Bornstein postulated that there were substances liberated from growth hormone, one that was an insulin antagonist and one was an insulin promoter, and he was actually able to isolate two substances from sheep brains with these actions. So he told me that for the next step, "You have to see if you can find these substances in humans."

By an absolute fluke, perhaps serendipity, within six or seven weeks into my PhD, using the same laboratory methods that he had used to isolate these substances from the sheep brain, I was able to find in the blood a substance which inhibited insulin action – yes, the insulin antagonist, and we actually published this in the *British Medical Journal*. I couldn't find in the blood an insulin-like substance so I had to look in other biological fluids so went for urine, and there I was able to isolate from the urine a substance which when we gave it to rabbits, caused the blood sugar to fall.

Kelly: Wow, that's incredible.

Dr. Zimmet: So to cut a long story short, he had demonstrated the possibility that this insulin-like peptide, which he thought was from growth hormone, was a potential future drug for diabetes. Then there was about a 25-year gap after Bornstein passed away. I tried with my co-inventor, Professor Frank Ng, to convince people in the pharmaceutical industry that this was a compound worth studying, but none of the drug companies were very interested. In 2001, a small biotech company came to us and asked if we had any biotechnology discoveries that could help the company out. So this company came along and they were going to give us $1,000,000 to start working on this drug properly, and on September the 15, State Treasurer John Brumby, who's now Premier of Victoria, was going to announce this at the Parliament. Then along came September 11th. So four days before we were going to get our million dollars, the markets crashed.

Kelly: Ohhhh.

Dr. Zimmet: After about a year, the company, Dia-B Technologies, came back and said, 'We've got a couple of hundred thousand, can you deal with that?" And so now we started on the work. We did animal studies, we were able to synthesize a lot of the peptides, did toxicity, all of the preclinical stuff was successful, and late last year we started the phase 1 clinical trials with the peptide which is now concluded safe in both controls in people with diabetes. We're now looking for people or partners to build the next stage to it because the company obviously hasn't got the funds.

John: Seems like great potential….

Kelly: We'd definitely advocate exploring partnerships, now that there is phase 1 data. Can you say how much you have explored partnerships?

John: Please fill us in a little more about where the drug comes from.

Dr. Zimmet: It's actually a four-amino-acid peptide, so it's so damn easy to synthesize. And it's also orally active. The fascinating thing is that now we think it may not even be related to growth hormone because we've done studies that showed that it co-localizes in the beta cell with insulin.

John: Oh, so there might be cause to treat it …

Dr. Zimmet: And it will. What we think is there are two potential actions: firstly, insulin in the pancreas is in a hexameric form bound by zinc, and we've discovered that the ISF-402 pulls out the zinc and converts the hexamers to monomers, which makes insulin active. The other thing we've discovered is that for some reason, it keeps insulin longer in the circulation.

John: Do you see this as being a therapy for type 2s, type 1s, or both?

Dr. Zimmet: So we think it's predominantly type 2 diabetes, and of course, I have a different concept of treatment now. I think pre-diabetes is also a target.

Kelly: Pre-diabetes. Wow. That makes great sense.

Dr. Zimmet: Pre-diabetes should be also treated in any case, you know.

Kelly: Yesssssss. There just seems so much resistance in the US, and so misplaced, but certainly it's happening off-label …

Dr. Zimmet: Yes, look, this is all like a fairy tale in a sense. It's a bit like Shrek. Are we there yet? But the issue you raise about type 1 diabetes is interesting – it may well be that combining it with insulin may potentiate the effects of the insulin. It may affect the insulin in the circulation with those actions.

Kelly: The idea about pre-diabetes is also really compelling because there's such a great need, isn't there?

Dr. Zimmet: Well see, before, back in 1965 when the first WHO Committee came out with the diagnostic criteria for diabetes, people said that a 240 mg/dl blood sugar level at two hours after a load was diagnostic. And then with the wisdom of more information, the WHO Committee in 1980 and the American Diabetes Expert Committee made the diagnostic level 200 mg/dl, with a 140 to 199 mg/dl being impaired glucose tolerance. I think that most sensible people now would regard those cut-offs as not being really valid. The risk of complications both micro-vascular and macro-vascular is a continuous increasing risk. And so these cut-off points are artificial in a sense, and I think we should be much more aggressive about treating pre-diabetes.

John: Right …

Dr. Zimmet: There's been a lot of, I think, stupid statements saying that the metabolic syndrome was invented by the pharmaceutical industry. It's true that they may promote knowledge about it, and I know a number of the companies that feel that their drugs should be used earlier, and so there will be accusations that this is being driven by the pharmaceutical industry again. But anyone who really thinks through the story realizes that once you diagnose diabetes in adults, while it's not necessarily too late, the fact is that they may have already been developing complications for five or six years. It's important we get in early.

Kelly: Do you think they should be measuring the insulin levels or is that too complicated?

Dr. Zimmet: The measurement of insulin is almost totally useless in individuals. It's useful in population studies, but there's so much variability in insulin in the individual that's affected by genetics, exercise, what people eat, etc. that a single insulin level in a person doesn't give you any information.

Kelly: Do you think that there is any chance that the TZDs would be approved for pre-diabetes? Or do you think at this point because of all the safety concerns that it's kind of a lost cause?

Dr. Zimmet: The studies we need relating to the safety of TZDs are going to be very hard to do, and it's hard to convince a whole group of people to go on Avandia if they've read the newspapers about this increased heart risk. It's a difficult thing because people with diabetes already are at increased cardiovascular risk in the first place. It's well established that the TZDs

work in pre-diabetes, but if you stop taking them, of course, like in the DREAM study, then you sort of go back to diabetes or the same risk.

John: So what do you think about other drugs for pre-diabetes?

Dr. Zimmet: There are going to be studies now with DPP-4 inhibitors and Byetta. I mean you'd expect with Byetta that if you're giving it to obese people, they're going to lose weight and reduce their risk of developing diabetes. Byetta is a very exciting drug for sure. I had patients flying to America for it.

Kelly: Wow, powerful, did you really?

Dr. Zimmet: Yes, but it's been approved now and we've got a lot more patients on it with some terrific responses. However, there are also a number of people who just can't tolerate the nausea.

Kelly: I think that the nausea associated with the once-weekly form of exenatide should be much less. Do people mind taking the shots, or not so much?

Dr. Zimmet: Not if they know that they're going to lose weight and get better control of their diabetes.

John: Right.

Dr. Zimmet: The biggest question with Byetta, of course, is whether the effect continues in the long term. Byetta is actually beta cell-directed, and the experience so far is that it is beta cell protective, but everyone says eventually beta cells are going to fade. So we don't know yet whether Byetta is going to change the natural history.

