DIABETESCLOSEUP

The Leading Source of Diabetes Business News

No Time to Waste **October 2008 • No. 84**

From the Editor

We just got excellent news in from San Francisco's City Hall that they will LIGHT City Hall blue for World Diabetes Day, coming right up on November 14! Now, we're trying to help get Google's homepage lit in blue for World Diabetes Day – please sign the petition at www.diabetesdoodle.com. (Note: don't click the donate now button afterwards unless you want to donate to ipetition.)

So what's the political buzzword in 2008? "Change", of course. It's a "change" election. Well, DCU has always been politically non-partisan, and we continue that tradition with this issue. However, we can certainly embrace the "change" mantra – a change in our country's priorities in treating diabetes. Putting the spotlight on any disease serves a wonderful purpose, but we're puzzled why diabetes is never discussed as one of America's leading public health threats. We believe Barack Obama mentioned "obesity" once in passing during the debates, but you'd think it would just be good politics to recognize diabetes, given how many people are affected by it (75 million in the US including pre-diabetes). It's possible that there is a stigma against type 2 diabetes – a "preventable" disease that many people acquire because they are overweight. We disagree with that type 2 interpretation – we think the epidemic is a far more complicated story – but we also think any candidate who discussed type 2 in the context of creating healthier communities, particularly for children, would strike a chord.

We don't know which candidate will be "better" for diabetes, or who will fund the NIH more aggressively or make better appointments to HHS and FDA or emphasize preventive care or disease management or even support lousy bike paths so kids can exercise safely or just encourage climbing more stairs. We just hope that the next president hears the quiet rumbles of vast diabetic community that is searching for a champion.

On to this issue . . . Rury Holman! This month, we were fortunate to speak with Dr. Rury Holman of Oxford University, who has led many important trials, including UKPDS, ADOPT, DREAM, and EDIT, among others. We discussed with him the remarkable ten-year UKPDS follow up data shown at EASD and their clinical implications. I have never been so excited about new data, as I think the implications for patients are abundantly clear: Act. Now. (So to speak.) In our talk, Dr. Holman also shared his views on the current regulatory environment and his lessons from UKPDS and ACCORD. You might say it's an EASD issue - our conference report focuses on the huge amount of new data coming out of Rome last month, and our literature review addresses that NEJM piece written by the UKPDS team.

As we are hearing more and more, and as Holman's UKPDS data seem to show definitively, the worst response to have to diabetes is inertia and complacency – patients and doctors and families and payors must be proactive about identifying and addressing it intelligently. While the importance of early and aggressive therapy has been suspected for many years, it has always been extremely hard to address.

After hearing the UKPDS results, I believe two things are dovetailing:

- *It's easier to treat diabetes, as the devices and drugs have improved significantly in recent years.*
- *And, the data have just crystallized the importance of early, aggressive diabetes management. The study demonstrated a 'metabolic memory' effect, showing that glycemic control can have a lasting effect even after A1cs and other metabolic parameters from all study arms have come together. For further details, see our literature review on page 30. These results should have a particularly positive clinical and commercial implication in that they should get patients on therapy earlier and should get them moving to combination therapy sooner. Why? Because the study showed early treatment reduce both microvascular complications and also macrovascular complications, when treated early. Take THAT, ACCORD!*

And on the note of earlier aggressive therapy – it was like the ADA/EASD writing group read UKPDS' mind! (Well… Dr. Holman was part of both influential groups.) So the ADA and EASD released new guidelines last week on how to treat type 2 diabetes. We'll have more out on this next month (we published a detailed overview in Closer Look), but in short, the guidelines suggest that an A1c > 7% be seen as a 'call to action' and the guidelines are incredibly clear that ACTION is needed whenever an A1c floats above this level.

On the obesity front, it's been a month of setbacks for drug development. In a span of three weeks, Pfizer dropped its obesity pipeline, Merck stopped development of taranabant, and Sanofi halted sales of rimonabant in the EU. There has been a constant shadow over this drug class (i.e. CB1 antagonists) because of its association with increased depressive symptoms. This leaves open the question of how can we treat obesity if the majority of patients don't engage in exercise and lifestyle modifications.

The story of CB1 compounds underscores the incredibly high safety bar for obesity drugs – obesity is clearly not perceived as a disease at FDA and from a regulatory perspective, obese people are not sick, per se – thus, the risk tolerance is exceptionally low. Risk tolerance should be low, in our view, but we should also prioritize finding compounds that work, and work safely. We will be watching with interest obesity drugs that act peripherally rather than centrally – maybe anything that crosses the blood-brain barrier is just out. Certainly we do think that there's going to be a lot more interest in diabetes drugs that cause weight loss in coming years – and at this point, we can't envision any drug that prompts weight gain being approved for diabetes. At this point, there are too many good alternatives recently approved or in development that are weight neutral or cause weight loss.

While we've seen all sorts of progress in diabetes drug development – advances over the last decade include TZDs (1999), rapid-acting insulin analogs (1996), long-acting insulin analogs (1998), GLP-1 (2005), DPP-4 inhibitors (2006), and lots of exciting things on the horizon – no company has successfully tackled obesity. This is ironic, since obesity is propelling the diabetes epidemic and since arguably there is a far bigger market for obesity than exists for diabetes. From a public health perspective, we need treatments for both, or a lot of help on adherence. Or maybe a president who believes that national fitness is as important as national security.

Sincerely,

Kelly L. Close

Major Headlines

Interview with Dr. Rury Holman – page 20

UKPDS 10-year follow-up data demonstrates a "legacy effect" – page 25

Data highlights from EASD 2008 — page 25

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/:

- **October 27:** Mediterranean Diet Slips Away as Pounds Pack on Population
- **October 26:** Welcome mental illness measures approved in Congress for people with diabetes
- **October 25:** Online Health – welcome attitude from Dr. Kalnicki
- **October 8:** TODAY takes on diabetes
- **October 5:** Taking Control of Your Diabetes – see Dr. Steve Edelman before the year is out!

Videos

Below are our favorite Internet videos in diabetes this month:

- World Diabetes Day Doodle: http://tudiabetes.com/video/video/show?id=583967:Video:304205
- Human clinical trials with porcine encapsulate islets allowed in New Zealand: http://www.3news.co.nz/Video/National/tabid/309/articleID/76719/cat/64/Default.aspx#video

Coming soon in DCU…

Be on the lookout for our notes from the Discovery on Target meeting that took place October 20-23, 2008 at the World Trade Center in Boston, MA. Coming up soon after we'll be reporting from Barcelona, Spain at the World Congress on Controversies to Consensus in Diabetes, Obesity, and Hypertension from October 31 – November 2 followed by the Diabetes Technology Meeting in Bethesda, MD from November 13-15. Stay tuned…

1. Quotable Quotes in Diabetes

Sobel on Nissen – how do you really feel?

"Then came the Nissen monstrosity. I can't call it anything else. We have fallen prey to the problem of supernumerary nonsense."
— Burton E. Sobel, PhD (University of Vermont, Burlington, VT) commenting at World Congress on the Insulin Resistance Syndrome (WCIRS) 2008 on the controversy over rosiglitazone and TZDs in general.

Handelsman lifestyle lamentations

"We live in an unphysiological way today where we are getting abundant nutrients with little physical activity. Clearly, part of this obesity epidemic is that we live in such a wonderful, technological society that strives to make things convenient for individuals. I think that we always think that intervention works but maintaining the improvements is the more difficult thing. We need to focus on figuring out ways to maintain lifestyle changes so that the benefits do not merely last a few months."
— Yehuda Handelsman, MD (Metabolic Institute of America, Tarzana, CA) highlighting how difficult it is to get patients to initiate and maintain lifestyle modifications at WCIRS 2008.

DeFronzo on science and reality discord

"I would say most doctors do not know what to do because they do not understand the science. I'm not saying that this is an easy thing to do because there are a lot of obstacles to overcome. Patients need to understand that complications arise from this disease, and some will understand it and take the medications and others will not. You do the best you can in explaining the science."
— Ralph DeFronzo, MD (University of Texas Health Sciences Center, San Antonio, TX) responding to Dr. Grant's comment about what to do about patients who stop taking their medications at WCIRS 2008.

From the Obesity Society President – why bother measuring?

"I believe that if you are going to measure something, it will change your therapeutic decision. What am I going to do differently if I measure that? We need to keep this point in mind as we treat our patients."
— Robert Kushner, MD (Northwestern University, Chicago, IL) at the Obesity Society 2008 Meeting pointing out that physicians need to think carefully about which tests they give their patients and whether or not it will be beneficial in devising a treatment regime.

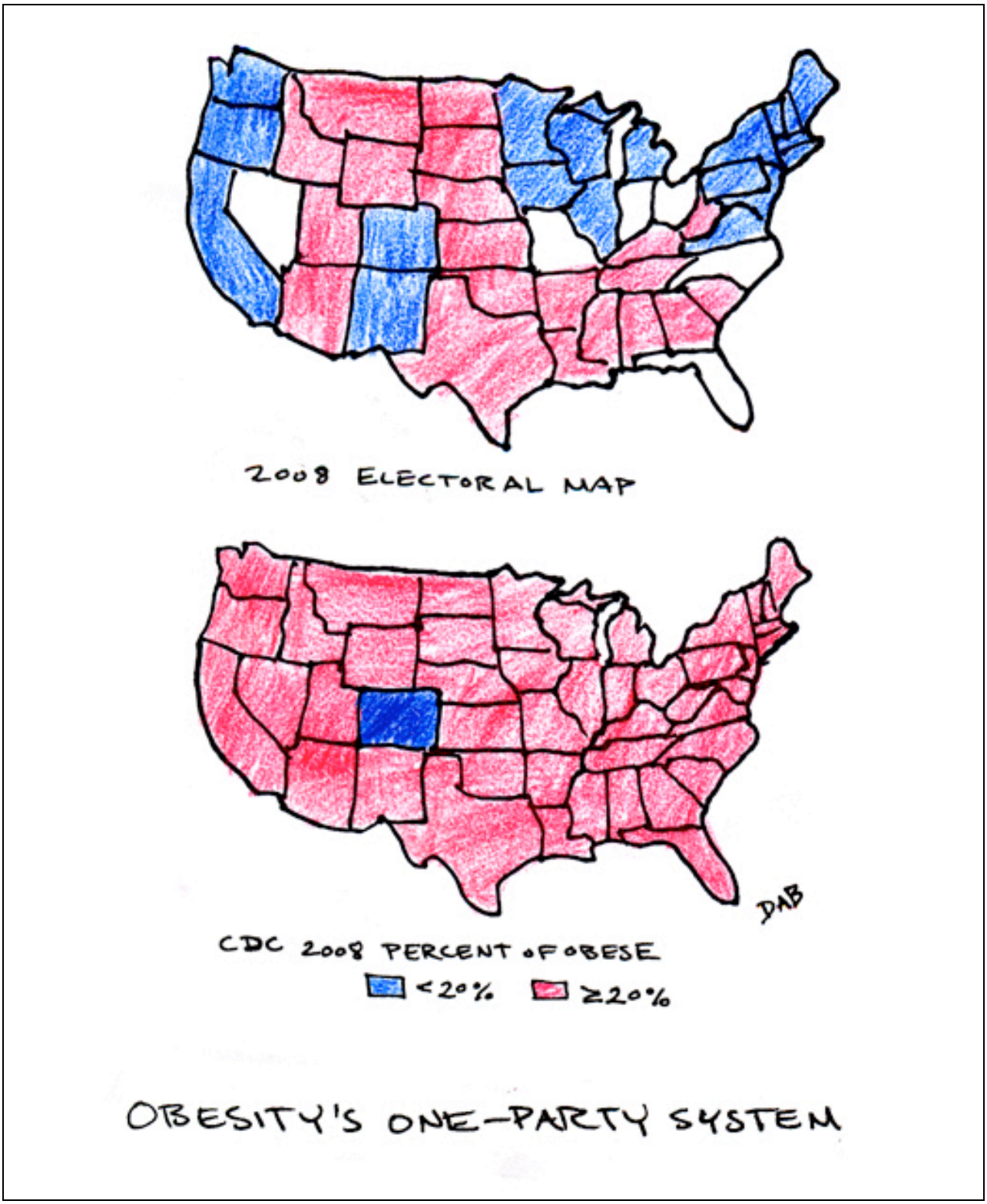
Gerstein on the importance of insulin

"Insulin is not a last line therapy even though it has often been used that way in the past and was typically prescribed before the priest came to give last rites. More recent studies have shown that it can be used early in different ways."
— Hertzel Gerstein, MD (McMaster University, Hamilton, Ontario) prefacing his discussion about the three ways to lower glucose levels during the Canadian Diabetes Association 2008 Meeting CDA 2008.

Death to sulfonylureas!

"I think sulfonylureas are the cockroaches of the pharmacological arsenal. No matter how much data we have against them, they still stay around."
— Lawrence A. Leiter, MD, FRCP, FACP (University of Toronto, Toronto, ON) agreeing with Bernard Zinman, MD, FRCP (University of Toronto, Toronto, ON) at the Canadian Diabetes Association 2008 Meeting that there should be a reduced use of glyburide.

