DIABETESCLOSEUP

The Leading Source of Diabetes Business News

Awaiting EASD **August 2008 • No. 82**

From the Editor

The ACCORD trial was a major topic in last month's DCU, but we are not done talking about it! Last month, I expressed concern that ACCORD would be misinterpreted and generalized by the diabetes community. While on the whole the diabetes community appears to be embracing the conclusion that the ACCORD trial applies only to a specific group of patients with advanced type 2 diabetes, and that the current ADA guideline (which suggests targeting an A1c of 7.0%) is appropriate, we did hear some things at AADE that gave us pause (we'll be out with our full AADE summary next month). While we were especially happy about the article that we reviewed last month in Diabetes Close Up by Drs. W. Cefalu and K. Watson (July, 2008) arguing for reason along these lines, we still believe there is some danger ahead and we look forward to hearing from more thoughtful leaders on this front. We rang up Dr. David Kendall, who has returned to clinical practice at IDC from a stint at Amylin, and he wrote us back the following message:

> *In my opinion, there are still very convincing data that support the use of intensive tight glycemic control for patients recently diagnosed type 2 diabetes - including those who develop type 2 diabetes at a younger age. The ACCORD data do not allow us to dismiss the landmark findings of DCCT for patients with type 1 diabetes nor can we reject the previous findings of UKPDS. Additional analysis of the ACCORD, ADVANCE and VADT data are necessary if we are to fully understand both the risk and benefit of intensive glucose control in specific populations of patients. I anxiously await the perspective of ADA, EASD, AACE and others - who can hopefully provide a clear and definitive statement about the established importance of glucose control in diabetes. Reaffirming the current targets - and the need to individualize these targets - is essential.*

I sincerely hope that primary care physicians who continue see the majority of diabetes patients in this country hear the messages. IDC has a most valuable model where endos and PCPs and educators work together. Imagine this! We would also hope to see more of this going forward.

ACCORD may not have gone the way that many people expected, but the results of the study do not conflict with previous research. Rather, as Dr. Kendall indicated, they refine our understanding of intensive glucose control. In comparison to the ACCORD studies, the UKPDS and EDIC studies were conducted in a population that was much earlier in its disease progression. The studies suggest that intensive glucose control is more effective at preventing heart disease earlier in diabetes progression. As Kendall pointed out to me in a follow up talk, "There are two steps in developing heart disease: 1) pipes

getting bad (the development of atherosclerosis; and 2) pipes getting plugged (coronary events). It seems logical that it may be difficult to make very old pipes work well - simply by lowering blood glucose."

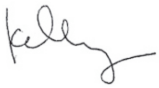
Looking forward, EASD (Rome, Italy) feels like it is around the corner (we can't wait for all the cappuccino), and the oral sessions and poster sessions are chock-full of interesting information. On the drug side, we are particularly looking forward to seeing results from Biodel on VIAject, from BMS/AZ on Onglyza, and from Diamyd on its rhGAD65 vaccination. There are several oral sessions and posters on exenatide and liraglutide as well, and we will be taking careful note of the results and conclusions they come to about these two drugs. On the device side, it appears there is a great deal of attention being given to continuous glucose monitoring (CGM). Following on an incredible artificial pancreas workshop sponsored by FDA, NIH, and JDRF last month, we hope to see more about CGM, integrating CGM with insulin pumps, and moving closer to an artificial pancreas.

Of course, I can't conclude my letter without touching briefly on the issue of Byetta and pancreatitis. In case you've escaped the sensationalist media reports about the issue, the FDA has issued a new warning after six cases of necrotizing pancreatitis in Byetta users have come to light. Overall, the numbers are small: the FDA reports that there have been 36 cases of pancreatitis among the 700,000 or so patients who have taken the drug. The annual rate of pancreatitis among people not on Byetta is about 17 per 100,000 people, which is actually above the rate seen in people on Byetta. Furthermore, this baseline number ignores known associations of diabetes, obesity, and dyslipidemia with pancreatitis. In addition, other drugs often taken with Byetta including sulfonylureas, ACEI/ARB, diuretics, and fibrates increase risk of pancreatitis.

There may be more cases of pancreatitis that went unreported among patients taking Byetta, but with the current tenuous association that has been described we think that a "black box" warning on Byetta is unlikely. More likely, pancreatitis warnings will be slightly expanded (up from "bolded precaution" status). Dr. Zach Bloomgarden believes that this issue calls attention to the need for better reporting of adverse events to the FDA. He argues that, on the whole, "we need a better system," and that such a system might well exonerate Byetta. In his words, "to say that Byetta increases the risk of pancreatitis is a meaningless extrapolation from the well-recognized massive underreporting of adverse events to FDA." I would agree.