John: What sort of a study would you like to see to be able to determine that?

Dr. Zimmet: I guess even any clinic that just follows up on their patients over a long period of time will see it happen. It may take ten years. I don't know what the rationale for Byetta would be for pre-diabetes except predominantly the weight loss potential and improving beta cell function.

Kelly: Does it make you think that insulin resistance especially needs to be studied more? Is that one of the hallmarks of the PTP1B inhibitor? Oh, and I would also love to go back to ISF-402 and the company Dia-B because I realized we didn't really get a good clear sense of what the next steps were on that.

Dr. Zimmet: Sure. Well, phase 1 for ISF-402 is now finished. I don't think that they'll be able to raise the money for phase 2 from the shareholders. You know, Dia-B is only a small company. The best bet is to get another pharma company that may be interested in partnering out to the next stage.

Kelly: Yes – what are your impressions of current treatments?

Dr. Zimmet: Whatever treatments we have with type 2 diabetes now are clearly not perfect. People are starting to say, "Oh, you know, we've now got the DPP-4 inhibitor, we've got Byetta." But you need several drugs for type 2 diabetes. It comes back to your question about insulin resistance. I always, until recently, was totally convinced type 2 diabetes was predominantly insulin resistance. I didn't think the beta cell aspect was that important. I thought it was a failure of the beta cell due to the insulin resistance. I'm changing my view now, which I guess I'm entitled to do. There are genetic and epigenetic factors determining beta cell function, and beta cell function and insulin resistance are both key factors in driving diabetes. In different people there is a different contribution of each, you know, and we really need a drug that tackles that total picture.

Kelly: What made you change your mind?

Dr. Zimmet: I just think the mounting research evidence. It was our epidemiological research that convinced me that having insulin resistance was the main problem. But now we have the suggestion that Byetta is protective. And at least in animals, the beta cell protective effect of the glitazones appears to be independent of their effects on insulin resistance.

Kelly: Do you have any speculation on how valuable the DPP-4 inhibitors might be?

Dr. Zimmet: I think they're valuable in addition to what we already have. On their own I don't think the effect is all that dramatic, but when they're combined with metformin, patients certainly get an improvement. I mean, metformin is amazing whatever you say about it. It's just an amazing drug.

John: Do you prescribe metformin for pre-diabetes?

Dr. Zimmet: I don't – it is not approved for the purpose of pre-diabetes in Australia.

Kelly: Are you more optimistic about GLP-1 or about DPP-4 inhibitors in terms of being able to be a real treatment for pre-diabetes?

Dr. Zimmet: I think it's reasonably clear that Byetta is better in the sense that you have both improved glycemic control with beta cell function and weight loss. I mean, it's intuitively stupid that most of the treatments we have for type 2 diabetes, including insulin, result in weight gain, when the important thing you need to do is lose weight in type 2 diabetes. So Byetta obviously has got an advantage, and metformin comes next as do the DPP-4s, but the sulfonylureas and the glitazones and insulin can put weight on.

Kelly: Do you think the sulfonylureas will be dead soon?

Dr. Zimmet: Well, there was a very famous German diabetologist, the late Michael Berger, who reckoned that they should be thrown out. He made speeches about this. I actually agreed with him but with my increasing understanding that there may be beta cell problems in type 2 diabetes, they may still have a role, I think there is a limited role for sulfonylureas overall and especially in people with MODY type diabetes where they have a genetic defect which is causing impaired insulin secretion.

John: What do you think are prospects for some of the other new classes? Can you talk a little bit about PTP1B inhibitors?

Dr. Zimmet: Well, I have a conflict of interest in that I'm the Chairman of the Scientific Advisory Board of the Institute for Diabetes Discovery (IDD), which has one.

Kelly: Actually, that's why we asked, because we know how knowledgeable you are about the class.

Dr. Zimmet: Well, I think it's a molecule of great promise. The question is in the specificity because if they are inhibiting an area that does not include diabetes, we might have some problems. So I think the biggest issue with the PTP1B inhibitor is the specificity of its action.

Kelly: There is some worry about the DPP-4 inhibitors, too, and I don't know if now that they've been used a little more widely maybe there's less concern about it.

Dr. Zimmet: At the moment, there's less concern, but they've only been used for a couple years now so we don't know. You know what we need? I had to say this: the best thing for managing diabetes is increased physical activity.

John: To tell you honestly my view — and I invite you to criticize it — but my view is that even if the government steps forward and says, "Here's a very large quantity of money to tackle this problem," no one is precisely sure how to actually spend the money because diet and exercise seem to be a tricky thing to get people to do.

Dr. Zimmet: The Australian government last year announced two major priorities: climate change and detecting type 2 diabetes. And $200 million has been allocated — $100 million from the federal government and $100 million from the states combined — to start a type 2 diabetes prevention program. I'm on the advisory group.

Kelly: Wow. (*silence*) That is incredible.

Dr. Zimmet: Now they're hoping by September to introduce a pilot diabetes prevention program (DPP) type project for about 150,000 Australians. They'll use to a certain extent the Finnish model, not the DPP model. Diabetes is on the agenda and at the moment our group is for example developing a risk questionnaire. You can't go around glucose tolerance testing everyone.

Kelly: Right.

Dr. Zimmet: So there's a FINDrisk questionnaire, but Finland is a homogenous population. Australia is like America in that 30-40% of people are from overseas, so we are developing a special questionnaire that can be used in Australia for general practitioners to apply. People will be able to go on the Internet and see if they're at risk.

John: This is wonderful. What is specially tested in the pilot program that you're doing?

Dr. Zimmet: Basically the Finnish model, but without the intervention lifestyle strategies. If you're in the program, you're taught to do exercise regularly, but you could also just do the course and go home and watch television again, right?

John: Right … tell us more about the early phase, if you would.

Dr. Zimmet: The first phase is the pilot of study of about 150,000 people, and then they're going to need a lot more money allocated for the whole community intervention. But the whole issue is that it's made diabetes much more front-page and upfront.

John: That's wonderful.

Kelly: Were you surprised at the outcomes of your five-year national diabetes study? I think the results were kind of startling, especially in the younger age groups.

Dr. Zimmet: Yeah, I was surprised to an extent, but not surprised about what happened. We see a tendency in Australia to follow America and you just have to wander around here now and then to see younger women who may not be obese, but you can see underneath the tank tops, folds of fat pushing out. So I don't know that I was too surprised. We're actually planning a ten-year follow-up of AusDiab, our national diabetes study run by my institute, in 2010. We're just waiting now for funds for us to follow up the people who we studied in 2000 to 2005, but we'll also recruit a new cohort of people.