2. diaTribe FingerSticks



-by Daniel A. Belkin

3. DCU Company Watch

- **Sanofi – Acomplia (rimonabant) pulled in the EU:** Sanofi announced October 23 that it would pull Acomplia from the market in the EU after the European Medicines Agency recommended suspending the market authorization for the company's CB1 inverse agonist for the treatment of obesity. The Committee for Medicinal Products for Human Use (CHMP) announced its decision after concluding that the benefits of Acomplia no longer outweighed the risks of the drug in its currently approved indication. Under the terms of the suspension, the company can (and will) continue with phase 3 trials to provide additional risk/benefit information, and commercialization may be resumed if additional supportive evidence is provided. During Q&A, management noted that there are 24,000 people enrolled in Acomplia trials right now. According to management, the data safety monitoring board for the CRESCENDO trial (CV endpoints and outcomes for Acomplia) has not given any indication of a need to stop the trial. However, the company has proposed stopping phase 4 studies of the drug. Jean-Claude Leroy, EVP, Finance and Legal, pegged the total revenue impact of this suspension at 50 million Euro ($75 million) net of tax. Management stressed that throughout the development, approval, and post approval of Acomplia, information on psychiatric side effects were continuously updated and strengthened to include further contraindications and upgraded warnings to manage these risks. Over 700,000 people have been treated with Acomplia to date.

- **Johnson and Johnson — Problem with Ping being resolved this week:** Animas said October 24 it was issuing a preemptive product recall and replacement on the remote control meter for the new Ping (OneTouch Ping Blood Glucose Management System) pump. The Ping is a traditional insulin pump (a lot like the Animas 2020, slightly bigger) attached wirelessly to a handheld meter and remote. The unique feature of the Ping is that it has a remote controlled meter that communicated with the Animas 2020 pump wirelessly for easy transmission of blood glucose readings to the pump. The meter also acts as a remote control for controlling certain pump functions including bolusing. This recall comes in light of one reported case in which the following failure mode was uncovered: "If the Ping meter and the Animas Pump are not paired and in radio frequency (RF) communication, or if the two devices are paired and not in RF communication, the bolus calculator on the Ping meter may malfunction giving an incorrect recommended dosage. Animas management notes that this issue only occurs when the blood glucose value, manually entered into an unpaired/non-communicating meter, is lower than your target value, but higher than 70 mg/dL. It is important to note that below 70 mg/dL, this programming glitch is not an issue since you get a warning message on your pump." This reinforces to us the complexity of insulin pumps - nearly every pump on the market has experienced voluntary recalls. Typically the financial considerations are larger than in this case; since this is a software problem, it should not be a big problem for patients and the costs to replace the remote should be far less than to replace pumps themselves, especially since there probably aren't too many out, since it's a new pump that began shipping only recently. Still, this gives competitors in this highly competitive market a potential negative talking point or two and takes the focus away from the field temporarily. As we understand it, current Ping users will be receiving instructions on replacement in late October.

- **Novo Nordisk — Building a greater focus on stem cell therapy:** On October 23, Novo Nordisk announced a research agreement with Cellartis AB, a stem cell biotechnology company and Lund University Stem Cell Center for the development of insulin-producing cells from human stem cells. The goal of the partnership is to create a stem cell therapy for the treatment and possibly cure of diabetes. Curing diabetes has long been a part of Novo Nordisk's vision, and we believe it is a major part of what attracts and drives the top-flight researchers, management, and staff throughout the company. Novo Nordisk has collaborated for some time with Cellartis through its Hagedorn Research Institute, its basic science research center in Denmark. Hagedorn is recognized as a leading stem cell

research institute and a central player in understanding beta cell autogeny. The terms of the agreement show Novo Nordisk acquiring development and commercialization rights for diabetes while Cellartis has rights for other products. So far, work has centered on how insulin-producing cells formed during embryonic development could be created with stem cells in culture. The next stage will focus on programming stem cells to turn into insulin-producing beta cells; from a recent conversation with management, we believe they have come to understand in much more detail how to monitor the various steps that a cell has to pass through in the process from stem cell to beta cell. Type 1 is the primary target while in type 2 the goal would be to make cells more efficient. Cellartis will receive €100 million as a technology access fee and more funds based on development and sales milestones. We are impressed with the vision in this area and hopeful about potential for beta cell development, long-term. The terms of the agreement imply that Novo Nordisk is optimistic about the area and that clinical potential is a step closer – welcome news for patients and providers. In terms of timing, this is still early preclinical research; the hope is after a five-year period, the company would be ready to move into preclinical development in preparation for clinical development perhaps five to ten years out, or around 2015.

- **Eli Lilly — Maintains strong sales of Humalog and Humulin in 3Q08:** On October 23, Lilly announced that it achieved strong global Humalog sales of $432 million in 3Q08, up 19% year over year. Global Humulin sales of $271 million in 3Q08 rose 12% year over year. Humalog strength was driven by international sales that rose 23% (US sales rose 13%). Sequentially, Humalog sales were roughly flat compared to $438 million in 2Q08. As seen in the TRx growth rate chart given in the presentation slides, US Humalog performance has shown a positive trend in script growth. Humulin sales were also driven by international strength; international sales rose 16% year over year while US sales increased 5% in the same period. Humalog is now annualizing at over $1.7 billion, quite impressive given strength in the basal analog category (where Lilly doesn't have an offering). The basal insulin class is considered "easier" to take than a rapid-acting analog since it has once-daily dosing. In terms of insulin strength overall, we believe that Humalog growth is coming from the recent focus on earlier, more aggressive therapy combined with a push to move away from therapies that are not working. On the incretin front, Lilly's share of Byetta revenue rose to $109 million, a 25% increase year on year. Total sales of Byetta grew to $201 million in 3Q08, a 22% increase year on year from $161 million in 3Q07 and a 3% increase quarter on quarter from $195 million. International sales of Byetta were $21 million, up from $17 million in 2Q08.

- **BMS — No update given on its diabetes pipeline:** During the 3Q08 call on October 23, the diabetes pipeline was not mentioned aside from the reiteration that the NDA submission for Onglyza (saxagliptin) occurred on July 23 and was accepted by the FDA on September 2. The press release also noted a study that was recently shown at EASD 2008 demonstrating that Onglyza was safe and efficacious when used in combination with metformin and a sulfonylurea or thiazolidinedione. Aside from Onglyza and dapagliflozin, the company's website lists two drugs that are currently in pre-clinical or early clinical development: the first is a DPP-4 inhibitor backup, and the other is an 11beta-hydroxysteroid dehydrogenase (11βHSD) inhibitor. Little information is available on the DPP-4 inhibitor backup, which is likely being kept around in case anything wrong happens with Onglyza. When a drug target is developed, many potential drugs are identified and the best one is usually developed quickly while others are kept in the library just in case. The other drug listed is 11beta-Hydroxysteroid dehydrogenase (11βHSD) inhibitor. 11βHSD catalyzes the conversion of inactive cortisone to active cortisol, a steroid hormone that binds to the glucocorticoid receptor. Cortisol stimulates gluconeogenesis in the liver, inhibits glucose uptake in muscle and adipose tissues, and creates substrates for gluconeogenesis from the breakdown of fat in adipose tissues. By inhibiting this enzyme, it may help to inhibit hyperglycemia. We are awaiting further information on this drug before deciding how effective it might be in limiting hyperglycemia.

- **GSK — Avandia (rosiglitazone) sales remain stable and work continues on sirtuins:** On October 22, GSK CEO Andrew Witty led GSK's 3Q08 earnings call. Avandia's sales of just under $360 million were essentially flat (in pounds) with the first two quarters of this year and down 23% from ~$460 million in 3Q07 and down 54% from $800 million in 1Q07, before concerns about the drug's potential association with MI were brought forward in a meta-analysis by Dr. Steven Nissen (Cleveland Clinic, Cleveland, OH) in May 2007.

3Q08	£191 million ($357 million)
2Q08	£194 million ($386 million)
1Q08	£191 million ($380 million)
4Q07	£231 million ($472 million)
3Q07	£153 million ($463 million)
2Q07	£349 million ($692 million)
1Q07	£414 million ($811 million)

Sales for the quarter in the US were £99 million ($185 million), down 28% year on year; in Europe sales were £48 million ($98 million), down 16% year on year; and in the rest of world sales were £44 million ($83 million), down 16% year on year.

Alli (orlistat) 3Q08 sales remained stable at £18 million (US$34 million) down 50% year on year from £34 million ($70 million). Alli was launched in 2Q07, and we are unsure as to what the future of this product will be in face of the significant decline in sales it has seen this past year. As a reminder, Alli sales were £18 million in 2Q08, £9 million in 1Q08, £40 million in 4Q07, £34 million in 3Q07, and £76 million in 2Q07.

There was a short comment made during the call about GSK's acquisition of Sirtris, and how it has allowed collaborative studies on the sirtuin class of drugs. We believe that GSK's bold acquisition of the small Boston biotech company could eventually lead to several blockbusters, from diabetes to neurodegenerative disorders and even cancer, all of which share inflammatory and mitochondrial underpinnings; we are not surprised that GSK is expanding research on this potential drug target. Witty mentioned a new R&D center in China aiding the investigation of sirtuins. This note was the only update given about the pipeline, and no update on other drugs in development was given.

- **Merck — Continued robust growth of the DPP-4 inhibitor market:** Merck reported 3Q08 earnings on October 22 in a call led by CEO Dick Clarke. Worldwide sales of Januvia (sitagliptin)/Janumet this quarter were $480 million, up 135% year over year and 18% sequentially. Global Januvia sales came in at $379 million while global Janumet sales exceeded $100 million for the first time – up over five times from a year ago to $101 million. US Januvia sales of $279 million nearly doubled year over year, while international Januvia sales more than tripled to $82 million in the same time period. Janumet provided nearly 40% of total growth this quarter and represented just over 20% of total sales.

  Although it wasn't discussed on the call, the ADA/EASD's decision not to include DPP-4 inhibitors in the preferred scheme of the newest diabetes treatment algorithm had to come as a disappointment to Merck. While we were a little surprised that the organizations didn't add both incretins to the algorithm, we assume that more safety data available for GLP-1s weighed heavily in the decision and that DPP-4 inhibitors will be added after the next review, assuming Januvia/Janumet safety data continues to expand. Given that adherence seems important to the groups, we would have thought the DPP-4 inhibitor class might have qualified based on tolerability improvements it brought to diabetes – certainly, primary care physicians have been voting with their feet as the Januvia franchise is now annualizing at a $1.9 billion run rate, up from $1.6 billion last quarter and $800 million just a year

ago. From a competitive perspective, we expect Merck to have the US market to itself for at least a couple more quarters – although Takeda submitted its DPP-4 inhibitor alogliptin (SYR-322) to the FDA last January, the company has said that the decision will be delayed, apparently due to FDA resource problems. BMS/AZ submitted Onglyza (saxagliptin) in July 2008. Lastly, Novartis has reiterated that it will not seek resubmission of Galvus (vildagliptin) in the US. For now, Merck's Januvia franchise continues to take advantage of its US monopoly of the DPP-4 market – its execution to date has been extremely strong and we continue to be very impressed with the growth.

- **OSI Pharmaceuticals — Growing royalty revenue from DPP-4 patents:** OSI Pharmaceuticals announced its 3Q08 results on October 22, in a call led by CEO Colin Goddard. OSI reported royalty revenue from DPP-4 patents of $13 million, triple the figure of a year ago, benefiting from Merck's strong Januvia franchise sales. Research and Development expenses for 3Q08 totaled $33 million, of which 25% was allocated to diabetes/obesity research. While OSI's short-term focus will remain on Tarceva (oncology), its long-term focus includes four key development candidates, including two diabetes/obesity candidates: PSN821 (a GPR11 agonist) and PSN602 (a next generation sibutramine competitor). According to Goddard, there has been appreciable progress in developing these drugs even though they are still in phase 1 programs. OSI has identified control of body weight and glycemia as analogous areas of focus in the diabetes/obesity arena.

- **Amylin — Byetta (exenatide) sales stable from 2Q08, guidance falling:** On October 21, President and CEO Daniel M. Bradbury reported total revenue of $218 million for Amylin, up 14% from the same period in 2007. The quarter marked the first time quarterly product sales exceeded $200 million, although management reduced guidance for 2008 to $850-875 million primarily due to reduced Byetta expectations and lower revenues from collaborative agreements. Byetta 3Q08 sales of $180 million increased marginally, sequentially, compared to $177.5 million in 2Q08. Symlin sales quarter on quarter fell slightly from $22.8 million in 2Q08 to $21.5 million, a decrease of 6%; year on year sales increased from $16.3 million in 3Q07. Right before the conference call, Amylin announced that it had entered into a product supply agreement with Eli Lilly for exenatide once weekly. Eli Lilly will make an initial cash payment of $125 million to Amylin as well as a reimbursement of $500 million capital investment for its share in the Ohio facility through the cost of goods sold for exenatide once weekly. These days, of course, any non-dilutive cash is a positive.