Broadly speaking, it seems that no diabetes medication can completely escape warnings these days,and I worry that the expansive list of warnings makes patients and healthcare providers more likely to ignore the serious and more validated warnings. With so many millions of patients taking diabetes drugs, tenuous relationships between drugs and adverse effects are sometimes discovered. This gives the very newest classes of drugs an advantage; they come to market with little baggage and fewer warnings labels. We of course also emphasize that long-term data is very important to collect and to report on responsibly. Byetta may have picked up some poorly-supported baggage of its own, but overall we think that GLP-1 will ultimately viewed as one of the safest classes in the armamentarium by patients and healthcare providers. On that note, we hope studies looking at pre-diabetes potential and cardioprotection begin.

Wishing you a wonderful end of summer (winter to our friends in the southern hemisphere),



Kelly L. Close

Major Headlines

In This Issue

Blogwatch

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

- **August 23:** Pay now, save later
- **August 22**: Weight driving more kids to drugs
- **July 17:** Employees and insurers see financial loss with weight-loss surgery

Videos

Below is our favorite YouTube video in diabetes this month:

- "TuDiabetes"
  http://www.youtube.com/watch?v=uluTso-kU5E

Coming soon in DCU…

We're heading to two conferences in the next month — the anticipated 2008 EASD conference in Rome and the insulin resistance meeting in Los Angeles. Stay tuned…

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1. Quotable Quotes in Diabetes

"I wanted to share this quote from a Chinese medical text with you: 'Superior doctors prevent the disease. Mediocre doctors treat the disease before evident. Inferior doctors treat the full blown disease.' We are still in the inferior phase. Hopefully, we will get to the mediocre phase sometime in the future."

—Curtis Triplett, PharmD, RPh, CDE (Texas Diabetes Institute, San Antonio, TX), speaking about the need for earlier interventions in diabetes at AADE 2008.

"What have you done in the past 24 hours? Well in that time 4,100 people have been diagnosed with diabetes. Even more startling is that of the 24 million Americans who currently have diabetes, 55 will go blind, 120 will be put on dialysis, 230 will require amputations, and 810 would have died."

—Evan Sisson, PharmD, MHA, CDE (VCU School of Pharmacy, Richmond, VA), highlighting the severity of the current diabetes epidemic during his presentation at AADE 2008.

"I think most of you have seen Legally Blonde and remember when Elle Woods stands in front of her Harvard Law School class and says, 'We did it!' I receive a lot of e-mails from patients, but one question I haven't received in a long time is, 'What is a diabetes educator?' The public knows who we are. We did it, and we will continue doing it!"

—Janis Roszler, RD, CDE, LD/N (Dear Janis, South Florida), pointing out the advancements in diabetes education awareness during her acceptance speech for the 2008 AADE Educator of the Year Award.

"We do not exercise. We are a country of observers. We pay a lot of money to watch another person sweat. It is shocking how much money we spend to watch other people lose calories."

—John Andrew Sapala, MD (Brooklyn Medical Center, New York City, NY), emphasizing at AADE 2008 that lifestyle changes need to be made to prevent a diabesity epidemic.

"There is a lot of opportunity for all of us to make a difference on a global level. Knowing that in some way I can touch people in remote areas who I will never meet or never know is very rewarding. I thank you all [CDEs] for being the true heroes in this battle as we soldier on to defeat this disease."

—Francine Kaufman, MD (UC Children's, Los Angeles, CA), at AADE 2008 stressing how diabetes is becoming a global epidemic and applauding the CDEs for their work in educating the public about diabetes.