Kelly: This is just a side question. In the U.S. there has been some trouble getting new doctors to focus on diabetes. Medical students aren't choosing to specialize in diabetes care. How in Australia do you keep the younger people interested in treating diabetes?

Dr. Zimmet: I'll tell you where the problem is. I, as a physician, have only one procedure I can do—blood sugar—which is $15, and my colleagues in gastroenterology can put down gastroscopes and do five before lunch and earn $8,000 to $10,000.

Kelly: This is the problem in the U.S.

Dr. Zimmet: It never occurred to me when I went into medicine that I would be thinking about what income I could make. So young people are now choosing their careers to a certain extent on what they can earn.

Kelly: Could you talk about which countries you think are doing the best jobs in tackling diabetes? One of the things that you said at the pre-conference was really interesting about China and India and how it seemed like maybe they were taking a little bit more aggressive approaches to diabetes.

Dr. Zimmet: Again, that's a very hard question to answer. Clearly, the United Nations' declaration on diabetes has been very important to getting all countries to know it's a problem that must be focused on. The real epidemic of diabetes is taking place in India, China, and the Middle East - you know, in the Arab Emirates and Saudi Arabia.

John: So what governments are responding best?

Dr. Zimmet: I'd have to say probably Australia and Finland. Finland is probably way ahead of everyone. Australia has the opportunity of being another Finland. I'm not sure where the United States is going. If I were Hillary Clinton now, I'd be going for the diabetes vote. You know, you've got 30 to 40 million votes out there.

Kelly: Yeah, I know. I wonder if you could also go back to the different alternatives that might be available to patients in the future. Do you have any thoughts about any of the other new classes like SGLT2 inhibitors? I mean, we've heard everything from, "Oh it's not going to be that much greater than maybe urinary tract infections" versus, "Oh, this is another new class that could be promising or encouraging."

Dr. Zimmet: I'm not terribly impressed by any of the new classes. The SGLT2 inhibitors don't make physiological sense to me. I haven't seen anything else on the horizon that I'd be excited about. I think there hasn't been enough focus on tackling the microvascular complications. One thing I could get excited about is the drug sulodexide.

Kelly: Tell us more about that, please.

Dr. Zimmet: It's a drug that's being tested here and internationally that reduces albuminuria, which of course, the ACE inhibitors do, too. The actual studies of it look very good in terms of reducing microalbuminuria.

I've had an interesting dialogue with the JDRF on the issue of new drugs for complications after they knocked back a joint funding proposal for a drug for diabetic neuropathy. It's one thing to cure diabetes, but what about the complications? They're so focused on stem cells and islet cell transplantation. I think they need to refocus a little bit themselves.

Kelly: Islet cell transplantation has obviously been pretty disappointing, from a patient perspective.

Dr. Zimmet: I agree with you that yes, it's curing diabetes but also preventing complications and making day-to-day life better. They've become a little more popular in the US in the last few years because they have been doing more work on continuous monitoring and the artificial pancreas. People are very curious to see how that goes. The whole problem is paying for these things because they are quite expensive.

John: Some would say that until a few years ago there was almost 100% "find the cure, find the cure." But that has definitely changed now.

Dr. Zimmet: That's good. So I thought I would challenge them on the grounds that even if it's not successful, maybe they can refocus on where they stand.

Kelly: We're very supportive from a patient perspective on what they are trying to do for CGM development and access. Switching gears - do you have any thoughts about the regulatory pathway for drugs, particularly in the US, which has implications globally?

Dr. Zimmet: It is very easy to be critical of the FDA and even Australian agencies. I feel that some of the decisions in Australia are more related to finance than to the reality of the need of people for the drug. On the other hand, I think that with rimonabant, all of the drug's actions are very impressive except this concern about suicidal ideation, which I guess if you're careful about and treat your patients right, you should be okay with it. On the other hand, a lot of obese people do have depression. There have been some recent instances where the caution they have shown seems very justified. So you have what is best described as a delicate situation.

Kelly: You mean like Rezulin (troglitazone).

Dr. Zimmet: Yes, but not just from diabetes. I mean in the cardiovascular area and also in the arthritis area. There have been drugs that are being withdrawn. So there is this very delicate balance of trying to get effective drugs on the market for people and on the other hand to ensure that there aren't long-term complications. I don't know how we'll ever get it right actually. If companies put $1 billion in developing a drug and then they've got to test for 10 years to know the safety and all that, the patent life is small and there's little incentive to innovate.

Kelly: Could you talk about what companies you're very impressed with in terms of their commitment to scientific innovation and bringing new drugs out?

Dr. Zimmet: I'm partly influenced by the fact that most of the companies now are laying off their research staff. Over the last couple of months, you've had the Novartis layoffs as well as Pfizer, BMS, Genentech - there's a long list.

Kelly: And you think that's hitting diabetes disproportionately or not as much?

Dr. Zimmet: Well, it's hard to say. Some of those companies such as Genentech aren't very much into diabetes.

Kelly: As you look at ongoing research, what do you think is some of the most innovative work that's going on?

Dr. Zimmet: We are still scratching the surface of diabetes. There are some really interesting things going on. For example, there is some evidence now that bone may be producing a hormone that influences beta cell function. And it brings up the question of why people with diabetes are more likely to get osteoporosis. There's a scientist, Dr. Jeffrey Gordon, who has recently shown that certain bacteria in the gut are more likely to be obeseogenic from a causative view than others. There are just so many new areas of research, and the field is always expanding.

Kelly: We need to look into that! Anything else that you find particularly exciting?

Dr. Zimmet: The importance of the role of the brain in diabetes. That will become a more important area of study in the future, I think. There's always something new and exciting.

John: (Ed. note – we've pushed ahead to February) Dr. Zimmet, can you tell us your views on ACCORD and ADVANCE?

Dr. Zimmet: I don't think we have enough information yet on ACCORD. This was a trial in adults with type 2 diabetes at especially high risk for heart attack and stroke. The exact reasons for the increased mortality in the intensive treatment group are unclear. It certainly looks like intensive treatment to target blood glucose levels below HbA1C of under 6.0% may not be appropriate for some patients, especially those at high risk of heart attack or stroke. Given the results came out as a press release, it will be interesting to see if they can get the results published in a peer review journal!!!

The ACCORD results are not supported by the ADVANCE trial, also conducted in type 2 diabetes subjects where there was no increase in mortality in the intensive glycemic arm of that trial despite an achieved A1C similar to that reported in ACCORD. However, the people in ADVACE were less likely to have severe cardiovascular disease. At present, we do not have enough information to advise people with diabetes to make any changes to their treatment or targets.

Kelly: (Ed. note – back in December) Thank you *so* much Dr. Zimmet, this wraps up our questions, and we really appreciate your time and insights very much. We can't thank you enough for taking the time and we've loved drinking Shiraz here on the Melbourne harbor…

John: Haven't we!