  On Byetta, prescriptions were "resilient," but a slight drop in prescriptions did occur, likely attributable to the FDA announcement on pancreatitis based on concerns that we believe are overblown. Bradbury said he expected prescriptions to stabilize and increase as people were better educated about the costs/benefits of Byetta. Notably, Bradbury said that patient enrollment for a cardiovascular study would be initiated in early 2009. Amylin is still awaiting a conversation with the FDA to finalize the details of the study. We are a little worried about how such studies will impact the development of diabetes drugs. Amylin has also met with the FDA on updating Byetta's label, which should be completed by the end of 2008.

  Several updates were provided elsewhere on the regulatory front: 1) enrollment has been completed for the phase 2b study of pramlintide/metreleptin, and the results from this dose-ranging study will be used to support dose selection for phase 3 trials of this drug combination; 2) Amylin's second generation amylinomimetic was moved into phase 2, and results are expected in the second half of 2009; 3) enrollment for DURATION-2 was also completed and will compare the safety and efficacy of exenatide once weekly, a thiazolidinedione, and a DPP-4 inhibitor all on background metformin therapy.

- **Pfizer — No diabetes update in 3Q08:** During the October 21 3Q08 earnings call, Pfizer's DPP-4 inhibitor program was not discussed nor were there any questions or prepared comments on Pfizer's

obesity program. Earlier in October, Pfizer dropped all obesity compounds in development except their CB1 antagonist (CP-945598). Their CB1 antagonist remains in phase 3, and we believe that the company will look for a buyer although this class is not a popular one at present given Merck's decision to shelve taranabant earlier this month. Pfizer management briefly mentioned Exubera, the failed inhaled insulin program, in reference to after-tax charges, decreased cost of sales, decrease in selling, informational and administrative expenses, and decreased R&D expenses. On a related note about Exubera, Pfizer announced on September 16, 2008 that they would transition a subset of Exubera patients to Mannkind's Technosphere Insulin (AFRESA). This subset of patients was reported either to be extremely needle-phobic or unresponsive to subcutaneously administered insulin. Details about the actual number of patients, or their glycemic conditions were not provided.

- **Roche — Declining sales in Diabetes Care in 3Q08:** In a conference call on October 21, Roche discussed its results for 3Q08. Important progress continued on the drug front: Roche recently started phase 3 trials of their once-weekly GLP-1 analog taspoglutide (R1583). We have been impressed by the improved glucose control (A1c down ~1% from an 8% base) and weight loss results from its phase 2 trial, though we believe it faces a competitive market environment since there are two other major competitors ahead of them (Amylin/Lilly and Novo Nordisk). That said, with the GLP-1 class added to the ADA/EASD algorithm for type 2 diabetes treatment, there may be room for more.

  According to the presentation, out-licensing is still planned for R1579, Roche's DPP-4 inhibitor candidate. Management reiterated during the question and answer session that their decision to out-license R1579 was driven in part by the lack of weight loss, and they felt that their drug needed to differentiate itself in this highly competitive drug class – late stage competitors include Januvia (Merck's sitagliptin), Galvus (Novartis' vildagliptin), Onglyza (BMS/AZ's saxagliptin), and alogliptin (Takeda's SYR-322). To the best of our knowledge, significant weight loss has not been reported in any DPP-4 inhibitor monotherapy study. For R1439, a PPAR-gamma modulator, guidance remained the same from what was indicated in 2Q08 with a go/no-go decision for phase 3 planned in early 2009.

  On the device side, Roche Diabetes Care posted growth in USD but a loss without currency effects this quarter, with quarterly blood glucose monitoring and pump sales of CHF 725 million (USD$630 million), down 6% year on year and 7.5% quarter on quarter. Year-to-date sales of CHF 2,207 million ($1.9 billion) grew 10% in US dollars and declined 5% from a year ago operationally. While management admitted that this quarter was "slow," they said that Roche had succeeded in defending its number 2 spot versus the competition.

- **Enteromedics — Net loss improves slightly in 3Q08:** On October 21, Enteromedics reported a net loss of $10.2 million for 3Q08, down slightly from 2Q's $11.2 million loss. As the company went public in November 2007, year on year comparisons are not yet available. R&D expenses were at $8.2 million, down about 8.5% from $8.9 million in 2Q08. Net loss accumulated over the last nine months (ending September 30, 2008) was reported at $30 million. Cash, cash equivalents, and short-term investments at the end of September were around $29 million. The prepared statement mentioned the potential for use of VBLOC therapy, an appetite suppressing implantable device, in diabetic and hypertensive populations based on some positive data coming out of the 13the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). Greg Lea, SVP and CFO, expressed confidence that projected cash flow would be able to support the ongoing feasibility trial in diabetes as well as a future study in hypertensive patients.

- **Novartis — Promising sales results released for Galvus (vildagliptin):** In a call led by Chairman and CEO Daniel Vasella on October 20, Novartis announced sales results of $25 million for Galvus and Eucreas. As a reminder, Eucreas is a fixed dose combination of Galvus and metformin,

and it is the first single-pill DPP-4 inhibitor combination available in Europe. Notably, the majority of sales in Europe and Latin America can be attributed to Eucreas, reinforcing the importance of combination therapy. Past data has shown a ~1.5% A1c reduction for the combo product from a mid-8.0% A1c baseline; monotherapy was roughly half as effective. Galvus was the second DPP-4 inhibitor marketed in Europe after Merck's Januvia – it was approved and launched in early 2008. A disadvantage for Galvus is that patients using the drug are required to have a liver screening conducted at the start of treatment, every three months after starting therapy for the first year, and then on occasion thereafter. This extra screening increases the "hassle factor" involved with the drug and would be considered a marketing negative. Management did not mention a change from its decision in 2Q08 not to pursue resubmission of Galvus in the US. The decision by Novartis not to pursue resubmission of Galvus in the US followed several negative statements made by the company about its discussions with the FDA. Most likely the FDA required a long and expensive clinical outcomes trial that would have provided no guarantee of approval. Currently, there are no other diabetes or obesity compounds shown in the company's publicly available pipeline.

- **Novo Nordisk — Results from the highly anticipated LEAD 6 study:** The results from the first head-to-head study (LEAD 6) between liraglutide (Novo Nordisk's Victoza) and exenatide (Eli Lilly's/Amylin's Byetta) were presented at the Canadian Diabetes Association meeting in Montreal, Quebec in poster form on October 17. As a reminder, top line data for the study had been released before the ADA meeting in June and generated some controversy because few details were provided at the time about the methodology of the study (see DCU #81). LEAD 6 was a 26 week study designed to compare the efficacy and safety of treating type 2 patients inadequately controlled on metformin and/or sulfonylureas with either liraglutide (Novo Nordisk's Victoza) or exenatide (Eli Lilly's/Amylin's Byetta).

	Liraglutide (1.8 mg once daily)	**Exenatide (10 ug twice daily)**	**P-value**
Number of participants	233	231	—
Baseline BMI (kg/m²)	33	33	—
Baseline A1c	8.2%	8.2%	—
Duration of diabetes (yrs)	8.5	7.9	—
Mean FPG (mmol/L)	9.8	9.5	—
Number completed (%)	202 (86%)	187 (81%)	—
Change in A1c	-1.12%	-0.79%	<0.0001
% achieving an A1c <7.0%	54%	43%	0.0015
% achieving an A1c <6.5%	35%	21%	<0.0001
Change in FPG (mmol/L)	-1.61 (-29 mg/dL)	-0.60 (-10 mg/dL)	0.0001
% achieving an FPG <7.2 mmol/L (130 mg/dL)	42%	26%	0.0001
Change in PPG after breakfast (mmol/L)	-3.2 (-58 mg/dL)	-3.9 (-70 mg/dL)	0.0124
Change in PPG after dinner (mmol/L)	-3.1 (-56 mg/dL)	-3.6 (-65 mg/dL)	0.038
Change in weight (kg)	-3.24 (-7.0 lbs.)	-2.87 (-6.4 lbs)	NS

Change in HOMA-B	+32%	+3%	<0.0001
Number of major hypoglycemic events	0	2	
Minor hypoglycemic events (events/patient/year)	1.9	2.6	0.0131
Nausea (5 weeks)	8%	18%	—
Nausea (10 weeks)	4%	13%	—
Nausea (26 weeks)	3%	10%	—

These 26-week trial results were presented October 17. Liraglutide showed a superior efficacy and safety profile when compared to exenatide, as was suggested when the top-line results were released in press release form in June. We were surprised to see such a low nausea rate and modest change in A1c level in the exenatide arm given that in previous studies such as the AMIGO trials, a greater percentage of nausea and reduction in A1c was seen. At first, we thought it may have been a result of dosing, but during the Q+A session, Lawrence Blonde, MD (Ochsner Clinic Foundation, New Orleans, LA) said that all patients were put on the maximal dose and were not allowed to back titrate.

We also wondered about whether they made the liraglutide patients inject twice daily with one dummy and one active dose because if not, patients/doctors would know which drug they were on. Without knowing the compliance rate, we cannot be sure that the exenatide patients were using the drug as prescribed. This point would be particularly important for this study because liraglutide is injected once daily and exenatide is injected twice daily. In response to a question about adoption about liraglutide, Dr. Blonde noted that the once a day formulation of liraglutide may help adoption by primary care physicians, and said that in general, it has been shown that patients adhere better to a drug that is only administered once a day rather than twice a day. It will be interesting to see how once-daily (Victoza) or once-weekly (Eli Lilly/Amylin's LAR) compares to twice-daily.

Dr. Blonde did not offer any perspectives during the Q+A session at the CDA on why the nausea was so low. It may come down to how patients characterized nausea – both compounds had lower nausea rates than typically seen. Dr. Blonde also pointed out that A1c reduction characterization depends on whether the A1c drop quoted is from baseline or from placebo – he pointed out that in the AMIGO trials, A1c in the control group appears to have deteriorated slightly (0.1 or 0.2%), making the difference in A1c in treated and control groups slightly larger as it was reported as placebo-adjusted. The LEAD trials have all reported A1c reductions from baseline. Two notable points that were made during the Q+A session was that LEAD 6 did not show a statistically significant decrease in systolic blood pressure the way LEAD 4 did but that there was a reduction seen though in the LEAD 6 extension study. The current drug development milieu seems to be pointing to carrying out cardiovascular outcomes studies, so the decrease in blood pressure would be advantageous for liraglutide. Another topic that has garnered a great deal of interest has been GLP-1s and pancreatitis. Dr. Blonde mentioned that they did see one episode of pancreatitis in the liraglutide arm, and no episodes of pancreatitis in the exenatide arm. According to Dr. Blonde, when they delved into the patient's history, they noted that the individual had already been experiencing epigastric pain at the time of entry, and the case of pancreatitis was chronic, not acute. We continue to think that focus on pancreatitis is overblown given that people with diabetes are at higher risk for it.

We think the most notable element of the presentation was Dr. Blonde's assertion that the GLP-1 group in general had potential for great growth – he seemed very positive on the group, especially since they have an effect on satiety and gastric emptying that is not seen with other drugs. We imagine

positivity will grow the closer that Novo Nordisk comes to market – we recall Novo Nordisk having been very strong in marketing another product, Novolog, that was second to market some years ago. It will be important to see what happens March 2 (the date for the advisory committee meeting) and when Amylin/Lilly's LAR is submitted.

- **Boehringer Ingelheim — Early data for its DPP-4 inhibitor development programs:** During the October 17 R&D update, management discussed Boehringer Ingelheim's DPP-4 inhibitor and SGLT-2 inhibitor programs, in phase 3 and phase 2, respectively. The company now plans to file its DPP-4 inhibitor, BI-1356, in 2010. BI-1356 is similar to Januvia and alogliptin in that it is a non-peptidomimetic that is not metabolized; however, the compound has a much longer half life – what difference if any this makes clinically is unclear. While efficacy in the small proof of concept trial was sub-optimal (0.5% placebo-adjusted drop from an A1c baseline of 7.0%), we look for larger trials to show better results given that the decision to move this drug to phase 3 has been made. We believe that DPP-4 inhibitors are relatively undifferentiated; therefore, marketing strength will be critical for any drug in this class. Following positive data at ADA 2008 for the SGLT-2 class, we continue to expect growing interest in this drug class given that the side effect profile looks more positive to date than expected. Boehringer Ingelheim aims to expand its diabetes portfolio to include an 11-beta hydroxysteroid dehydrogenase type 1 (11B-HSD1) inhibitor, which is being developed with Vitae Pharmaceuticals.