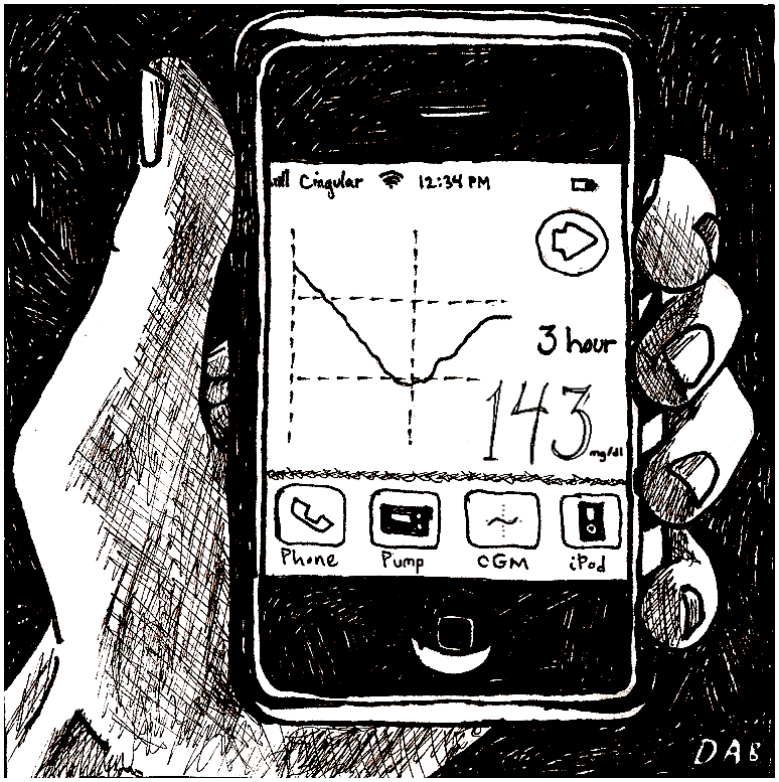
"My comment is, that it is unbelievable that with an expected pancreatitis rate of somewhere >0.01% in the general population, and with more than 700,000 persons having taken the drug, one would expect >70 cases -- leaving aside the well known associations of diabetes and of obesity and of dyslipidemia with pancreatitis -- and then add to this the likelihood that these patients also take sulfonylureas, ACEI/ARB, diuretics, fibrates, etc all further increasing the expected incidence. So the reported 36 cases represents an unknown fraction of the expected cases, no more than half, but probably well under one quarter. To say, then, that Byetta increases the risk of pancreatitis is a meaningless extrapolation from the well-recognized massive underreporting of adverse events to FDA with the thought that, then, there may be "many more" cases unreported, which of course is an absurd way of knocking 12% off the share price of Amylin! We need a better system!"

—Zachary Bloomgarden, MD (Mount Sanai, New York, NY), commenting on recent press regarding pancreatitis and Byetta.

"In his Nobel Prize Lecture, Dr. Banting stated that 'insulin is not a cure for diabetes; it is a treatment.' It is important that we keep this point in mind as we try to find a way to cure diabetes."

—David Harlan, MD (NIDDK, Bethesda, MD), talking at CWD FFL 2008 about the history of insulin and the need for treatments that stop the immune system from attacking the beta cells.

2. diaTribe FingerSticks



-by Daniel A. Belkin

3. DCU Company Watch

- **Medtronic - Medtronic Diabetes up 12% with international driving growth**: Medtronic Diabetes reported results August 19, with revenue $269 million, up 12% globally and down just $6 million from its best-ever fiscal fourth quarter reported in May, 2008. International pump strength is driving growth - outside the US, Medtronic Diabetes sales increased a whopping 31%. In the US, the increase was in the low single digits. Disposables and CGM were big contributors to revenue. US growth is slow – we assume this is summer, "overhang" from the end of the 2008 fiscal year when Medtronic reported $1 billion in diabetes sales, a very tough "year over year" comparison, stronger than expected competition, and a weak economy. The key question for the market will be whether the US market jumps back or if the economy takes a toll - we do believe the economy is contributing on some level to consumer caution and to the relatively lower US result for pumps. It does seem like Medtronic has products in the pipeline that they aren't quite ready to reveal yet. Management alluded to new launches planned in the next year or two, and referred to substantial R&D funding redirection to move forward new pumps that will allow them to expand into the type 2 and hospital markets. Great news – innovation drives faster innovation everywhere and this is excellent all around for patients and HCPs overall. We continue

to hear good news on the reimbursement front for CGM and look for patient interest to increase as we do HCP interest. We published in *Closer Look* recently positive results from our AADE survey (n=108) – if you didn't receive this let us know.

- **MannKind—Waiting for phase 3 data at EASD:** During MannKind's 2Q08 earnings call on August 11, management focused on the company's preparations for the NDA submission of Technosphere Insulin (TI) by the end of 2008. In particular, management emphasized that MannKind's pre-NDA meeting with the FDA on July 14 was successful, and that the FDA has not requested additional cardiovascular or cancer safety trials.

  MannKind expects to report initial phase 3 results from the pivotal 009 study at EASD on September 16. Given TI's purported super-rapid action, we expect to see a significant reduction in hypoglycemia and weight gain as compared to regular insulin; a significantly greater reduction in A1c with TI is also possible and would be a big win for the company. In terms of the pipeline, management discussed NKC-180, a pulmonary Technosphere formulation of a natural hormone that controls satiety for the treatment of obesity. Management acknowledged that it was a peptide but did not specify which one. Toxicology studies are underway in order to support a 2Q09 research filing in Europe presumably because the regulatory pathway there is easier.

  On the financial end, the net loss for the second quarter of 2008 was $79.8 million, which compares to a net loss of $72.0 million for 2Q07. Cash and cash equivalents were $180.5 million at June 30, 2008, compared to $269.1 million at March 31, 2008 and $368.3 million at December 31, 2007. MannKind's cash burn for the past four quarters has been $80 million in 3Q07, $86 million in 4Q07, $99 million in 1Q08, and $89 million in 2Q08. Mr. Pfeffer said that MannKind anticipates its cash burn to increase over the next few quarters and then decrease. This is due to clinical trials and costs for the new manufacturing facility. They expect to be able to fund operations until at least the end of 2009 due to Al Mann's contributions.