Dr. Zimmet: And thank you so much as well.

7. Conference Pearls: 27th Workshop of the AIDPIT Study Group

January 27-29, 2008 • Igls, Austria • www.aidpit.org/

The 2008 Artificial Insulin Delivery, Pancreas, Islet Transplantation (AIDPIT) conference, a subset of EASD, was quite Euro-centric and less industry-focused than other diabetes technology conferences. This was truly a gem of a conference, with approximately 200 dedicated attendees who gathered to discuss diabetes technology in the shadow of the beautiful Tyrolean Alps. In comparison to last year's meeting, we found there to be much more talk about CGM (or 'real time CGM' as the Europeans like to say). As far as the artificial pancreas was concerned, it became clear to us at the meeting that progress toward the artificial pancreas might be a little faster than most people would expect. Even a lot of what some would characterize as dry talk about regulatory approaches really just reflected the fact that we are going to see a lot of human closed-loop data generated over the next 12 months. There are many sites in the USA applying for IDE's right now. Exciting!

- **Dr. Lutz Heinemann provided some controversial views on the value of SMBG.** He does not believe that: SMBG is performed well by patients, SMBG is a simple and reliable procedure, SMBG is a commodity or that SMBG will soon be replaced by CGM (at least not in the next few years). Dr. Heinemann doesn't believe CGM will grow quickly, or that it will replace SMBG (those are two very different things, of course!) - he cited reimbursement, calibration, and body image issues as reasons and stressed that to date, there is no good evidence that CGM provides any benefit to patients with diabetes in terms of published, large, randomized controlled trials. In the meantime, he's expecting better communication between the meter and the pump (as we see with Insulet, for example).

- **Dr. Marc Prentki sought to take the conventional wisdom that type 2 diabetes is characterized by an inadequate beta-cell response to insulin resistance a step further.** He suggests that type 2 is a beta-cell disease caused by an excess amount of glucose. Insulin resistance is basically a byproduct and defense mechanism to "glucolipotoxicity" (the synergistic toxic effects of hyperglycemia and dyslipidemia), which in turn kills beta cells in susceptible individuals and leads to type 2. His conclusion: we should be working to fix the mechanisms that drive glucolipotoxicity, which should simultaneously fix both insulin resistance and beta-cell death. Hence, we shouldn't be focusing on insulin resistance alone or simply lowering blood glucose if we want to stop progression. This theory certainly fits with current treatment strategies.

- **Dr. Helene Hanaire-Broutin stressed that pumps are best for patients with severe hypoglycemia, who are above target, or have wide glucose fluctuations** – this seems to be a big-time European (sorry to generalize) view that we've heard of late. Sure, pump therapy can help improve these problems, but we would hate to see pumps limited to these groups. We're so hooked on pump therapy we would probably resort to poor self-care for a period of time in order to qualify for pump therapy: how screwed up is that? Well, it's reality in the UK where only ~1% of type 1s can qualify for pump therapy. What can be improved in the future? New pumps – smaller, simpler "patch pumps" such as OmniPod and Valeritas, says Dr. Hanaire-Broutin – that are easy to use and have automatic needle insertion, which might help pumps to take off for type 2 patients. Ultimately, Dr. Hanaire-Broutin expects to see devices combining insulin delivery, glucose monitoring and advice to be established as the norm. Wow. The most important thing is how patients use pumps: doctors and patients have to learn how to translate CGM data into therapy adjustments. From our view, the power of combining CGM data with insulin pumps is really something.

- **Medtronic is set to raise the bar in CGM development.** Medtronic is looking at simplified use and placement of CGM in the hospital. Dr. Alan Marcus also stated that they are pursuing CGM that doesn't need fingerstick confirmation. Wow, again! The company wants to give options for "flexible delivery," so a patch pump system is in line for development. This will be worn on the body and offer a full-featured or simplified controller. For therapy management, the goal is to gather information combining insulin, meals, glucose levels, and activity. The patient (or caregiver) should have accessibility everywhere – on their watch, on a Blackberry, in the next room, when the child is at school, or even on the "dashboard on my car". Medtronic is also working on a system that stops the basal insulin of a pump when the patient has hypoglycemia and doesn't respond to alarms – we first learned about that at the Global Diabetes Summit in Columbus, which we wrote about last month. We also learned following the conference that the next generation of the CGMS Gold will be called iPro. Very Apple! That's excellent ~ we know this to be a major step up from the former system and as we understand it, the reimbursement is actually be quite good.

- **The real goal of technology-driven diabetes therapy is attaining euglycemia.** An A1c of 7% is a mean blood glucose of nearly twice what a person without diabetes experiences. Even with nine fingersticks a day, we spend less than 30% of our time in the euglycemic range, according to an oft-cited *Diabetes Care* study by Dr. Bruce Bode. So get this - that's 30% of the day over 180 mg/dl and two hours a day hypoglycemic.

- **Despite the fact that diabetes is diabetes everywhere, there are huge variations in reimbursement within the EU.** It's not a European *Union* at all. The EU badly needs a unified treatment and reimbursement approach. Advocacy is key. EuDTT needs to develop consensus statements. The risk for the future is that it will become harder to gain reimbursement for new technologies in the EU, leading to underinvestment. Industry only invests in 'definitive' long-term studies when it's clear that a positive outcome means guaranteed reimbursement.

- **NICE is the National Institute of Clinical Excellence in the UK. The $64 million (billion) question is – how much clinical excellence does NICE help deliver?** With pumps, NICE found "dubious" cost-effectiveness, a "dubious" gain in control, and limited advantages in hypoglycemia. So they were only recommended for limited use in type 1. NICE is revisiting pumps in 2008 – we are expecting wider use in type 1 diabetes, but not type 2. NICE has recommended insulin analogs, SMBG use before insulin initiation (thanks!), and limited use of Byetta (exenatide) for people with obesity that are likely to need large insulin doses (making it

more cost comparable). On that note, it's great to see Byetta getting some coverage but it sounds like the heavier someone is, the greater the chances of coverage – is this right?

- **Put bluntly, according to Professor Philip Home, each person on a pump for a year removes one month of healthy life elsewhere in the UK National Health Service (NHS).** The idea is that if you prescribe an expensive technology in a cash-limited system, then you are taking away the potential for health improvement elsewhere, he reasons. He pointed out that the UK pays $40K per year of health per person. Assuming that the quality of life impairment due to diabetes is about 3% (we're not sure how this is measured), it doesn't make sense to pay $4,000 for CGM/pumps etc. because a 0.5% reduction in A1c is "worth about $1,000" in the UK. However, he added that severe hypoglycemia is a different matter.