- **Abbott — Solid growth at Diabetes Care driven by FreeStyle Lite and Freedom Lite:** On October 15, The Diabetes Care branch reported global sales of $355 million representing a 10.2% reported increase in sales. Without the currency effect, underlying growth was still solid achieved sales of over $350 million. The results marked an important milestone for Abbott Diabetes Care, and are the best results ever posted for the franchise. International diabetes care continues to be a strong suit at Abbott where sales of $210 million grew by 19.3% (up 8.1% without the effects of currency) while US sales came in at $145 million, down 0.7% from a year ago. Overall, sales were driven by the FreeStyle Lite and the FreeStyle Freedom Lite. Navigator sales were not broken out individually, and we expect it will be some time before we see them because we expect the continuous glucose monitoring (CGM) market to grow slowly in the early years until the devices are easier to use, education expands, and reimbursement is not as hard to wrangle. Although CGM reimbursement has improved faster than expected, this improvement has been from a low base, and reimbursement still requires an inordinate amount of work from healthcare providers. This situation should improve with progress towards the artificial pancreas but becoming a standard of care for any demographic is still a long way away.

- **Johnson and Johnson — Strong growth in 3Q both domestic and internationally:** On October 14, VP Finance and CFO Dominic Caruso reported 3Q08 global sales in its Diabetes Care franchise of $667 million, up a reported 14% year-on-year (10% sans FX) with 9% growth in the US and 12% growth internationally (21% including the currency effect). Much of the call focused on new candidates in the pharmaceutical pipeline; of note, there is an SGLT-2 inhibitor in phase 2 in-licensed from Mitsubishi Tanabe Pharma as well as a new compound in obesity. Decisions on phase 3 for both compounds will be made early next year. Overall, J&J expressed its commitment to pursuing emerging markets and new indications for pharmaceutical products, and it increased earnings guidance overall for J&J which was a welcome sign given the recent economic turmoil. Although J&J did not report revenue for pumps, they did say that the pump franchise grew over 30% and that market share increases were driving growth. This was extremely impressive in our view given that Animas grew 30% in 3Q07 – it is safe to say that was a tough comparison even if we cannot report the baseline. We believe that Animas is doing particularly well in Europe, which represents an increasingly fruitful area of growth for pumps, following a long period of low reimbursement in many

European countries. While reimbursement continues to be very tough in some areas, penetration is increasing in countries like the UK.

- **Vivus — Positive blood pressure data from Qnexa studies:** On October 6, new Qnexa data (15 mg phentermine and 100 mg topiramate) demonstrated that systolic blood pressure decreased by 3.9 mmHg (neutral effect in placebo) and triglycerides decreased by 19 mg/dL (0.6 mg/dL in placebo). These beneficial cardiovascular signals should be positive in the regulatory review process given the FDA's concern over cardiovascular safety signals. We have previously reported positive data on the glycemic impact of Vivus's Qnexa (15 mg phentermine and 100 mg topiramate) from the OB-202 study in 200 type 2 patients with diabetes. To recap, Qnexa was found to decrease A1c levels by 1.2% compared to 0.6% in the placebo arm after 24 weeks of treatment (8.6% A1c baseline). A significant decrease in fasting blood glucose of 33 mg/dL was also observed with Qnexa compared to 7.6% in placebo. Body weight decreased by 8% (17 lbs) in the treatment group and 1.2% in the placebo group. Treatment with Qnexa decreased the number of other drugs prescribed during the study period. Qnexa treatment caused an increased incidence of side effects, but they did not result in higher withdrawal from the study. It also reduced cardiovascular risk factors such as blood pressure and lipid levels, and resulted in a significant reduction in body weight.

- **Amylin — Two year pramlintide safety data presented:** On October 4, Amylin presented full two year tolerability and safety data on pramlintide during a poster session at the Obesity Society's annual meeting. This was a 12-month open-label extension of the previously reported phase 2b four month dose ranging and eight month single-blind pramlintide studies. The aim of the study was to assess long-term safety and tolerability of 120 mg, 240 mg, and 360 mg doses of pramlintide. After two years of pramlintide therapy, mean weight loss from a baseline of 230 lbs was 12.5 ± 1.76 lbs (5.7 ± 0.8 kg). 100 subjects were evaluated in this analysis. The nine evaluable subjects initially randomized to the 360 mg BID dose in the four month dose ranging study maintained a weight loss of 15.6 ± 4.4 lbs (7.1 ± 2.0 kg). Nausea was typically most evident at the onset of pramlintide treatment, and investigators report that the profile of nausea in this group was high at onset (17%), reduced after about seven weeks (6%) and resolved after about 40 weeks. No safety signals from electrocardiogram, physical examination, vital signs, and clinical lab measures were observed. No neuropsychiatric adverse events occurred with ≥ 2% incidence.

- **Orexigen — Contrave for treating the metabolic syndrome:** On October 4, Orexigen discussed phase 3 data on Contrave, which is a sustained release formulation of naltrexone and bupropion. In a retrospective analysis of the data from a phase 2 study, investigators applied the ATP III definition of the metabolic syndrome to the 32 mg naltrexone group, which had been found to have the most favorable risk/benefit profile during the NB-201 study. By this definition, metabolic syndrome was incident in 30% of subjects at baseline and decreased to 14% in the intent to treat group. Data from the 32 mg naltrexone group as well as further pooled data suggested that subjects with higher baseline levels of fasting insulin and fasting triglycerides (suggestive of higher insulin resistance) had better resolution of the metabolic syndrome. From our view, reduction of pre-diabetes is a very real way to get payors' attention – although obesity isn't really seen at the moment as a disease, moving from "pre-diabetes" to "normal" is attention-getting provided the side effects are minimal.

  Orexigen also announced quality of life data for Empatic, a fixed dose combination of zonisamide (Z) and bupropion (B) currently in phase 2 studies. While the company is most likely to actively pursue the Z360/B360 mg and Z120/B360 mg dose combinations, given 48-week weight loss profiles reported, the lower doses could be an interesting alternative for patients very sensitive to side effects or requiring slower initial weight loss. Quality of life data following a dose optimization study were obtained at baseline, and at weeks 12 and 24. Subjects treated with Z360/B360 mg dose showed

statistically significant improvement in physical function and self-esteem based on Impact of Weight on Quality of Life-Lite (IWQOL-Lite) scores at week 24 compared to placebo. As we have written before, we have reservations about CNS-targeting drugs for obesity given the potential for serious and unexpected neurological effects and the high hurdle for FDA approval. Although the drugs contained in Contrave and Empatic are currently FDA approved in the US, the FDA's tolerance of safety risk for obesity is likely much lower than for purposes that the drugs are currently approved for (e.g. depression, seizures) since many more people would likely take it.

- **Merck – Discontinuing taranabant phase 3 development:** On October 2 Merck announced that it will drop further development of its phase 3 CB-1 receptor agonist, taranabant, citing side effects and lack of efficacy. Dr. John Amatruda, senior vice president and research head of diabetes and obesity, said the overall profile did not support further development. The move follows disappointing phase 3 results, presented at the 57th Annual Scientific Session of the American College of Cardiology in Chicago, on March 31 2008. Following the publication of this study, Merck announced that it would only focus on developing the lower dose of taranabant. We are not surprised that Merck decided to terminate the entire taranabant program, given the low traction that rimonabant has had. We assume that taranabant's side effect profile in particular, combined with lower weight loss at lower doses, clinched the decision to halt development. Merck's pipeline now includes three compounds in phase 1 for diabetes (MK-941, MK 4074, and MK-8245) and one in phase 2 (MK-0893). All mechanisms are undisclosed; interestingly, MK-941 looks to be a capsule taken on top of basal insulin, perhaps designed as a way to delay mealtime insulin.

- **Pfizer — Drops obesity pipeline:** On September 30, Pfizer President Martin McKay announced the decision to end further efforts to develop early-stage obesity drugs (among other therapeutic areas) and focus on medications for Pfizer's stated "high potential" areas, including oncology, pain, inflammation, diabetes, Alzheimer's disease, and schizophrenia. Several other drugs for heart disease and bone health were also abandoned at Pfizer. For now, Pfizer is still developing its latest-stage obesity drug, a CB1 antagonist in phase 3, but given that the regulatory environment for obesity and diabetes drugs has been challenging, we would not be surprised to see a shift on this when data emerges. Although the pipeline on the company's website includes various obesity compounds, as we understand it, everything outside phase 3 is set for out-licensing or for discontinuation of development. Pfizer had five obesity drugs in its pipeline: CP-945598 (CB1 antagonist), CE-326597 (CCK A agonist), PF-2575799 (undisclosed), PF-4325667 (undisclosed), PF-3932295 (undisclosed). Their CB1 antagonist was in phase 3 while the CCK A agonist was in phase 2. The remaining three undisclosed drugs were still in phase 1.

- **Novo Nordisk — Preview of LEAD 6 data and update on pipeline development:** During Novo Nordisk's Capital Markets Day on September 26, CEO Lars Sørenson discussed the company's broad corporate strategy and CSO Mads Thomsen gave an R&D overview. Peter Kristensen, SVP Global Development, presented the latest information concerning the liraglutide development program. Particular attention was paid to the non-randomized 14-week LEAD 6 extension study. The extension study found a statistically significant 0.3% A1c drop in the patients switched from Byetta to liraglutide. This drop was from ~7.2% after 25 weeks on Byetta. Fasting plasma glucose was reported to have dropped 16.2 mg/dl (0.9 mmol/L) from about 155 mg/dl (8.6 mmol/L) after 25 weeks on Byetta. Kristensen outlined the liraglutide phase 3 obesity program noting a commencement period before year-end with one-year data available by 2011 – this allows for two-year follow-up. The program is expected to randomize between 4,500 and 5,000 obese (BMI >30) or overweight (BMI >27) patients with comorbidities.

  On the issue of pancreatitis, management succinctly summed up three factors to consider, all of which were reported to put liraglutide in the clear regarding increased pancreatitis risk: the overall rate is in

the ballpark for a population with diabetes (1 to 4 case per 1000 patient years); no temporal relationship between initiation of therapy and pancreatitis has been found (within the first 30 to 40 days); resurgence (or exacerbation) of pancreatitis following re-initiation of liraglutide therapy after temporary stoppage due to onset of pancreatitis has not been reported.

During the future insulin presentation, SVP Diabetes Research, Peter Kurtzhals, discussed next generation basal insulin, non-invasive insulin and peptide delivery, and tailored insulins. NN5401 is a pre-mixed insulin that is expected to have a more of a "true basal-bolus" profile (i.e. no "shoulder" after the initial peak and more of a basal tail). He expressed confidence in the future of the company's pre-clinical oral peptide delivery program.

- **Private Company Roundup:**

  - **Enject, Inc. raises funds in record time to develop glucagon pen:** Enject, a small Washington-based startup, has closed on an initial $2.5 million to pursue development of a glucagon pen ("GlucaPen") for treating emergency hypoglycemia. The innovative element is that the glucagon is in a very cool modern "auto-injector" pen device similar to a insulin pen. As many patients and caregivers know, currently marketed glucagon products (a vial and prefilled syringe) have numerous challenges in the preparation and delivery of treatment. The Enject product looks quite different as this seems very easy to use and straightforward to manufacture. As we understand it, from a conversation with CEO Dick Rylander, one reason for the short development cycle is that virtually all of the components are used in currently approved products. Rylander describes the GlucaPen concept as analogous to the EpiPen, used to treat anaphylactic shock due to severe allergies. To better understand the hassles of current glucagon choices, see http://youtube.com/watch?v=Mwk4g5es6fo. High hassle!

    We believe that penetration of current glucagon solutions are low due to the hassle factor – Enject sounds like it has a much easier approach to the problem of severe hypoglycemia and we would think it would be welcomed by patients, families, payors, and healthcare providers. Intriguingly, because the company has found a way to use only components that are readily available today for purchase, GlucaPen could be submitted for FDA approval within 18 months in 2010 – this should be welcome news to many patients, families, healthcare professionals and payors. We believe the potential for this market is substantially higher than the sales of the current glucagon products (Eli Lilly and Novo Nordisk both market glucagon hypokits), and we will be closely tracking Enject's progress. The company appears to be backed by smart money – prominent industry professionals from both big pharma and biotech who have been very successful. We think payors will welcome Enject in particular, since emergency room costs for severe hypoglycemia are well-documented. Glucagon is purchased as insurance against a life-threatening emergency, and we think that GlucaPen's user-friendliness will make it have a higher likelihood of actually being used when needed. Patients often complain about dosing of glucagon in current kit. The company plans a pediatric version called GlucaPen Jr., which we think is a great idea given the uncertainty many parents face about hypoglycemia in children – especially very young children who can't yet speak (there are a surprising number of stories about patient's blood glucose levels soaring to 300 mg/dL and higher after hitting a 30 mg/dL bottom and taking glucagon).

    We see the market for a user-friendly glucagon as all type 1 patients and all type 2 patients on insulin – a market that should be expanding due to recent modified ADA and EASD guidelines for patients with type 2 diabetes calling for ever tighter control.