- **Insulet—Reduced visibility bring short-term woes:** Insulet reported disappointing second quarter results on August 12 in a call led by CEO Duane DeSisto. 2Q08 revenue was $7.4 million, more than doubling the $3.2 million sales result from a year ago and up just over 10% sequentially from $6.7 million reported last quarter and up nearly 40% excluding a favorable one-time $1.7 million deferred revenue impact. Nonetheless, this result was below analyst expectations (~$7.7-$8.2 million) and given the higher ramp expected to reach lowered guidance of $38-$44 million, we would have liked to have seen revenue comfortably above this point. Gross margins remained negative, showing slight improvement over the first quarter. Net loss was just under $24 million, up from $20 million in the first quarter, reflecting higher than expected costs, likely related to customer acquisition as well as replacement pods. The company closed out the quarter with cash and cash equivalents of ~$99 million, an increase of 37% from last quarter's end. Management said it expects to break even on a gross margin basis in 3Q08 and to report positive quarterly gross margins by 4Q08.

  New OmniPod users numbered 1,650, up nicely from 1,200 new users in the first quarter, though not enough to achieve sales estimates this quarter. Attrition sounds like it has increased to close to 10% - undoubtedly higher than management would like to see given high customer acquisition costs. With approximately 1,650 new patients on the OmniPod at the end of 2Q08, the total number of users is closer to 6,000 taking into account attrition rates.

We believe the Insulet Omnipod represents pump innovation at its best and this pump is certainly not going away. Many patients on the OmniPod remain very happy from our field checks but any negative publicity is clearly unfavorable. Nonetheless, visibility on the sales and cost fronts seems low, suggesting to us that estimates may well come down further for the second half of this year and for 2009. We don't think this threatens patient positivity in any way barring some disruptive competitive move, and we remain very positive on the product, if not on the near-term financial visibility of the company. The biggest potential patient catalyst in our view would be making the pod smaller – even though this would likely take until at least 2010 to achieve, this would be a major demand driver in our view.

- **Diamyd Medical—Diamyd vaccination lowers risk of insulin treatment in LADA patients:** Approximately 10% of all diabetes patients have LADA (Latent Autoimmune Diabetes in Adults), and they tend to require insulin treatment a few years after diagnosis. Diamyd announced August 11 that its vaccine significantly lowers the risk of requiring insulin treatment in LADA patients. The vaccine is based on the 65kDa isoform of recombinant human glutamic acid decarboxylase protein (rhGAD65) and is meant to induce immune tolerance to this self protein (auto-antigen). According to top-line data, beta cell function improved six months after vaccination, persisting over the five years of the study. According to the abstract published online at the EASD website, 40 patients were randomized to placebo, 2, 20, 100, or 500 mg of Diamyd. At the end of five years, the number of patients starting insulin treatment was as follows: placebo (64%), 4 mg group (71%), 20 mg group (14%), 100 mg group (14%), and 500 mg group (63%). Researchers also measured fasting C-peptide levels, which declined in the placebo (mean decline=0.18) and 500 mg group (mean decline=0.33), but did not change in the 4, 20, and 100 mg groups. The abstract also indicated that no serious adverse events were seen during the study. The full results will be presented at EASD by principal investigator Professor Carl-David Agardh (University Hospital Malmö, Sweden). We'll be interested to learn more about study details and why the highest dose treatment seemed to be the least effective. We're also curious whether Diamyd reduced the average insulin dose required compared to placebo in those patients who did initiate insulin treatment. We note that these initial positive results reflect the increasing focus on disease prevention as well as disease progression in diabetes research, both for type 1 and type 2.

- **DexCom—Third-generation sensor submitted to FDA:** During the 2Q08 earnings call on August 5, we learned that DexCom management had filed its third-generation CGM for FDA submission. The new sensor was reported to incorporate significant improvements in accuracy, trend arrows, input options, and customizable alarms – this was far more progress than we had realized. In addition, a fourth-generation system is in the works that has an enhanced membrane system for even greater accuracy, and we assume the improvements include reducing the range of substances that can interfere with readings. A fifth-generation system is being tested in humans. No specifics on the improvements in this new system were given.

  Development of an integrated CGM and pump with both Animas and Insulet continues to move forward. Management said that it hoped to launch a combined product with Animas by the summer of 2009. Hopefully, a product with Insulet would follow later in 2009. Both Insulet and Animas were quite open about their partnerships with DexCom during the recent AADE conference. A favorable result from the upcoming JDRF trial would help to spur CGM growth, but management expressed confidence that CGM would fare well even if the trial shows a reduction in glycemic variability without a reduction in A1c.