- **Dr. Aaron Kowalski's response was that this was a flawed static analysis because the health improvement is worth a lot more over a patient life**. We second that. We don't know so many who can stare down Dr. Home – and so nicely. This is all a new way of thinking. We sure hope the JDRF trial shows what was expected and that it's compelling, most of all on hypoglycemia.

- **FDA approval has been granted for using synthetic (*in silico*) subjects to test algorithms for the artificial pancreas at the preclinical stage.** The JDRF Artificial Pancreas consortium will be involved in offering these *in silico* models that should speed up development of closed loop algorithms. Model Predictive Control (MPC) is a newer control algorithm for the closed loop. The concept is to use a model that can reliably predict blood glucose at some point in the future (e.g. one hour ahead) and then try and vary insulin to get the desired outcome. This process gets repeated every few minutes to make sure all is going to plan. Using the synthetic subjects they were able to show that MPC performs better than PID (proportional, integral, differential) algorithms with meal announcement.

- **At the University of Graz, Austria, an ICU insulin dosing algorithm was implemented in the Medical and Surgical ICU and got great results – more than 50% of readings were in the zone.** Blood glucose readings were taken 2.5 to 3 hours apart. Everything was automated, so nurses were not required to interpret readings and there was a low training burden. No outcome studies as of yet, but this certainly bodes well for the future.

- **More from Graz: it appears you can deliver insulin and measure glucose at the same site with a single catheter!** This is big news in terms of looking toward integrated pumps and CGM that can do this to reduce the amount of "body real estate" used by machines. Two catheters were tested – a 60 gauge microdialysis catheter (using a membrane), and a 24 gauge microperfusion needle (holes made by a laser – slightly large in our opinion).

- **Biodel's VIAject was definitely one of the hot topics of the conference.** ViaJect is a novel formulation of human insulin designed to be faster acting than the current analogs. It reaches its maximum concentration in only 60% of the time required with insulin lispro. Onset of action is earlier and the insulin is also out of the system faster. In a crossover study with 16 patients, Viaject had a much lower post-prandial peak that was actually in the normal range compared to lispro and regular insulin, which caused patients to go out of range in the first 90 minutes. Phase 3 trials are fully enrolled and ongoing. We expect the results in the last part of 2008. Following Biodel's presentation, there was a lot of excited talk about reducing delays in the system using faster-acting insulin; Biodel seems to have won itself some fans at this conference.

- **ISGIID is the International Study Group on Innovative (formerly Implantable) Insulin Delivery.** This group pioneered work on implantable pumps, but this is probably its last

meeting because of the lack of broader support for this approach. Studies show that implantable pumps provide better post-prandial glycemic control and lower A1c than subcutaneous infusion pumps. Nevertheless, they are not popular and have been reserved primarily for patients that have problems injecting.

- **The closer we get to the bloodstream, the better the artificial pancreas will work, as we eliminate delays, shorten time of action, and improve reproducibility.** Unfortunately, this also makes devices increasingly dangerous, invasive, and impractical for home use. That's why it looks like subcutaneous glucose measurement and insulin delivery is set to win, particularly when faster insulins like ViaJect come along.
- **Mean absolute relative difference (MARD) clamp studies imply that the Navigator is most accurate in the euglycemia and hypoglycemia ranges.** However, there are some difficulties associated with CGM accuracy studies that use clamp methods – a mealtime test is better. A poster from Dr. Howard Zisser et al showed us that DexCom's SEVEN sensor is a strong improvement over the three-day sensor and shows very good accuracy, particularly the longer the sensor has been inserted. DexCom CEO Terry Gregg said that DexCom's goal is to get MARD down to the single digits.
- **On the topic of approval for closed loops, the artificial pancreas (AP) is considered an "active implantable medical device."** This means that it's a "Group B high risk device," which raises the bar for approval.

—By Kaku Armah and John Close

8. Literature Review: Intensive Insulin Therapy in the ICU

In the January 10th issue of NEJM*, Dr. Frank Brunkhorst and colleagues report the results of a randomized trial comparing conventional and intensive insulin therapy in 537 patients with severe sepsis. In short, the study results suggest that most hospitals may be unable to sufficiently control hypoglycemia using intensive insulin therapy. Note, however, that the results of this trial cannot and should not be generalized to all ICU patients, much less to all hospital patients, since the patient population studied (patients with sepsis) comprised only a small subset of all inpatients. The trial was halted early due to an increased risk of hypoglycemia in patients receiving intensive insulin regimens; surprisingly, this increased risk was not associated with any discernable treatment advantage. Hypoglycemia also increased the chance of a prolonged hospital stay; as a result, despite the potential merits of intensive insulin therapy in the hospital if not met with hypoglycemia, this study suggests that treating septic patients with intensive insulin therapy may increase hospital costs at the same time that it places patients at unnecessary risk. The results of this highly-awaited trial are controversial and are in contrast to previous studies including the highly-regarded randomized prospective Leuven studies (Van den Berghe, et. al.) showing improved outcomes for intensively treated patients in the intensive care setting; these studies looked at all ICU patients, rather than only those with sepsis.*

We note that there are several aspects of this study's design that have been called into question. To start, it is relatively small for a hospital study of this kind (n=537). This calls into question whether it was adequately powered to show the potential benefits of tight glycemic control. Too, there are several explanations for why the study showed more hypoglycemia and related complications than other similar studies; these were not addressed in the piece. For example, fluid resuscitation may have confounded glycemic control, the nursing staff's laborious monitoring protocol may have resulted in poor compliance, and most importantly, tight glycemic control may well prevent infections but not treat pre-existing infections – none of these are reasons for about-face negativity on all use of tight glycemic control in the hospital.

While in our view publication in the prestigious NEJM *validates any study in the minds of many readers,, we do note that there was no accompanying editorial; no signs that* NEJM *was so sure about the study conclusions that it would make any major statements actually against tight glycemic control in the hospital. Controversy about the clinical benefits of intensive insulin in the ICU setting will likely continue until the publication of interim data from the 6,000-patient Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial*[2].

- **The randomized trial described in the January 10 issue of *NEJM* compared intensive insulin therapy to conventional insulin therapy in 537 patients with severe sepsis.** Both insulin regimens used continuous insulin infusion (50 IU Actrapid HM, Novo Nordisk) guided by glucose measurements taken in capillary or arterial blood at one to four hour intervals using a blood glucose monitor (Hemo-Cue). The conventional insulin group (N = 290) was treated with insulin after blood glucose rose above 200 mg/dL, for a target value between 180 and 200 mg/dL. The intensive group (N = 247) was similarly treated to maintain blood glucose between 80 and 110 mg/dL. We note that for a trial like this, many would like to see larger numbers of patients included; we also believe that a trial specifically examining tight glycemic control in the hospital may be a better way to assess the efficacy of this protocol. We do note that patients in both treatment groups were well matched for age (~65 years), BMI (~27) and the prevalence of baseline diabetes (~30%). The cause of sepsis and other co-morbid diseases were similar between groups.