  - **Phenomix — Collaboration with Forest Laboratories on DPP-4 inhibitor:** Phenomix announced on October 23 that it had entered into a collaboration with Forest Laboratories to develop and commercialize dutogliptin (PHX1149T). Dutogliptin is an orally administered DPP-4

inhibitor in phase 3 studies for use patients with type 2 diabetes. Under the agreement, Phenomix will receive an upfront payment of $75 million. Upfront and milestone payments could reach $340 million – this is actually a little lower than we had expected given how blockbuster the class is though by the time it enters the market, it may be fairly crowded. Still, good for Forest! Once dutogliptin is commercialized, Phenomix will be responsible for promoting dutogliptin to endocrinologists and endocrinologists while Forest will be promoting dutogliptin to primary care and specialty physicians. According to the agreement, Forest will have exclusive rights to develop and commercialize dutogliptin in Canada and Mexico, and Phenomix will retain exclusive rights to develop dutogliptin outside of North America.

- **SmartCells — A new way to deliver insulin:** SmartCells Inc., pioneers of SmartInsulin, a once a day, glucose dependent insulin formulation in development, received $1 million in partnership funding from the Juvenile Diabetes Research Foundation (JDRF) on October 23. The funds are earmarked for the development of a SmartInsulin formulation that will be geared towards the treatment of type 1 diabetes. SmartInsulin is an engineered complex that holds insulin molecules held in place in an insulin polymer conjugate. The conjugate is also bound to a multivalent glucose-binding molecule (GBM), which has active sites to bind glucose molecules. The therapy is designed such that the insulin polymer conjugate attached to the GBM are injected subcutaneously like normal insulin. A small depot is formed below the skin level. The insulin remains bound to the polymer plus GBM complex and remains inactive until unbound. Unbinding only occurs once the concentration of glucose around the complex reaches a certain threshold level (at least 130 mg/dL from preclinical studies). We assume that once a certain proportion of active sites on the GBM have been filled with glucose molecules active insulin molecules are released through an allosteric regulation mechanism. After the released insulin has mediated sufficient cell uptake of glucose, the concentration of glucose molecules surrounding the complex decreases past the threshold and insulin release is halted. Early data suggest that there is no insulin release when glucose levels are below 70 mg/dL.

  Both hyperglycemia and hypoglycemia reduction would be benefits of this therapy. Ideally, active insulin in SmartInsulin is only released in a glucose concentration-dependant manner. This means that there will always be basal levels of insulin being released in response to the basal levels of glucose constantly found in blood. Likewise, during and after a meal, insulin concentrations will rise to bolus levels but only as much as is needed for carbs or a correction dose. The company plans to produce separate formulations for type 1 and type 2 diabetes.

  SmartInsulin is currently in pre-clinical (non-human) testing. The company believes the insulin-polymer matrix for type 2 diabetes would likely reach the clinic first. Early proof-of-concept studies have demonstrated the key capabilities of SmartInsulin. The team has tested a number of in vitro and in vivo features. The company reports to have synthesized a self-contained material, prevented insulin leakage from the matrix, and shown the reversibility and response to physiological glucose concentrations. They have also reported that insulin release is not temperature dependent. In vivo testing has also examined the polymer-insulin bioactivity and demonstrated the rapid response to glucose challenges and negligible insulin leakage. SmartCells will likely try to get a working formulation into clinical testing by mid-2010. By early 2009, the company plans to finalize IND-enabling work on SmartInsulin. Human data in ~10 diabetic subjects should be ready for external review by mid 2011.

- **XOMA — Enters equity financing with Azimuth Opportunity over two years:** On October 22, XOMA announced entry into a committed equity financing facility which gives them the option to sell up to $60 million worth of registered common shares to Azimuth Opportunity over 24 months. This would appear to be a very favorable deal for Xoma given the terms of the

agreement: 1) XOMA has no obligation to use this financing and can enter other financing deals; 2) No commitment fee or warrants were signed with this deal; and 3) XOMA decides timing, dollar amount, and floor price per share of each draw under this facility subject to certain conditions (no further elaboration). This agreement gives XOMA extended financing options in driving development of XOMA 52, their anti-IL1 beta monoclonal antibody, which targets inflammation in type 2 diabetes.

- **Jenrin Discovery — A new approach to CB1 antagonists:** On October 5, we learned about Jenrin Discovery, which is aiming to revolutionize the technology of CB1 antagonists. Jenrin has a candidate compound, JD-5006, that is designed to work on peripheral CB1 receptors in a way similar to rimonabant (Sanofi-Aventis) and taranabant (Merck's discontinued CB1 antagonist), but it is not able to enter the brain. Hypothetically, this drug candidate should produce weight loss from the peripheral effects without having the negative psychological side effects that are seen with other CB1 antagonists. Preclinical studies in animal models demonstrated that after 21 days, JD-5006 reduced diet-induced weight gain in a dose-dependent manner (up to a 20% reduction in weight gain with a 30 mg/kg dose). Triglycerides also fell and HDL cholesterol returned to control levels with treatment. In comparison to the CNS side effects of the brain-penetrant cannabinoid receptor antagonist SLV-319 (at one time developed by Solvay) in mice, the Jenrin compound exhibited far less negative side effects. We are very interested in this approach, but we are unsure whether or not the peripheral effects of CB1 inhibition will be effective in producing weight loss in humans. The reaction from physicians seems to be positive overall, and the biggest concern with this new class of drugs is whether or not the amount of weight loss achieved will be at all comparable to brain-penetrant antagonists like rimonabant and taranabant.

- **Genaera — Targeting PTP-1B for weight loss:** At NAASO 2008 on October 6, Genaera presented preliminary data on trodusquemine, its candidate for type 2 diabetes and obesity that acts by selectively inhibiting protein tyrosine phosphatase 1B (PTP-1B). PTP-1B downregulates the insulin receptor, thereby decreasing insulin sensitivity; therefore, PTP-1B inhibition increases insulin sensitivity. Although PTP-1B is a well-validated drug target, a number of attempts to develop PTP-1B inhibitors have failed. The problem is that phosphatase inhibitors are notoriously non-specific, but according to management, trodusquemine is 200 times more specific than any other PTP-1B inhibitor currently available. This phase one study was designed to evaluate safety, tolerability and pharmacokinetics of single doses of the drug in obese patients with type 2 diabetes poorly controlled on metformin (≥1000 mg/day). The drug was administered intravenously over two hours in doses of either 3, 6, 10, or 15 mg/m^2. The poster presented seven-day data, but management indicated that data was also collected on day 14 and day 21, so we assume that data will be presented in the future – we look very forward to seeing this. Preliminary pharmacodynamic data seem to support going forward with the 6 and/or 10 mg/m^2 doses since the dose response seems to die off in the 15 mg/m^2 dose range. Approximately half of the subjects in the placebo and in the treatment arms reported at least one treatment emergent adverse event. There were no serious adverse events or severe adverse events reported. Infusion site reaction (N=5), headache (N=3), and nausea (N=2) were the most frequent events in the treatment group. In the placebo group, coughing (N=2) was the most frequent event reported. One person reported an infusion site reaction, one person reported headache, and no nausea was reported. In addition, according to management there were no CNS or behavioral problems, which is a positive for an obesity drug, especially since rimonabant (Sanofi-Aventis) and taranabant (Merck) have been associated with questionable psychological side effect profiles.

- **Synvista — To launch biomarker test at AHA in mid-November**: Synvista Therapeutics announced on September 11 during a presentation at the 2008 Cardiovascular Biomarkers and Surrogate Endpoints Symposium that its proprietary monoclonal enzyme immunoassay can indicate a person's haptoglobin pheno/genotype, aiding physicians in predicting cardiovascular risk in diabetic patients. Synvista's poster demonstrated that the rate of renal failure and severity of renal failure and the death rate is higher in hp22 diabetes. We believe the move toward more individualized therapy bodes well for haptoglobin diagnostic technology and we are optimistic about a test that could give more knowledge to patients with diabetes about their risk for cardiovascular disease.

  Some background on the haptoglobin marker: in the body, there are thousands of proteins, including one protein called haptoglobin. Its primary purpose is to bind up the hemoglobin and prevent it from hanging around in the blood and bring it back so it can be reinserted to red blood cells. In the population there are three kinds of haptoglobin; identifying the type of haptoglobin a patient has can determine which patients are born with the more negative variant of haptoglobin. The three different proteins are Hp1-1, Hp2-2, and Hp1-2 - HP2-2 is the negative haptoglobin that puts patients at highest risk for the disease. Just over 35 % of patients with diabetes will have the "HP2-2" haptoglobin and thus be at significantly higher risk of cardiovascular disease; the rest have low or medium risk. Specifically, the chance of having a heart attack, stroke, or CVD death appears to be about five to seven times higher if a patient has a "bad" haptoglobin.

  Synvista's test aims to assess haptoglobin in order to help determine who is at risk for cardiovascular disease; this would effectively segregate different forms of diabetes, which could be helpful in developing more targeted treatments. This research is interesting to us as we believe acceptance and realization that we are in the age of pharmacogenomics; biomarkers can help us understand risk better, which could be a step toward making intelligent, targeted treatment more possible. We would also assume this could drive interest in earlier, more aggressive therapy particularly for these patients, who would be at higher risk for cardiovascular disease. This test may also drive more low-cost treatment - we look forward to learning more about this at AHA in New Orleans in mid-November, where Synvista will be formally launching the test.

  — by Kaku Armah, Kelly Close, Brendan Milliner, and Melissa Tjota

4. DCU Dialogue with Dr. Rury Holman

Dr. Rury Holman is currently Professor of Diabetic Medicine at the University of Oxford. In the past he has served as Academic Chairman of the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM); Director of the Diabetes Trials Unit; and an Honorary Consultant Physician to the Oxford Radcliffe Hospitals NHS Trust. He was a joint recipient of the prestigious ADA Banting and Best medal in 1999. He divides his time between clinical care of patients, teaching, and researching diabetes prevention, prevention of complications, and appropriate treatment of type 2 diabetes. Professor Holman, who has published over 250 peer-reviewed papers, is currently co-chair of the NAVIGATOR trial, and chief investigator of the 4-T trial, the Acarbose Cardiovascular Evaluation (ACE) trial and the UK Prospective Diabetes Study (UKPDS).

Implications of the 10-year follow up results from UKPDS

Kelly Close: Thank you so much for spending some time with us Dr. Holman. We were thrilled at EASD to hear the stunning results of the 10-year follow up to UKPDS, which certainly seemed to reinforce the importance of early, intensive therapy and maintaining a healthy A1c in order to avoid complications. Could you talk to us about what you think

are the major takeaways from these results?

Rury Holman: Certainly. The first takeaway I think is the importance of the legacy effect, by which we mean the continued and increased benefit we saw from earlier improved glycemic control. Interestingly there does not seem to be a German word for "legacy," and we were asked to provide a definition. It is similar to what the DCCT called "metabolic memory" but as yet we do not know the mechanism. The second is that we now know for certain that improved glycemic control does have a positive benefit with respect to the risk of heart attacks or premature death. Third, since many cardiovascular patients also have diabetes, it is important for cardiologists to include good glucose control as part of their risk factor management programs, something I was discussing only last week with Steve Nissen and Robert Califf.

Kelly: What was the process like, preparing the NEJM manuscript and preparing the talk for EASD - what is the impact of being published in such a prestigious journal and presenting at a major meeting the very same day?

Dr. Holman: It was amazing! When the primary UKPDS results were published in 1998, we were keen to have them published the same day and had two papers in the Lancet and three in the British Medical Journal. This time we talked to the New England Journal of Medicine, and they were willing to consider publishing the follow up data concurrent with the oral presentation we were giving at EASD 2008. We went for it, and everyone involved worked extremely hard to ensure that the two articles and the EASD presentation were finished in time – we think it is important for major trials to publish their data as soon as possible after they are made public to ensure that everyone has access to the full results and all the details.

Melissa Tjota: With UKPDS results in mind, what are the implications for how early we should start treating patients? Have you done any thinking about how to identify patients earlier?

Dr. Holman: Given these new results from the UKPDS, it is now crystal clear that we need to start treating people with diabetes as early as possible. Even though glycemic control improved in both groups after the trial finished, the conventional therapy group did not catch up with the intensive therapy group. Our ten-year follow up data show conclusively that you get extended benefits by improving glucose levels early and also underscore the importance of offering metformin from day one of diagnosis. In relation to your second question, I am on a couple committees looking at how we can best identify individuals with pre-diabetes and considering when and how they should be treated. We simply cannot wait until someone reaches an A1c of 7.0% or starts to exhibit signs of microvascular complications before starting them on treatment.

Melissa: Are you continuing to follow the patients to see if the legacy effect continues even further?

Dr. Holman: We have no funding to follow UKPDS individual patients any longer, but we have a national register in the UK, which means that we can continue to monitor mortality rates.

ACCORD and UKPDS

Kelly: It would seem to us that UKPDS is more definitive for the newly diagnosed and average patients, while ACCORD might apply more to the patient with quite advanced disease.

Is that a reasonable way to think about it?