- **Home Diagnostics—Hits home run in 2Q08:** On August 20, Home Diagnostics, a manufacturer, marketer, and distributor of diabetes testing supplies, reported that it has received

510(k) approval from the FDA for its two new blood glucose meters, TRUEresult and TRUE2go. Both meters will be available in the fourth quarter of this year. Home Diagnostics reported 2Q08 results on August 7 in a call led by CEO Dick Damron. For the quarter, revenues were $33.4 million, up a robust 19% year over year. In terms of specific channels, retail sales dropped 2.2% (compared to a 0.9% drop in 1Q08), distributor sales increased a whopping 32.6% (compared to a 20% decrease in 1Q08), and mail service sales increased 22.3% (compared to a 1.5% decrease in 1Q08). They explained that the significant increase in the distribution channel was due to both strong orders before this year's trade season and the fact that 2007 was a particularly weak quarter for distribution sales. The drop in retail sales can be explained by a $0.7 million return provision for the Sidekick, which may be partly replaced by the launch of the new TRUE2go. The Sidekick will still be available at some retailers, and remains a key part of the company's international strategy. Discussing the mail order revenue increase, management cited success with new and existing customers. Home Diagnostics is trying to establish itself as a value offering compared to other branded products, and we believe that this quarter shows this strategy paying off – not a bad strategy for these economic times, needless to say.

- **Alkermes—Earnings call provides update on once-weekly exenatide:** On August 8, Alkermes released its fiscal first quarter 2009 results in a conference call led by CEO David Broecker, who modestly referred to once-weekly exenatide as a "potential blockbuster" – we're certain it's going to be a blockbuster, and that it has the potential to be a multi-billion dollar product. This call did not have a great deal of diabetes news except for a reassuring note that Amylin/Lilly/Alkermes had a recent meeting with the FDA, and it sounds like things are on course to submit their filing by mid-2009. Making sure that samples for trials match manufacturing grade product continues to be the main priority – it does sound like opportunities to accelerate the program still exist. When asked about the needle gauge, management confirmed that once-weekly will have a 23-gauge short needle but pointed out that 90% of those in the trial went on to the extension, implying that none of them had a major problem with it - we also got that impression from the poster at ADA 2008 and will be curious to see how the once-weekly injection feels versus the once-daily pen needle for Novo Nordisk's liraglutide.
- **Novo Nordisk—Weak growth of diabetes care sales in 2Q08:** CEO Lars Rebien Sørensen led Novo Nordisk's second quarter sales and earnings call on August 7, which highlighted that diabetes care sales rose just 5% year-on-year to 8.0 billion DKK ($1.66 billion USD) in 2Q08 from 7.652 billion DKK ($1.59 billion) in 2Q07. As in past quarters, sales of insulin analogs drove overall diabetes care growth, growing 18% in local currency over the past three months. Within modern insulins, although Levemir has historically played second fiddle to Sanofi's Lantus, Levemir this quarter stayed steady at above 60% sales growth, buffeting the analog group, while growth of both Novomix and Novolog dropped to 16% and 12%. for the first half, down from 27% and 28% growth for the first quarter respectively – suggesting little if any second quarter growth. On the other hand, for the first time, Novolog sales for the previous 12 months hit $1 billion Human insulin sales were weak and we gather that Lilly is gaining share here.

  In local currencies, global sales of modern insulins, human insulins, oral anti-diabetic products, and insulin-related products for the quarter were 4.103 billion DKK ($853 million, +18% year-on-year), 2.966 billion DKK ($617 million, -8% year-on-year), 0.478 billion DKK ($99 million, -10% year-on-year), and 0.460 billion DKK ($96 million, +5% year-on-year), respectively. These are not particularly strong results. World market sales of modern insulins showed growth over the first half of 2008, with NovoRapid, NovoMix, and Levemir generating sales of 3.6 billion DKK ($749 million, +12%), 2.6 billion DKK ($541 million, +16%), and 1.7 billion DKK ($353 million, +61%), respectively. However, as noted, growth has slowed for all insulins except Levemir.

Market share growth against Eli Lilly and Sanofi-Aventis appears to have flattened. Novo Nordisk continues to hold 52% of the total insulin market and 44% of the modern insulin market, both measured by volume. These stable market shares were similar to what was stated in the 1Q08 call, and a departure from the increases reported in previous quarters. Overall, as measured by volume, Novo Nordisk continues to maintain a strong presence in the US with 42% of the total insulin market and 31% of the modern insulin market. In Europe, Novo Nordisk holds 56% of the total insulin market and 51% of the modern insulin market, while in Japan it holds 73% of the total insulin market and 64% of the modern insulin market.