- **In addition to evaluating insulin therapy, the study compared two strategies for restoring body fluid levels.** Patients were randomized to receive either 10% pentastarch (hydroxyethyl starch, HES) or modified Ringer's lactate, independent of insulin treatment group. Neither HES nor Ringer's lactate was expected to have specific interactions with insulin. Some believe that the infusion fluids used in the fluid resuscitation arm of the study confounded glycemic control and clouded the results of the TGC arm of the study.

- **The primary endpoints of the trial were mortality at 28 days and morbidity as assessed by the Sequential Organ Failure Assessment (SOFA).** The SOFA measures six organ systems (cardiovascular, respiratory, coagulation, renal, hepatic, and central nervous system) on a scale of zero to four with increasing scores indicating more serious organ disease.

- **The length of stay in the intensive care unit and mortality at 90 days served as secondary endpoints.** Renal failure, time to hemodynamic stabilization, frequency of vasopressor therapy, SOFA sub-scores, red-cell transfusions, and duration of mechanical ventilation served as additional secondary endpoints.

- **Severe hypoglycemia was used as a primary safety endpoint**. Severe hypoglycemia was defined as a plasma glucose ≤40 mg/dL.

- **The study was terminated early due to an increased risk of severe hypoglycemia in patients managed with intensive insulin therapy.** In total, 42 patients (17.0%) assigned to intensive insulin therapy developed severe hypoglycemia compared to 12 patients (4.2%) in the

[2] The NICE-SUGAR trial consists of two trials: the 4,000-patient Normoglycemia in Intensive Care Evaluation (NICE) study conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Survival Using Glucose Algorithm Regulation (SUGAR) trial funded by the Canadian Institute of Health Research. NICE-SUGAR will enroll 6,100 patients at approximately 35 centers throughout Australia, New Zealand, Canada and the USA over a three year period. Current enrollment exceeds 4,000 and interim data may be presented this year. Patients in the study are randomized to two targets for blood glucose - either the lower range target of 4.5 - 6.0 mmol/L (81 - 108 mg/dl) or the higher range target of 8.0 - 10.0 mmol/L (144 - 180 mg/dl).

conventional treatment group. Severe hypoglycemia was also associated with an increased risk of prolonged hospitalization. In addition, HES treatment increased the chance of developing renal failure, providing further justification for early study termination.

- **Intensive insulin therapy was not associated with a statistically significant change in morbidity or mortality.** At 28 days, mortality was 24.7% in the intensive insulin treatment group compared to 26.0% in the conventional group. Mean SOFA scores, a measure of the incidence and severity of organ dysfunction in critically ill patients, were also similar: 7.8 and 7.7 for intensive and conventional insulin therapy, respectively. No other secondary endpoints showed a statistically significant association with either insulin regimen.

- **The authors put forward that intensive insulin therapy appears to increase the risk of severe hypoglycemia in patients with sepsis without providing any discernable long-term benefit.** Hypoglycemia was associated with prolonged hospital stays, suggesting that intensive insulin therapy is likely to increase costs at the same time that it places patients at risk. These results are in contrast to a previous study performed in surgical ICU patients, where intensive insulin therapy was associated with a survival benefit; however, in the previous study, patients were given a glucose load prior to insulin treatment, suggesting that intensive insulin therapy may have functioned in part by preventing the negative effects of glucose loading.

- **This study has garnered some criticism due to its small sample size and complex design.** Given that only 537 patients were enrolled in this study, some researchers including Dr. Stanley Nasraway of Tufts and Dr. Ilse Vanhorebeek of Leuven, Belgium, have published abstracts questioning whether it was adequately powered to show the benefits of tight glycemic control. There are several possible explanations for why tight glycemic control in this study caused more hypoglycemia and related complications than in other similar studies. One explanation is that the fluid resuscitation arm of the study may have confounded glycemic control, thereby clouding the tight glycemic control arm of the study. Another possibility is that the nursing staff's laborious 1-2 hour monitoring protocol resulted in poor monitoring compliance; we believe that using an automated method could significantly improve safety in future studies. Finally, the previous literature on tight glycemic control suggests that it can help to prevent infections but may not be useful in treating pre-existing infections. Given that all patients in this study had pre-diagnosed sepsis, the results should *not* be generalized to all inpatient situations. Controversy about the clinical benefits of intensive insulin in the ICU setting will likely continue until the publication of interim data from the 6,000-patient Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial.

—By Kelly Close, Michael Dougan, and Mark Yarchoan

9. Conference Previews: First International Conference on Advanced Technologies & Treatments for Diabetes (ATTD) and more

Looking ahead to meetings we wouldn't dream of missing ...

- **Advanced Technologies and Treatments for Diabetes, Prague, Czech Republic, February 27 - March 1**. See below for our in-depth preview.
- **Diabetes Reimbursement Summit, Washington, D.C., March 12-13**. Luminaries speaking include Ann Albright of the CDC, Dr. Francine Kaufman, former ADA President and endo extraordinaire, Dr. Judy Fradkin, NIH diabetes leader, AADE President Ampere Gonzalez, JDRF's Larry Soler, and Avalere Health President Dan Mendelson and Medtronic's Claudia Graham. Oh, and

John Close! See more at www.avalerehealth.net/conferences/2008-forum-on-diabetes/index.html.