Dr. Holman: The two trials studied quite different patient groups. UKPDS only recruited people with newly-diagnosed diabetes whereas ACCORD looked at those with longstanding diabetes, many of whom already had cardiovascular complications. This meant we were looking earlier in the disease process and largely at primary prevention of complications whilst ACCORD was looking at much later intervention.

Kelly: As a corollary, then, ACCORD appears to be relevant to patients who have had diabetes over a long period and are at high risk for cardiovascular disease. On that note, do you think that the ACCORD organizers chose patients who were at high risk for cardiovascular disease because they wanted to see how this group was affected or because they would be more likely to have cardiovascular events sooner?

Dr. Holman: It was mainly the latter to ensure enough cardiovascular events occurred to provide the study with enough power. As a reminder, the study was designed to have a power of 89% to detect a 15% reduction for patients in the intensive-therapy groups compared to the standard-therapy group. Unfortunately, since the study was stopped after just three years, we do not have long enough follow up to see the real impact of aggressive glucose control on all of the outcomes studied as it did not reach the expected power. In UKPDS it took at least three years to begin to see a difference in microvascular complications and even longer for macrovascular complications. In my view, outcome studies in diabetes really need to run for six years or more to ensure we capture the real benefits and fully understand the possible risks involved.

Kelly: How does UKPDS offer a lens with which to view ACCORD, ADVANCE, and VADT? How do you think the results will impact the general community? We recently talked to a doctor who worried about how the pendulum was swinging too far to macrovascular complications, and people were forgetting to focus on glycemic control. Now, it seems that we have been shown the extent to which early tight glycemic control can significantly reduce both microvascular and macrovascular complications, correct?

Dr. Holman: UKPDS emphasizes the need to treat early and shows that improved glycemic control is beneficial with respect to both microvascular and macrovascular complications. People often forget that extending their lives by successfully treating cardiovascular risk factors means that the risk of getting microvascular complications will be greater unless good glycemic control is maintained.

Melissa: Do you have any thoughts on the hazard ratios seen in ACCORD for various drugs?

Dr. Holman: ACCORD was not designed to study specific pharmacological agents, and patients were encouraged to take any or all drugs available in an attempt to obtain A1C values less than 6%. In practice, many patients took three, four, or more agents making it virtually impossible to get a clear view of what any one drug was doing.

Kelly: Do you have a hypothesis on the early deaths in ACCORD that you could share? Do you think ACCORD will have any lasting damage?

Dr. Holman: No definitive answer has emerged as yet. Overall there was a 10% trend to fewer cardiovascular problems in the aggressively treated group, but I suspect that many of these patients may have learned to tolerate chronically low blood glucose levels. This issue would possibly have left them vulnerable to cardiac arrhythmias in the event that

they did have a heart attack.

Drug development

Melissa: How do you think about drug development today? Do you think that outcome studies will be required in for drugs to be approved by the FDA going forward?

Dr. Holman: I believe the agency is likely to make cardiovascular outcome studies mandatory as part of the licensing process. They are in a tough spot just now following the high-profile safety concerns over some drugs developed for diabetes.

Kelly: Even for drugs that are very far along in the development like Novo Nordisk's liraglutide, do you believe they will be required to show cardiovascular outcomes?

Dr. Holman: I think all new drug classes will need to be evaluated to understand their true benefits as well as the need to ensure we do no harm.

Kelly: Dr. Holman, this was an incredibly informative conversation, and we appreciate all the contributions you have been and will continue to be making to improve the treatment of diabetes.

— by Kelly Close and Melissa Tjota

5. DCU Dialogue with Dr. Michael Jaff

Dr. Michael Jaff is the Director of the Vascular Center at Massachusetts General Hospital in Boston, MA, which is a large collaborative program encompassing over 100 doctors who diagnose and treat patients with different forms of peripheral vascular disease (PVD). Our conversation with Dr. Jaff focused on peripheral arterial disease (PAD), which affects approximately 10-12 million Americans a year, and it is a common complication of diabetes that can have serious side effects, particularly amputation. We were amazed to hear that in individuals who have both diabetes and PAD, there is a threefold increased risk of dying from **any** *cause over the next five years, not just from cardiovascular disease. This point highlights the need to treat diabetes as early as possible before complications appear because as Dr. Jaff said, it is "a bad marker of things to come."*

Kaku Armah: Dr. Jaff, thank you for taking to time with us to discuss an increasingly worrisome complication of peripheral arterial disease (PAD). For our readers, as a reminder, PAD is the hardening of the arteries of the legs, a process similar to artery blockage in the heart that 10-12 million people in the US with diabetes suffer from.

Brendan Milliner: To begin Dr. Jaff, could you tell us a bit about yourself and your work?

Michael Jaff: So I am the Director of the Vascular Center at the Massachusetts General Hospital in Boston, Massachusetts. It is a large seven-specialty collaborative program that encompasses 120 doctors, 500 support staff, and we diagnose and manage patients with all aspects of peripheral vascular disease. I run the Vascular Diagnostic Lab here at the hospital as well as a large research lab that deals with emerging and novel therapies for patients with artery blockage.

Introduction to Peripheral Artery Disease

Melissa Tjota: We are particularly interested in learning about the connection between peripheral arterial disease and its connection to diabetes. Could you give us an introduction to peripheral arterial disease?

Dr. Jaff: PAD or Peripheral Arterial Disease is the hardening of the arteries of the legs, and it is a process similar to artery blockage in the heart, the brain, the kidneys, and so on. This is a very common disorder, and some individuals believe it is as common as heart artery disease. About 10 to 12 million Americans suffer from this problem every year, and the reason it should be of incredible interest to your particular patient population (i.e. diabetes patients) is that the most serious and common condition that leads to peripheral arterial disease is diabetes. About 40% of patients with peripheral artery disease have diabetes, and one of the greatest fears of patients with diabetes is limb loss or amputation.

Kaku: Is it known why so many people with diabetes have PAD? Do we have an understanding of the underlying mechanism that leads to increased risk of PAD?

Dr. Jaff: I think there are a lot of postulated mechanisms, but it correlates with the pattern of patients with diabetes having more diffuse and severe coronary heart disease and cerebrovascular disease. One of the interesting things about diabetes and peripheral artery disease is that the location of the artery blockage in patients with diabetes is quite different than that of patients who have peripheral artery disease but no diabetes. Patients with diabetes are more likely to have a much more severe version of the disease that tends to involve longer segments of arteries. It commonly occurs in the lower portions of the limb and the foot as compared to patients without diabetes in which they often have shorter, less severe, and diffuse artery disease that is higher up in the lower pelvis or upper leg. The disease then becomes much more challenging as the farther down the limb the blockage goes, the harder it is to treat. So, patients with diabetes are at higher risk not only for peripheral artery disease but also for blockage that is more severe and diffuse, which then challenges the treatment pathways.

Peripheral Artery Disease and Other Vascular Risk

Brendan: We have heard a little bit about peripheral artery disease being a marker for artery disease and other vascular risk. Could you comment on this topic?

Dr. Jaff: Someone who presents with peripheral artery disease has double the likelihood of having coronary heart disease and a 30% increased risk of having cerebrovascular blood vessel disease. The most incredible statistic though is if you take a patient with diabetes who has peripheral artery disease and compare that to a diabetes patient with normal peripheral artery circulation, the patient who has PAD has a threefold increased risk of dying from *any* cause over the next five years, not just from cardiovascular disease. So it is a bad marker of things to come.

Melissa: Along the lines of increased cardiovascular risk, could you give your thoughts on the FDA Advisory Meeting that took place on diabetes medications and cardiovascular risk?

Dr. Jaff: I cannot really comment on that specific meeting since I do not know too much about it, but the topic of the FDA and instituting changes presses a button that rings closely to me. About two years ago, the US preventive services taskforce recommended against ankle-brachial index testing for patients at risk for peripheral artery disease. Now, the ankle-brachial index test is the test that I mentioned earlier in the conversation. A non-invasive test can be done by anybody, and it costs nothing to do. We wrote a counter statement, and my personal sense is that any

patient with diabetes needs an ankle-brachial index done. I think if the FDA wanted to reassure the patients who had reasonable cardiovascular risks in a clinical trial of a diabetic agent, they could just as easily do an ankle-brachial index test, which costs nothing.

Final Comments on Peripheral Arterial Disease

Kaku: What do you think is the degree of awareness in the diabetes community about PAD?

Dr. Jaff: The degree of awareness in general is miserable. We have done a great job of getting patients to know that if they get pressure in their chest, they should not just take a Rolaids or a Tums because they might be having a heart attack. We have done a great job of getting patients to know if they suddenly go blind in one eye, it may be because they are having a stroke. Unfortunately, we have not done a good job of educating patients at risk for peripheral artery disease. We are failing to teach them to monitor signs of a disorder that triples their risk of dying in the next five years.

There was a paper published in *Circulation* last year in which a telephone survey was done of adults at risk for peripheral artery disease. This survey looked at how much adults knew about PAD compared to Lou Gehrig's Disease, multiple sclerosis, cystic fibrosis, and muscular dystrophy. The last four are unusual disorders that affect around 10,000 people a year. PAD affects about 12 million people a year, and only 25% of the patients ever even heard of the term.

Brendan: Lastly, one thing that we have followed are the CDC statistics, and it appears that over the past few years, the number of amputations related to things like PAD have declined. Do you have any idea of why this might be?

Dr. Jaff: I think we have less invasive and more effective technologies to treat peripheral arterial disease. I think that diabetologists and vascular specialists are becoming much more aware of the potential risks and hazards of just waiting and watching. Hopefully, those are the reasons.

Brendan: Dr. Jaff, thank you so much again for all your insights.

To read our full interview with Dr. Jaff, please see www.closeconcerns.com

— by Kaku Armah, Brendan Milliner, and Melissa Tjota

6. Conference Pearls: European Association for the Study of Diabetes

September 7-11, 2008 • Rome, Italy • www.easd.org

Living up to our expectations, the European Association for the Study of Diabetes (EASD) 2008 Meeting in Rome, Italy was the place to be to learn about current movement in the diabetes field from pharmacotherapy to diabetes devices to the UKPDS "legacy effect." As always, new data releases were the hot topic at EASD, and we have picked out the highlights for you to review below. We were particularly heartened by the results from the 10-year follow-up data on UKPDS. The original results of the UKPDS published in 1998 have had a huge impact on the treatment of type 2 diabetes in the past decade, and as the new results released at the conference on macrovascular benefit have suggested, it will continue to have a significant influence on the way diabetes is treated. Treating individuals as early as possible is becoming an increasingly prevalent message, and we highly support the measures being taken to mitigate diabetes and its complications.

Echoing a major ADA theme and following the controversial ACCORD study, the general consensus at EASD was that microvascular risk certainly is worth reducing through tight glycemic control. Several studies including ACCORD and ADVANCE have shown that tight glycemic control does not reduce macrovascular risk, whereas UKPDS showed that macrovascular complications were reduced after intensive control – this finding was shown after a decade follow-up. The ADVANCE study showed that intensive glucose control reduced microvascular disease outcomes (i.e. retinopathy, neuropathy, and nephropathy) by about 14% (statistically significant), but not macrovascular outcomes (i.e. heart attack, stroke, or cardiovascular death) – it would be interesting to move ahead a few years and see what ten-year follow up data would be. Given that 50% of people who begin dialysis treatment have diabetes, the observed benefits of intensive glucose control on microvascular complications are clinically and economically significant – to say nothing on the impact of quality of life for patients. The furor over macrovascular risk has overshadowed microvascular risk in the past few months, particularly following the FDA Advisory Meeting on diabetes medications and cardiovascular risk, but we agree with Dr. Steven Kahn who implored the audience at EASD to keep microvascular outcomes foremost in mind.

- **UKPDS Follow-up study results deliver definitive message on macrovascular benefit from tight control:** Prof. David Matthews, MD, (University of Oxford, UK) and Dr. Rury Holman FRCP, (University of Oxford, UK) presented results from the 10-year post-trial follow-up from the UKPDS. The study looked at three between-group analyses mainly focusing on two comparisons: between the sulfonylurea-insulin group and the conventional therapy group, and between the metformin group and conventional therapy group. There was also a third group that looked at tight versus less-tight blood pressure control. The results demonstrated a "legacy effect" of early glucose control and early metformin therapy in reducing microvascular and macrovascular complications, even though A1c and differences between groups disappeared during the follow-up. There was a good deal of buzz surrounding these results at the conference, and we think it is well founded. This 'metabolic memory' effect is notable, showing that glycemic control can have a lasting effect. We think that this has the potential to change the way diabetes is treated in a big way, and it might have a particularly positive implication for the treatment of pre-diabetes with early intensive and/or combination therapy. In the session, it sounded like the researchers are thinking along the same lines, so we may see real changes resulting from this study

- **JDRF CGM trial results show those that wore the devices got the best results:** This was a landmark study demonstrating for the first time that CGM can clearly lower A1c by a significant amount in a six-month time frame. In adults over 25, CGM reduced A1c by 0.53% (compared to control) after six months from an impressively low A1c baseline of 7.6%. In children 8-14 years old, A1c was unchanged, but secondary outcomes were positive for CGM (such as the percentage who lowered A1c by more than 0.5%). In adolescents and young adults 18-24 years, there was no difference in A1c or secondary outcomes. Generally speaking, people who used the technology found that it worked – we believe the data is less about which "segment" can benefit and more about who wears sensors – as sensors continue to be improved, we believe usage will go up in all groups and all groups would see significant benefit, especially as the sensors become easier to use. It was terrific to see this presented in Rome (alongside EASD, although results came in too late for it to be presented at the podium) and published simultaneously in NEJM.