Liraglutide was filed for regulatory approval for use as both a monotherapy and in combination with other diabetes medication in the US, Europe, and Japan as well as Australia, Canada, Turkey, and New Zealand, and the company has initiated a new trial comparing liraglutide with Merck's Januvia . We look forward to seeing these results in the second half of 2009 (the trial should be completed by 2Q09, according to management). Mr. Sørensen gave a quick summary of the LEAD 6 top-line results that were released in controversial fashion in early June to coincide with ADA 2008. He also discussed results from a 32-week extension of a separate study that looked at the effects of liraglutide on obesity. This study demonstrated that 52 weeks of treatment with liraglutide led to a mean weight loss of 7.5 - 8.0 kg, or a placebo-adjusted weight loss of 5.5 - 6.0 kg. Around 75% of the people treated with the highest dose of liraglutide achieved a weight loss >5% compared to only 25% of the placebo group. Most notable was the resolution of diabetes: at the start of the study, 30% of the participants had signs of pre-diabetes while after one year of treatment, only 20% of this group still showed signs of pre-diabetes. This achievement makes us believe that Novo Nordisk must be preparing liraglutide for evaluation as a pre-diabetes treatment.

Notably, a phase 2 clinical trial has been initiated for NN9535, Novo Nordisk's once-weekly human GLP-1 analog. This trial is expected to enroll around 360 patients and should be completed in the first half of 2009. Management said that it was too early to know about FDA expectations; a couple of weeks back, management was quoted as saying it expected a 6-12 month delay. Lastly, in a win for Sanofi-Aventis on the SoloStar lawsuit, management said it had not been able to convince the lower courts that the SoloStar infringes on Novo Nordisk's pen patents.

- **Orexigen Therapeutics—Contrave on track for NDA filing in late 2009:** Orexigen announced 2Q08 results on August 7. It ended the quarter with over $123 million in combined cash and marketable securities, and posted a net loss of $23 million. Management provided an update on its leading obesity drug candidate, Contrave, announcing that it has completed enrollment for all four phase 3 studies (enrolling over 4,500 patients) and expects results in the first half of 2009 with a possible NDA filing late in 2009. Recently, the company announced the issuance of a patent for the sustained release compositions of bupropion and naltrexone in a single dose form that extends patent protection for Contrave out to 2025. Partnering discussions are reportedly active, but likely won't get serious until phase 3 data is in hand. Still, looks like a good time for the company - on balance, it appears to be well on track with its clinical programs and should have adequate funding to pursue an NDA filing for Contrave without the support of a larger pharmaceutical partner. The company has initiated another phase 2b study of its second-generation obesity drug Empatic, a combination of zonisamide and bupropion, and expects results in the second half of 2009. On a related note, Orexigen is also developing OREX-003, a combination of zonisamide and olanzapine, as an antipsychotic drug candidate with less potential for treatment-associated weight gain than currently available antipsychotic drugs. The company expects to initiate a phase 2 proof-of-concept study in the third quarter of 2008.

- **Biodel—Positive results from VIAject phase 3 and glucose clamp studies:** On August 6, CEO Solomon Steiner led a FY3Q08 earnings call that focused on the recent phase 3 results of VIAject. For a detailed report of this event see page 20. Management also discussed positive results from phase 1 and phase 2 glucose clamp studies as well as a supply agreement with Organon made in early July. The results from the glucose clamp studies were published in *Diabetologia* (Steiner et. al., September, 2008) and the *Journal of Diabetes Science and Technology* (Hompesch et. al., July, 2008). Early in July, Biodel agreed to purchase a specified amount of recombinant human insulin from Organon for use in the company's VIAject insulin formulation. According to management, this insulin will be sufficient to cover the company's needs in ongoing and future clinical trials as well as support the company's needs for three years following the commercial launch of VIAject. Following previous guidance, Biodel expects to file an NDA by late 2008 or early 2009. The timing has been slightly delayed but the results seem very strong so, from our view, the potential delay is understandable. On a financial note, management said it has enough funds to cover all expenses through the NDA filing – the cash and marketable securities balance of $93 million has increased $13 million from a year ago. During FY3Q08, R&D expenses increased to $6.9 million because of a $1.3 million increase for phase 3 trials, and a $1.5 million increase for the preparation of commercial batches of VIAject. Total losses for the quarter were $10 million. We keenly await EASD and full data for its phase 3 VIAject trials – excitement may well abound.