- **NIH - Meeting on Clinical Research Supported by the Special Statutory Funding Program for Type 1 Research, Rockville, MD, April 29-30**. This will be a key meeting for anyone who cares about basic science research funding in diabetes – which is to say, anyone who cares about diabetes. The strength of the faculty here isn't to be believed – we'll be there with a full report to follow and we hope to see many of you there as well. http://www3.niddk.nih.gov/fund/other/Type1Diabetes/index.htm.
- **AACE, Orlando, FL, May 14-18.** Numerous exciting topics are being covered, from reimbursement to managing hypoglycemia (and everything in between). Given all the FDA/EU submissions coming in 2008 and the stream of phase 3 data to which we're looking so forward this year, we're very excited about what we may hear/see at this meeting – in the past, for example, this meeting was where much of Merck's Januvia data was and where we also learned extensively about incretins in the early days. Some of our best learning happens at symposia and there will be many, from Novo Nordisk, Abbott, BMS/AZ, Merck, Lilly, Daiichi Sankyo, GSK, Medtronic, Allergan, and others. AND of course, ring your gym clothes for the Power of Prevention (POP) 5K Fun Run! Conference details at: www.aace.com/meetings/ams/2008/
- **ADA, San Francisco, CA, June 8-14** (our most favorite conference venue). At ADA, we're hosting the Second Annual TCOYD fundraiser! Kelly will host a fast-paced 90-minute discussion with Dr. Steve Edelman, Dr. Wendell Cheatham, Dr. Bob Henry, Dr. Anne Peters, and other luminaries on Sunday, June 8, 5-7 pm at the Westin St. Francis (open bar is a bonus). Although there's an incretin session that doesn't end 'til 6 pm, we'll have DCU staffers running back and forth to key sessions to delivery summaries. Early bird rates will happen starting in early March – all the funds go to TCOYD (www.tcoyd.org), an incredible patient education resource led by Dr. Steve Edelman and his dedicated team. As for the ADA itself – we can't even begin to talk about how excited we are, having taken a good look at the sneak preview. There are a few days left to sign up for the ADA at the lowest rate until February 23 at www.professional.diabetes.org/Congress_Display.aspx?TYP=9&CID=58000. Stay tuned…we have a very full ADA preview coming soon.

ATTD, Feb 27 – Mar 1, 2008 • Prague, Czech Republic • www.kenes.com/attd/index.asp

If you've been looking for an excuse to travel to the beautiful city of Prague, this may well be it, evidenced by an amazing list of speakers and topics. Tickets are still a good deal – Delta rates from the West Coast are a mere $600! Here's a quick overview of the sessions we think should not be missed. We'll be there so let us know if you've time to share a pint with us… e-mail us at info@closeconcerns.com.

Wednesday, February 27

The meeting will open with company workshops from 2:30 pm until the opening ceremony at 6:30 pm – Medtronic will host four out of the five so we'll look to get a full update on pumps and CGM. During the opening ceremony, Sir George Alberti will give an address after receiving a tribute from Professor T. Battelino. He's an incredible speaker and very wise on diabetes research and goings on – we would not miss this.

Thursday, February 28

Thursday will feature what should prove to be an interesting debate on the use of insulin analogs; we expect some key opinions to come forth that could further inform pharma regarding the development and patient/physician uptake of fast acting analogs. There will also be a talk discussing whether GLP-1s are the "Magic Bullet" for type 2 diabetes and a slew of talks on pumps and meters including lectures from

Drs. Irl Hirsch and Satish Garg on lessons from meter downloading and continuous glucose monitoring, respectively. We're believers that meter downloading is sorely underused, due to lack of reimbursement – this is on our wish list for change in the US, as we've been blown away by some downloading software of late. We're curious as well to hear what technologies Dr. Yariv Yogev recommends for monitoring diabetes during pregnancy – an especially important time for tight glycemic control. The day will culminate in an hour's worth of oral poster presentations including talks by Drs. Howard Zisser, Dorothee Deiss, and Rattan Juneja among other thought leaders. Here are some of the most exciting sessions:

- *Global Perspectives On Diabetes: The Impact Of Technology* –Dr. Francesco Chiarelli–8:30-8:50 AM
- *Hypoglycemia – The Barrier To Glycemic Control – Hypoglycemic Unawareness* – Dr. Stephanie Amiel – 8:50 – 9:10 AM
- *Insulin Analogue Debate – Should We Use Them?* – Dr. Thomas Danne (pro), Dr. Frits Holleman (con) – 9:30 -10:15 AM
- *Lessons Learnt From Continuous Glucose Monitoring* – Dr. Satish Garg – 1:15 – 1:35 PM
- *The How And Why of Glucose Meter Downloading: What We Have Learned Since 1995* – Dr. Irl Hirsch – 1:55 – 2:15 PM
- *Use of New Technology For Monitoring And Treating Diabetes in Pregnancy* – Dr. Yariv Yogev – 2:15 – 2:35 PM
- *Measuring Metabolic Variables Through Exhaled Breath: Analysis Of A Novel Approach To The Prevention, Diagnosis And Monitoring Of Diabetes* – Dr. Pietro Galasseti – 2:35 – 2:55 PM
- *The Promise Of GLP-1: The "Magic Bullet" for T2 Diabetes* – Dr. Juris Meier – 2:55 – 3:15 PM

Friday, February 28

In the morning session on educational programs, Drs. Thomas Danne and Francine Kaufman will each speak on important topics: continuous sensor use and type 2 prevention in the community, respectively. We also think the talk by Dr. Zdenek Rusavy on insulin pumping in type 2s will be particularly interesting and look forward to asking about the reimbursement questions in particular. Following this, Dr. Aaron Kowalski will provide the JDRF artificial pancreas project update. Friday's roundtable discussion on the use of fluorescence resonance energy transfer (FRET) in glucose sensing should provide for some pretty hardcore physics after lunch, though we note that in addition to the engineering and physiology challenges, implantable sensors also face a greater number of clinical and regulatory hurdles than the currently-favored subcutaneous devices. The Abbott-sponsored early-evening session on the use of trending information in CGM should prove enlightening.

- *Why Do Some Patients Not Reach Glycemic Targets With Continuous Sensors - Is Education The Key?* – Dr. Thomas Danne - 8:30 - 8:50 AM
- *Prevention And Treatment Of Type 2 Diabetes - Community And School Based Programs* – Dr. Francine Kaufman - 9:10- 9:30 AM
- *Czech National Register Of Patients Treated With Insulin Pumps - Ten Year Results* - Dr. Zdenek Rusavy - 9:30- 9:50 AM
- *Insulin Pump Therapy In Diabetes Mellitus Type 2* - Dr. Zdenek Rusavy - 11:00 - 11:30 AM
- *JDRF Artificial Pancreas Project* - Dr. Aaron Kowalski - 12:00 - 12:20 PM
- *Advances And Challenges In Islet Of Langerhans Transplantation* - Dr. Thierry Berney - 12:20-12:40 PM
- *Session 10 - Round Table: Progress In The Development Of An Implantable FRET - Based Glucose Sensor – The P.Cezanne Project* – 1:40 – 3:00 PM
- *Session By Abbott Diabetes Care: Arrows And Trends In Real-Time – A New Dimension In Glucose Data And Analysis* – 5:00 – 7:00 PM

Saturday, March 1

Back-to-back talks by Drs. Bruce Bode and Francine Kaufman are always enough to get us pumped on a Saturday morning! Dr. Bode will start off the last day of the meeting with a discussion on in-patient hyperglycemia management. It would be great to get his take on the TGC debate (Do we have enough data to warrant it? Is 80 to 110 mg/dl the right range? If so, what protocols and technologies are needed to achieve this target?). Dr. Oliver Schnell will discuss the consequences of new, stricter guidelines for the treatment of post-meal hyperglycemia. Also of note will be the session on glycemic variation where the in-hospital TGC question will again be addressed and Dr. Joe Bugler will present "An estimation of the amount of data required to measure glycemic variability" right before the session aptly titled, "The Loop Club – Closing the loop". This final session of the conference will, appropriately enough, look toward the future of the artificial pancreas and will feature Drs. Bruce Buckingham (The Stanford Program), Roman Hovorka (The Cambridge Program), Stuart Weinzimer (The Yale Program), Moshe Phillip (The Tel-Aviv Program) and William Tamborlane (The JDRF Program). We're excited to hear about the work that each of these innovating centers has done to advance the technologies and therapies that could get us to the closed loop.