- **Data published in Lancet and NEJM – not bad!** We were pleased to see that not only was new UKPDS and JDRF data being presented at (or at least near) the conference but that it was also being released in peer-reviewed journals. The two main articles that came out during the meeting were Drucker et al., Lancet, 2008 and Holman et al., NEJM, 2008. The former discussed 30-week results of treating type 2 patients with exenatide once-weekly or twice-daily, and the latter published results

from the 10-year follow-up data of the UKPDS. We continue to believe we will see more simultaneous publishing of important results at conferences as this method creates a significant impact in this era of evidence-based medicine. Enabling people to be able to see full results and conclusions is critical if studies are to have a durable and sustainable impact.

- **Novo Nordisk LEAD 4 data demonstrates benefits of liraglutide on glycemic control, weight loss, and blood pressure:** For liraglutide (Victoza), Bernard Zinman, MD (University of Toronto, Canada) gave detailed results on LEAD 4, a 26-week, 533-patient trial that looked at liraglutide (1.2 mg and 1.8 mg) as add-on therapy to maximal doses of rosiglitazone (GSK's Avandia) and metformin. A1c dropped 1.5% in both liraglutide groups vs. 0.5% in placebo from a baseline of ~8.5%. Body weight fell 2.0 kg (4.4 pounds) for 1.8 mg, 1.0 kg (2.2 pounds) for 1.2 mg, and increased 0.6 kg (1.3 pounds) for placebo. Dr. Zinman focused on the drop in blood pressure with liraglutide (about 6 mm Hg systolic) and suggested that this was very significant because we know that decreasing SBP by 5.6 mm Hg reduces risk of death from CVD by 18%. Notably, nausea rates in LEAD4 were 40% for 1.8 mg, 29% for 1.2 mg, and 9% in placebo – higher than in the other LEAD trials.

- **Eli Lilly/Amylin present DURATION-1 results comparing exenatide LAR and Byetta:** John Buse, MD, PhD (University of North Carolina, Chapel Hill, NC) presented data from the DURATION-1 study comparing the effects of exenatide once-weekly (LAR) and exenatide twice-daily (Byetta). The results were published September 8: Drucker *et al.*, Lancet, 2008. At the end of this 30-week study, there was a similar amount of weight loss with both exenatide once-weekly and exenatide twice-daily. The differences arose in A1c reduction where exenatide once-weekly led to an average decrease of 2.7% for patients with an average baseline over 9% and exenatide twice-daily led to an average reduction of 1.8% from an average baseline of 9.7%.

- **The GALIANT study from Novartis shows non-inferiority of vildagliptin to a TZD:** Poster-914 was the GALIANT study, a 12-week 2,478-patient study that showed non-inferiority of 100 mg once daily vildagliptin (Galvus) to TZD as add-on to metformin – note that Novartis does not sell this dose because of hepatic enzyme changes in early trials. There was no word on whether or not Novartis will re-pursue this dose. The weight change was favorable for vildagliptin: -0.58 kg vs. +0.33 kg for the TZD. Adverse events were similar, including hypoglycemia. Critics might say that TZDs take some time to "work" so 12 weeks will unfairly favor vildagliptin. It would have been interesting to us to see an arm of the trial that was both vildagliptin and a TZD, just to see how well they worked together since the mechanisms are different. Obviously the point of this trial was to show competition between the classes, not synergy but we are curious nonetheless.

- **Merck presents a safety analysis for Januvia:** Poster-912 provided a pooled safety analysis of 6,149 patients including 12 large double blind randomized phase 2b and 3 studies of 18 weeks to 104 weeks duration showing that sitagliptin has no safety signals and led to 4.8 % fewer drug-related adverse events because of less hypoglycemia. There were 3,415 sitagliptin and 2,724 placebo or comparator patients. Sitagliptin exposures included monotherapy, initial combo with metformin, and add-on to metformin, pioglitazone, SU, SU plus metformin, and metformin plus rosiglitazone. The placebo/comparator patients were exposed to placebo, pioglitazone, metformin, SU, SU plus metformin, and metformin plus rosiglitazone. There was no difference in the incidence of adverse events between the sitagliptin-exposed patients and the non-exposed patients. We can imagine that many physicians perceive that less hypoglycemia means fewer phone calls – in the US system in particular, that's a positive since they aren't paid for advice given over the phone.

- **Phase 3 results for VIAject hurt by anomalous data from India:** Data indicated that after 26-weeks of treatment, there were significant differences between patients treated with VIAject (VIA)

or with regular human insulin (RHI) in weight gain and in hypoglycemic events for both type 1 and type 2 patients (both positive for VIAject) and that the A1c change in VIAject is "non-inferior" for type 1 (analysis excluded India – type 1 data were not non-inferior when the India data were included) and type 2 patients. From our view, problems with the India data reflect the mounting problems faced by pharmaceutical companies in finding enough accessible diabetes patients to test in the US and Europe. The problems with India data were most unfortunate in our view as this detracted from the most impressive data reported in the posters - the differences in hypoglycemia seen in type 1 and type 2 patients. There were approximately 50% fewer severe hypoglycemic events in the VIA group (13) compared to the RHI group (26) for type 1 patients and 44% fewer mild to moderate hypoglycemic events in the VIA group (1,566) compared to the RHI group (2,783) for type 2 patients. Mild to moderate hypo was essentially the same for the VIA (7,232) and RHI groups (8,128) for type 1, which surprised us – although on balance, we believe type 1 patients care more about avoiding severe hypo, it would be nice to see significant differences in both, as was seen for six-week data. On the weight front, it was good news for both type 1 and type 2 patients. Type 1 patients treated with VIAject saw a slight weight loss of 0.3 kg versus a 1.8 kg weight gain for those on RHI. This result was unexpected and certainly a positive surprise, particularly given the importance of managing weight that was seen in the new ADA/EASD guidelines.

- **Positive safety and efficacy data from BMS/AZ's dapagliflozin:** The 12-week 389-patient phase 2b study tested five doses of dapagliflozin, BMS/AZ's lead SGLT-2 inhibitor: 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg, against placebo and 1,500 mg metformin. A1c dropped 0.55% to 0.9% with dapagliflozin vs. 0.18% with placebo and 0.73% with metformin, from relatively low baselines of 7.7% to 8.0%. Weight loss was an impressive 2.5% to 3.4% of body weight vs. 1.15% for placebo and 1.67% for metformin – we assume there must have been some lifestyle component to the trial.

- **Potential for a once monthly injected therapy — XOMA's anti-IL1 beta monoclonal antibody:** We were intrigued with phase 1 data on XOMA 052, an anti-IL1 beta monoclonal antibody that could potentially be a once monthly injected therapy for type 2 diabetes. Marc Donath, MD (University Hospital, Zurich, Switzerland) published a paper on IL-1 receptor antagonism as a treatment for type 2 diabetes in NEJM in 2007. In the current study, a single intravenous dose of the anti-IL1 beta monoclonal antibody XOMA 052 was safe, had a half-life of 22 days (consistent with once monthly dosing), and produced dose-dependent A1c drops of 0.3% to 0.6% at 28 days (doses tested ranged from 0.01 mg/kg to 1.0 mg/kg) in type 2 patients. Islet production of insulin was improved at the two lowest doses out to three months compared to placebo (islet function at higher doses was not studied), there was a reduction in CRP levels that indicated improvement in systemic inflammatory status, and there was no "no effect" dose identified, so it is possible to test even lower doses. Dr. Donath said that XOMA 052 could be a new therapeutic approach to type 2 diabetes by targeting inflammatory damage to beta cells. Next steps are to finalize the dose regimen, evaluate the ability to stop progression of diabetes, and to evaluate other aspects of the metabolic syndrome/diabetes.

- **Could glucokinase activators replace sulfonylureas? Phase 2 data from Roche:** We saw data from an early phase 2 trial of Roche's glucokinase activator, RO4386920. In this 59-patient dose escalation study, the investigators tested doses of the drug from 10 mg to 200 mg twice daily, as well as 200 mg once daily. They found that the drug had a half life of 8.1 to 11.2 hours and lowered both fasting and postprandial glucose by about 30%, though baseline was not given. Concerning is that 2/8 and 4/9 of the patients in the 200 mg QD and 200 mg BID arms developed symptomatic hypoglycemia. From what we understand of the mechanism, GKAs are a bit like sulfonylureas in that they stimulate glucose-independent insulin secretion – SFUs certainly have received their share of criticism at recent meetings (stemming from criticisms associated with weight gain and

hypoglycemia) so other compounds that work in the same way with more benign side effect profiles would certainly be of value.

— by Melissa Tjota

7. Conference Pearls II: 1st World Congress on Interventional Therapies for Type 2 Diabetes

The stated aim of this meeting was to craft an agenda of health policy initiatives and seize the opportunity offered by novel interventional therapies in diabetes and obesity treatment. As Paul Zimmet, MD (Baker IDI Heart & Diabetes Institute, Alice Springs, Australia) emphasized, the 21st century is the most obesogenic environment in human history, and the numbers continue to grow… in the wrong direction. A common theme stressed during the two day conference was the need for studies to define the group(s) that will receive the most benefit from the different approaches to diabetes treatment: lifestyle intervention, pharmacological intervention, or surgical intervention. The 1000+ member audience comprised 67% surgeons, 14% endocrinologists, and a mixture of other attendees making up the rest.

Big picture themes coming from this meeting were:

- Bariatric surgery should be used in morbidly or extremely obese patients for weight loss and diabetes remission.
- Bariatric surgery in individuals with BMI<35 as a "cure" for diabetes will require long-term, randomized controlled trials to provide the medical evidence for the appropriateness of this intervention.
- These long-term studies will also help answer questions on patient and surgical procedure selection criteria.
- These studies will also provide insight into the mechanism of action of weight loss and diabetes remission following surgery, which can be leveraged to inform drug and device development in the field.
- Combination therapy including medical, surgical, and lifestyle intervention is an area more deserving of consideration.
- The area of bariatric surgery will engender a great deal more research and developmental activity going forward. Currently, there are over 60 drug targets, over 200 compounds in active development, and only 2 approved obesity drugs (most recently approved in 1998). On the device side, there are over 800 device patents, more than 40 devices in development, and only 2 approved (but same mechanism).
- Although there is a growing consensus on impressive return on investment for bariatric surgery, there is still the issue of substantial up front costs if such an intervention is to be widely used as a public health tool. There is also the issue about whether surgical intervention is the best place to make a huge investment especially in light of the majority, non-obese population that could be helped by an investment in prevention and pre-diabetes by increasing access to and education on available basic drugs like metformin, SFUs, and insulin.

— by Kaku Armah and Melissa Tjota

8. Literature Review: UKPDS 10 Year Follow-Up of Intensive Glucose Control in Type 2 Diabetes

Holman RR, Paul SK, Bethel MA, Matthews DR, and Neil AW (2008) "10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes." New England Journal of Medicince: published online; September 10.

The study looked at three between-group analyses comparing the outcomes of sulfonylurea/insulin vs. conventional/diet therapy, metformin vs. conventional/diet therapy, and tight vs. less-tight blood pressure control. The results demonstrated a legacy effect of earlier glucose control and earlier metformin therapy in reducing microvascular and macrovascular complications despite the fact that A1c values converged between the different groups at the end of the study. More and more studies seem to be demonstrating a 'metabolic memory' effect, showing that glycemic control can have a lasting effect even after A1cs and other metabolic parameters have. We think that the results from this study have the potential to change the way diabetes is treated in a big way, and they might have a particularly positive implication for the treatment of pre-diabetes and early intensive and/or combination therapy.