- **Vivus—Positive results of OB-202 Qnexa study during 2Q08 call:** On August 4, Vivus management provided a review of the OB-202 Qnexa study even though the results of this study were announced earlier this summer. As a reminder, OB-202 was a 28-week study that looked at the glycemic effects of Vivus' weight-loss drug candidate, Qnexa, in obese patients with type 2 diabetes. After 28 weeks, Qnexa produced an A1c reduction of 1.2% vs. 0.6% for placebo, an average weight loss of 8%, and improvements in various cardiovascular risk factors. The drug continues to appear well tolerated and the dropout rate was actually lower in the treatment group than placebo and very low in absolute terms (3%) – we assume because patients in the treatment group were obtaining better weight loss. This call had very little forward-looking information, but the company did confirm that results from the OB-301 (EQUATE) obesity study should be available by the end of 2008 – this phase 3 trial looked at the weight loss effects of Qnexa in ~700 obese patients after 28 weeks of treatment. At this point, no firm timeline for starting a phase 3 study of Qnexa in diabetes has been set up, although management did say they would move quickly to engage the FDA in the relevant discussions. We do find it noteworthy that the company appears willing to take a somewhat aggressive approach with Qnexa, including the possibility of engaging in a rigorous study to prove a clinical reduction in mortality and morbidity in order to achieve better labeling. On the financial front, Vivus ended the quarter with $155 million in cash but added another $63 million in capital shortly after the earnings announcement.

- **Arena—Update on phase 3 trials (BLOOM, BLOSSOM, and BLOOM-DM) for lorcaserin:** During Arena's 2Q08 earnings call on August 5, President and CEO Jack Lief focused on the late-stage development of lorcaserin and the goal of submitting an NDA to the FDA in late 2009. As a reminder, lorcaserin is the company's 5-HT_{2C} receptor agonist in development for the treatment of obesity. According to our database, Arena is the only company with a 5-HT_{2C} receptor agonist in clinical development in the US (Athersys' 5-HT_{2C} receptor agonist candidate is slated only for development in the UK).

  There are three ongoing lorcaserin phase 3 trials: BLOOM, BLOSSOM, and BLOOM-DM. BLOOM (n=3,200) is evaluating a twice-daily 10 mg dose of lorcaserin over two years in obese patients (BMI = 30-45) with or without co-morbid conditions, and overweight patients (BMI = 27-30)

with at least one co-morbid condition. BLOSSOM (n=4,008) is evaluating a once-daily or twice-daily 10 mg dose of lorcaserin over one year in obese patients with or without co-morbid conditions, and overweight patients with at least one co-morbid condition. Top-line data for BLOOM are expected at the end of 1Q09 with BLOSSOM top-line data following in approximately six months. Management noted during the call that enrollment for BLOSSOM was completed, and along with BLOOM, it will be the pivotal trial that forms the basis of the NDA submission. BLOOM-DM is an extension of BLOOM looking at the effect of lorcaserin in obese and overweight patients with type 2 diabetes, and it is still continuing enrollment, which is expected to be around 600 patients.

The company indicated that it is looking into partners for the future development and commercialization of lorcaserin although no further details were provided. Some possible companies we believe Arena may be looking to partner with include Pfizer, AstraZeneca, and Merck, all of which have shown an interest in obesity drugs, particularly Pfizer. We believe that these companies may be particularly interested in diversifying their obesity pipelines following increased negativity regarding CB1 antagonists (Pfizer and Merck have phase 3 CB1 antagonists, while AZ's CB1 antagonist is in phase 2). However, weight loss for lorcaserin has been somewhat underwhelming, with only about 30% of patients achieving 5% or more weight loss in phase 2.

- **AtheroGenics—2Q08 earnings call reveals little more about AGI-1067:** On August 5, AtheroGenics reported 2Q08 results and spent significant time reviewing the phase 3 results for AGI-1067 for type 2 diabetes, released July 31. AGI-1067 appears to lower insulin resistance and improve glycemia in people with type 2 diabetes by inhibiting redox and stress-sensitive kinases such as JNK-1, which regulates the expression of inflammatory genes and modulates insulin resistance. AtheroGenics, partnered with AstraZeneca, originally developed this small molecule for the treatment of arthrosclerosis, but in March 2007 it announced that the drug did not meet its primary endpoint in the phase 3 trial (ARISE). While AGI-1067 did not meet its primary endpoint, the study did show positive effects of AGI-1067 in patients with diabetes (n=2,200): there was an A1c drop of 0.5% at 12 months (baseline A1c = 7.2%) and patients were 63% less likely to develop new onset diabetes. These results were reported in a late-breaking session at ADA 2008 (see our ADA report for full details).