- *Management Of Hyperglycemia In The Hospital With Computerized Insulin Delivery* - Dr. Bruce Bode - 8:50 -9:10 AM
- *The Sensor Augmented Pump In Pediatric Subjects* - Dr. Francine Kaufman - 9:10 - 9:30 AM
- *Quality Of Life And Treatment Satisfaction In Adults With T1DM Treated With CSII Or MDI* - Dr. Antonio Nicolucci - 9:30 - 9:50 AM
- *The New Guidelines On The Treatment Of Post-Meal Hyperglycaemia - Consequences For Daily Practice And Technological BGSM Options* - Dr. Oliver Schnell - 9:50 - 10:10 AM
- *Measuring Glycemic Variation: Issues And Limitations* - Dr. Fergus Cameron – 10:40 – 11:00 AM
- *Mathematical Methods For CGM Time Series Analysis: Filtering, Prediction, Glucose Variability and Glucose Control* - Dr. Claudio Cobelli - 11:00 - 11:20 AM
- *Tight Glycemic Control In The Intensive Care Units* - Dr. Roman Hovorka - 11:20 - 11:40 AM
- *An Estimation Of The Amount Of Data Required To Measure Glycemic Variability* - Dr. Joe Bugler – 11:40 AM – 12:00 PM
- *The Stanford Program - The JDRF Artificial Pancreas (AP) Project, The Consortium Of Stanford, UCSB, Rensselaer Institute And The Barbara Davis Center* – Dr. Bruce Buckingham - 1:00 – 1:20 PM
- *The Cambridge Program* - Dr. Roman Hovorka - 1:20-1:40 PM
- *Studies Of The Artificial Pancreas In Children With Type 1 Diabetes: The Yale Program* – Dr. Stuart Weinzimer - 13:40-14:00
- *The Tel-Aviv Program* - Dr. Moshe Phillip – 2:00 – 2:30 PM
- *The JDRF Sensor Study* - Dr. William Tamborlane – 2:20 – 2:40 PM

—By Kelly Close and Kaku Armah

10. Diabetes Comings and Goings

- **Dr. Henry Anhalt** will become, in mid-March, the Director of Medical Affairs for Animas, part of J&J's Diabetes Franchise with LifeScan. This superhero of diabetes care will continue to see patients one day a week in his pediatric endocrinology practice.

- **Pamela Harris** was appointed as vice president for Diabetes Sales, Managed Care and Government Accounts at Novo Nordisk, and she will now lead the company's 2,000-person sales force, encompassing the field, managed care, and government accounts salesforces. She

previously shared this responsibility for managing the field force. Harris joined Novo Nordisk in 2005, and previously worked at BMS and Novartis

- **Dr. Jonathan Lakey** was named to DiaKine Therapeutics' Scientific Advisory Board..

11. The Diabetes Market

	13-Feb-08	14-Jan-08		2-Jan-08		13-Feb-07		IPO		Market Cap
GSK	43.66	52.75	-17%	50.17	-13%	57.82	-24%	-	-	138.88B
NVO	64.43	65.60	-2%	63.80	1%	45.85	41%	-	-	40.19B
AMLN	29.25	35.91	-19%	36.95	-21%	40.34	-27%	14	109%	4.52B
MNKD	7.53	7.95	-5%	7.86	-4%	16.72	-55%	14	-46%	736.69M
PODD	17.75	23.85	-26%	23.42	-24%	-	-	15	18%	549.22M
SIRT	12.01	15.11	-21%	13	-8%	-	-	10	20%	388.10M
OREX	12.03	12.91	-7%	13.94	-14%	-	-	12	0%	336.38M
BIOD	15.62	23.49	-34%	22.65	-31%	-	-	15	4%	384.86M
DXCM	8.95	8.85	1%	8.95	0%	8.53	5%	12	-25%	251.83M
HDIX	7.20	8.65	-17%	8.45	-15%	11.28	-36%	12	-40%	145.55M

There's not much positive one can say about this market of late, either versus a month ago, versus the start of the year, or versus a year ago. Novo Nordisk, of course, continues to be the standout, up over 40% compared to a year ago. For the month, DexCom is the only stock that was up even marginally. Versus IPOs that were all under a year ago, Insulet and Sirtris investors have done very well.

12. Final Thoughts – Remembering Molly Keane

I was devastated by the news that we lost a quiet heroine in diabetes last weekend, with the death of Molly Keane, who died in a tragic accident on Saturday, February 16. She drowned after trying without success to rescue her dog Bo in the North Pacific Ocean. A superb and experienced diabetes educator and advocate, Molly lived and breathed optimism, encouragement, and humor. She was someone who enabled triumphs as a matter of course. Her smile could light up a room. I had just seen Molly at ADA Postgrad earlier this month, and she was such a light to the whole conference, and with her typical energy was flitting back and forth among so many people, talking to John Buse, helping the coffee guy persuade the Berkeley doctor that he really didn't need soy milk, emphasizing with a glint in her gorgeous eyes the good that would follow and keep us all, if we would just keep trying.

A major player in Amylin's education efforts, Molly worked as part of the field medical group there. She was one of the only people who could make me feel, perversely, good about having diabetes. Good, for all there was to come, and for all the good work there was to do. I've never seen so much optimism combined with perfect realism in one person. Or so much laughter. Forty-two years old. May her family be keenly aware of how good she made so many people, sick and well, feel in their own shoes. She will be missed sorely by everyone that knew her, I am sure, but patients will feel her loss particularly acutely, especially this one.

Details for a memorial service for Molly to take place in Berkeley will be announced shortly. In lieu of flowers, tribute and/or memorial donations can be made to the East Bay SPCA in Molly's memory. ww.eastbayspca.org/donate/tributesandmemorials.cfm. Also see www.virtualmemorials.com.

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purchasers of Close Concerns' healthcare information include Abbott, Amylin, Bayer, Becton Dickinson, Biodel, DexCom, Insulet, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, and a number of private companies.