- **The NEJM published the results of the UKPDS concurrently with the presentation of the results at EASD.** The UKPDS results were published in 1998 and have had a huge impact on the treatment of type 2 diabetes in the past decade; prior to this study there was not as much of an effort to control blood glucose in type 2 diabetes. From 1977 to 1991 the study enrolled 4,209 newly diagnosed type 2 diabetes patients with FPG >108 mg/dl. Patients were randomized to one of three therapy groups: 1) intensive therapy with sulfonylurea/insulin (n=2,729); 2) conventional glucose control primarily with diet (n=1,138); or 3) intensive therapy with metformin (n=342) for overweight patients who were >120% of ideal body weight. The trial ended in September of 1997 at which point patients were enrolled in the 10-year follow-up study. The study showed that intensive therapy decreased microvascular outcomes by 25%. There was also a non-significant macrovascular risk reduction of 16% (p=0.052) for combined fatal or nonfatal myocardial infarction and sudden death.
- **During the follow-up patients were monitored in UKPDS clinics for the first five years and by survey during years 6-10.** A total of 3,277 were enrolled in the follow-up with a ten-year mortality of 44%. End of study median A1c values were 8.5% vs. 7.9% for intensive (n=2,118) vs. conventional (n=880) therapy in the sulfonylurea/insulin group, and 8.9% vs. 8.4% for the intensive (n=279) vs. conventional (n=309) therapy in the metformin group.
- **A1c differences between groups disappeared by one year follow-up.** Interestingly, overall A1c dropped from 1997 to 2002 (from about 8.2-8.9% to 7.8-8.0%), which can be attributed to the publication of the UKPDS itself because physicians became more aggressive about treating glucose in type 2 patients. By the five-year follow-up point, there were no differences between groups in therapies (5% on diet, 46% on orals, 49% on insulin).
- **Seven primary outcomes were defined:**
    - Any diabetes-related end point: sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction
    - Diabetes-related death: sudden death or death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia, or hypoglycemia
    - Death from any cause

- Sudden death or fatal or nonfatal myocardial infarction
- Fatal or nonfatal stroke
- Amputation of at least one digit or death from peripheral vascular disease
- Vitreous hemorrhage, retinal photocoagulation, or renal failure

- **Five of the seven outcomes were improved in the sulfonylurea/insulin group:** any diabetes-related endpoint, diabetes-related death, death from any cause, myocardial infarction, and microvascular disease. The sulfonylurea/insulin group had a 9% risk reduction for any diabetes-related end point (p=0.04) and a 24% risk reduction for microvascular disease (p=0.001), validating the benefits seen at the end of the study. Additional benefits that emerged in the follow-up were a 17% risk reduction in diabetes-related death (p=0.01), a 15% reduction in myocardial infarction (p=0.01), and a 13% risk reduction in death from any cause (p=0.007).
- **Four of the seven outcomes were improved in the metformin group:** any diabetes-related endpoint, diabetes-related death, death from any cause, and myocardial infarction. All of these were significant at the end of the trial. At the end of the follow-up there was a 21% risk reduction for any diabetes-related endpoint (p=0.01), a 30% risk reduction for diabetes-related death (p=0.01), a 33% risk reduction for myocardial infarction (p=0.005), and a 27% risk reduction for death from any cause (p=0.002). The lack of significant microvascular outcome benefit was due to the smaller size of the metformin group. The observed risk reductions of 29% at end of trial and 26% at end of follow-up are similar to sulfonylurea/insulin.
- **The authors describe these results as the "legacy effect" of early glucose control.** All of the benefits observed at the end of the trial remained significant and new ones emerged in the sulfonylurea/insulin group for diabetes-related death, myocardial infarction, and death from any cause.
- **The metformin arm showed impressive 39% myocardial infarction and 36% mortality reductions despite a smaller difference in A1c from the conventional arm compared to sulfonylurea/insulin therapy, which the authors attribute to the particular benefits of this drug.** We expect that this will add to the body of evidence that metformin should remain the first-line therapy for type 2 diabetes.
- **The authors suggest that longer duration of disease and presence of complications may explain the differences in results from ADVANCE and ACCORD.** Both ADVANCE and ACCORD showed only non-significant reductions in macrovascular outcomes. In ADVANCE there was a 6% reduction in major macrovascular events after five years and in ACCORD there was a 10% reduction in non-fatal myocardial infarction, nonfatal stroke, and cardiovascular death at 3.5 years. ADVANCE and ACCORD patients had diabetes for eight to ten years longer than the newly diagnosed patients in the UKPDS, respectively, and a third in each of these two studies already had cardiovascular disease.
- **In contrast, the UKPDS results fit with the DCCT/EDIC and STENO-2 results.** The DCCT included young patients (13 to 39 years) without cardiovascular disease. At the end of the 6.5-year study, the observed 41% reduction in cardiovascular events was non-significant, but the 11 year follow-up showed a 42% reduction in cardiovascular events that had persisted despite convergence of A1c values between the two groups (7.4% vs. 9.1% at end of study) and became statistically significant (p=0.02). The EDIC validated similar improvements in microvascular events. The STENO-2 follow-up is less illustrative because there continued to be differences between the two study arms, but a legacy effect could also have played a role in this study.

- **The authors speculate that the legacy effect comes from delaying the build-up of advanced glycation end products, which are implicated in the development of diabetes complications.** This would explain why there is a lag time for the benefits of tight control to appear, because the effect of the intervention is to delay events.
- **The authors conclude, "The findings strengthen the rationale for attaining optimal glycemic control and indicate emergent long-term benefits on cardiovascular risk."** We agree completely – we hope that these results will become as widely accepted as the findings of the DCCT follow-up study (EDIC), as they provide parallel evidence in type 2 patients that lowering glucose does reduce macrovascular as well as microvascular complications.
- **These results also add to the body of evidence that suggests that it takes a very, very long time to see the cardiovascular benefits of glucose-lowering drugs.** It will become increasingly difficult to design cardiovascular studies as preventive treatments have improved in general (as smoking rates, blood pressure, lipids, etc. improve). Conversely, several studies have now suggested that there may be an early increase in complications when we try to implement tight glucose control (retinopathy in DCCT, cardiovascular events in PROactive, mortality in ACCORD), particularly in advanced patients.
- **Our takeaway, which Dr. Rury Holman emphasized during his presentation of the results at EASD, is that we need to treat patients to goal as early as possible.** The UKPDS has shown us that intensive treatment early on will have benefits far into the future; it may also be safer than intensifying treatment later on when patients already have cardiovascular and other complications. In this way we can take advantage of the "legacy effect" of glycemic control and improve outcomes for the increasing numbers of patients being newly diagnosed with type 2 diabetes at younger and younger ages.

— by Kelly Close, Jenny Jin, and Melissa Tjota

9. Conference Preview: Annual Diabetes Technology Meeting

November 13-15, 2008 • Bethesda, MD • http://www.diabetestechnology.org/

For all those techies out there, we bring you a jam-packed preview of the annual meeting of the Diabetes Technology Society that will be taking place November 13-15 in Bethesda, MD. This conference is covering a gamut of topics from the artificial pancreas to tissue engineering to telemedicine and even nanotechnology! We are heartened to see the many diverse areas of technology that are being developed for ways to improve treatment of diabetes. To start the conference, the pre-meeting workshops are focusing on self-monitoring blood glucose (SMBG) and continuous glucose monitoring (CGM). We look forward to hearing from Dr. Howard Wolpert on support tools for analysis of glucose data and Dr. David Horwitz on software improvements. Friday brings a program that is primarily focused on the artificial pancreas and continuous glucose monitoring (CGM). We are particularly excited to hear any new updates or perceptions from Dr. Aaron Kowalski, head of the JDRF during the morning session "Technologies for Metabolic Monitoring" on the artificial pancreas. The last day is a hodgepodge of topics from insulin delivery systems, tissue engineering for insulin production, telemedicine, and technologies that improve adherence. We are looking forward to hearing what Dr. Sol Steiner will say about Biodel's VIAject, particularly following the data release at the European Association for the Study of Diabetes (EASD) 2008 in which they indicated problems with the data from India. On pharmacotherapy, we also cannot wait to hear Dr. Wayman Wendell Cheatham discuss therapies for type 2 diabetes other than insulin.

Pre-Meeting Workshops: Thursday, November 13

- **(2:15-2:35pm) Use of Continuous Glucose Monitoring to Assess the Effect of Low and High Glycemic Index Diets in Children with Diabetes.** Tonja Nansel, BSN, PhD (National Institutes of Health, Bethesda, MD)
- **(2:35-2:55pm) An Algorithm for Staged Management for Type 2 Diabetes.** Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN)
- **(4:40-4:50pm) Software to Improve Management of Type 2 Diabetes.** David Horwitz, MD, PhD (LifeScan, Milpitas, CA)
- **(4:50-5:00pm) Targeted Technology: the Value Chain of SMBG.** Matthias Axel Schweitzer, MD, MBA (Roche, Mannheim, Germany)

Day 1: Friday, November 14

- **(8:10-8:30pm) Accelerating the Availability of an Artificial Pancreas.** Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York City, NY)
- **(1:40-2:00pm) JDRF Real-Time Continuous Glucose Monitoring Trial.** William Tamborlane, MD (Yale, New Haven, CT)
- **(4:00-4:20pm) Barriers to Overcome in the Development of an Artificial Pancreas.** Arleen Pinkos, MT (Food and Drug Administration, Rockville, MD)
- **(5:00-5:20pm) Bi-hormonal Closed-Loop Control of Blood Glucose Using Dual Subcutaneous Infusion of Insulin and Glucagon in Type 1 Diabetes.** Ed Damiano, PhD (Boston University, Boston, MA)
- **(5:20-5:40pm) Advances in Closed-Loop Control.** Cesar Palerm, PhD (Medtronic, Northridge, CA)

Day 2: Saturday, November 15

- **(8:10-8:30pm) Current Phamacologic Therapy of Type 2 Diabetes, other than Insulin.** Wayman Wendell Cheatham, MD, FACE (US Navy Bureau of Medicine and Surgery, Washington, DC)
- **(8:30-8:50pm) A New Rapidly-Acting Mealtime Insulin.** Sol Steiner, PhD (Biodel, Danbury, CT)
- **(9:30-9:50pm) Oral Insulin: Current State of the Art.** Lutz Heinemann, PhD (Profil Institute for Metabolic Research, Neuss, Germany)
- **(1:35-1:55pm) Information Tools for a Personalized and Efficient Health Care Experience.** Suzanne Boren, PhD, MHA (University of Missouri, Columbia, MO)

— by Brendan Milliner and Melissa Tjota

10. Diabetes Comings and Goings

- **David Anstice,** previously Executive Vice President of Merck, was elected to the Board of Directors at Alkermes.
- **Dirk Boecker** left Pelikan earlier this year where he was CEO. He was replaced by Gerald Moeller, previously Managing Director of HBM BioCapital Management GmbH.

- **Francois de Carbonnel**, a consultant and corporate financial advisor, was appointed to the Board of Directors at Amgen.
- **Sally Crawford,** a healthcare consultant and former COO of Healthsource, replaced Alison de Bord on the Board of Directors at Insulet.
- **Stephen Doberstein, PhD,** was appointed Vice President of Research at XOMA.
- **Alex Gorsky,** will take on the role of Worldwide Chairman of the Surgical Care Group at J&J. He is currently Company Group Chairman and Worldwide Franchise Chairman of Ethicon.
- **Sheri McCoy**, currently Worldwide Chairman of the Surgical Care Group at Johnson and Johnson, will succeed Christine Poon as Worldwide Chairman of the Pharmaceuticals Group.
- **Holly McGarraugh** was named President and CEO of Apieron replacing Rich Lotti. She joined Apieron in January 2008 as Vice President of Marketing. This is newsworthy because even though Apieron is outside diabetes, Holly is very well known in diabetes and we expect she will return eventually to the field helping lead another small company. She was previously part of the very early management team at TheraSense and later a VP at Abbott Diabtes Care.
- **Douglas Oberhelman,** group president of Caterpillar, joined the Board of Directors at Eli Lilly.

11. DCU Stock Chart and Final Thoughts

	27-Oct-08	29-Sep-08		28-Apr-08		29-Oct-07		IPO		Market Cap
GSK	36.35	42.08	-14%	44.82	-19%	51.04	-29%	-	-	92.49B
NVO	46.52	51.98	-11%	64.48	-28%	59.47	-22%	-	-	33.77B
AMLN	8.31	19.36	-57%	29.18	-72%	46.58	-82%	14	-41%	1.14B
BIOD	1.95	3.41	-43%	13.74	-86%	17.04	-89%	15	-87%	46.14M
OREX	4.38	10.65	-59%	11.52	-62%	14.62	-70%	12	-64%	150.33M
PODD	5.85	13.86	-58%	19.81	-70%	26.89	-78%	15	-61%	162.09M
MNKD	3.40	3.85	-12%	2.23	52%	9.03	-62%	14	-76%	345.43M
DXCM	4.02	6.01	-33%	8.01	-50%	8.6	-53%	12	-67%	119.31M
HDIX	6.01	10.5	-43%	7.83	-23%	8.87	-32%	12	-50%	105.95M

It was another brutal month in the markets for virtually all diabetes stocks from virtually any standpoint, including versus companies that went public as long ago as the mid 1990s. Stocks versus a year ago have fallen between 20% and 90%, stocks versus six months ago have fallen between 15 and 80%, and stocks versus a month ago have fallen at minimum 10% (Novo Nordisk) and maximum Orexigen (48%). I feel humbled, as I have thought many times over the past month that we must have reached the low.

--Kelly L. Close