  In May 2007 AtheroGenics announced that it was shifting its focus to the use of AGI-1067 as a treatment for type 2 diabetes and initiated a phase 3 trial (ANDES) to study the effect of AGI-1067 in people with diabetes. This phase 3 trial (n=887 completed) analyzed two doses of AGI-1067 (75 mg and 150 mg) in 150 clinical sites in the US, South Africa, India, and Europe. Top-line data at six months showed statistically significant drops in A1c of 0.4% and 0.6% for the 75 mg and 150 mg arms, respectively (baseline A1c = 8.6%). However, the placebo group also dropped 0.2% from baseline, which contrasts with the more commonly seen rise in A1c observed in placebo arms of diabetes trials. This reduction in the placebo arm makes us wonder whether this trial included a significant lifestyle component that could have contributed to the A1c reduction. According to management, Eastern Europe showed a significant A1c drop of 0.5% in the placebo arm vs. baseline while India, South Africa, and the US showed an increase of 0.1% in the placebo arm vs. baseline. Despite the aberrant placebo result in Eastern Europe, the reduction in A1c from baseline was similar across all regions for the top 150 mg dose. Dr. Fleming highlighted that the placebo-adjusted drop in A1c approached or exceeded 0.7% in regions outside of Eastern Europe. In terms of adverse side effects, one patient in the 150 mg arm and two patients in the 75 mg arm exceeded five times the upper limit of normal liver enzymes, which was consistent with the rare events of hepatotoxicity seen in ARISE. Liver safety is, therefore, a significant question for the drug, but the company announced that a simple screening tool has been developed based on

ARISE and ANDES data to identify those who would be at risk for liver toxicity. (In the ARISE trial, there were 32 cases of increased liver function abnormalities in the treatment group vs. 11 in the placebo group, with one case of liver failure that was reversible by drug discontinuation.) More cases of atrial fibrillation also occurred among patients treated with AGI-1067 in the ARISE trial. AGI-1067 was not associated with weight gain or hypoglycemia, a meaningful positive, all else equal.

While the top-line improvement in glycemic control did not look terribly impressive to us, this drug may show some cardiovascular benefit. As the fields of diabetes and cardiology continue to converge, we believe that there will be increasing interest in treating diabetes with drugs that show potential cardiovascular benefit. To date, the only drug that has demonstrated cardiovascular benefit is metformin (UKPDS trial), although some evidence supports similar activity for both GLP-1s (mechanistic evidence and ACCORD subgroup analysis) and perhaps pioglitazone (PROactive trial). Overall, we certainly believe that "cardioprotective" drugs that are easy to take with few side effects could hold much promise – whether AGI-1067 shows true cardioprotective benefits will be an important question to assess with full data. Management expects to have agreement from the FDA about a second registration trial by late 2008.

On the financial side, AtheroGenics recorded no revenues in 2Q08 compared to revenues of $30.3 million in 2Q07 that were associated with the company's agreement with AstraZeneca for AGI-1067, which was terminated last year. The conclusion of ARISE has enabled the company to reduce R&D expenditures to $8.5 million in 2Q08 compared to $22.3 million in 2Q07. Overall, the company suffered a net loss of $14.3 million, but reported total cash, cash equivalents, and short-term investments of $66 million as of June 30, 2008.

- **AZ/BMS—Submission of Onglyza (saxagliptin) in the US and Europe:** During Astra Zeneca's 2Q08 earnings call on July 31, CEO David Brennan highlighted the joint submission of Onglyza (saxagliptin) with Bristol Myers-Squibb (BMS) in both the US and Europe. According to management, submission in the US was on schedule, but impressively, the European filing of saxagliptin was a full 15 months earlier than previous estimates. In part, they attribute this to positive results from the six phase 3 trials in which more than 3,000 subjects were given saxagliptin for up to two years.

  Partial phase 3 data for Onglyza were presented at ADA 2008 (see DCU #81 Company Watch for details). As we have indicated previously, the phase 3 data presented at ADA closely resembled phase 3 data for Merck's Januvia and Takeda's alogliptin. We do not think that any late-stage DPP-4 inhibitors will be differentiated on efficacy or even selectivity. Any differentiation will likely be based on side effects, as seen with Novartis' Galvus, which has been held up by the FDA on safety concerns. Additional phase 3 data for Onglyza are expected to be disclosed later this year at EASD. Given the drug's structural similarity to Galvus, we will be looking closely at any unexpected side effects. So far, the safety data for Onglyza have been encouraging.

  Management said that US and EU submissions for dapagliflozin are "on track" for 2010. Seven phase 3 studies for dapagliflozin are ongoing. Aside from saxagliptin and dapagliflozin, AZ has four other diabetes drugs in the pipeline: AZD2207, AZD1175, AZD6370, and AZD1656. AZD2207 and AZD1175 are cannabinoid receptor 1 (CB1) antagonists that are currently in phase 2 and phase 1, respectively. The last two drugs in the pipeline, AZD6370 and AZD1656, are glucokinase (GK) activators currently in phase 2 and phase 1, respectively.

- **Sanofi-Aventis—Lantus aims to be leading diabetes drug worldwide:** Sanofi-Aventis reported strong Lantus 2Q08 earnings results in a conference call on July 31 led by Hanspeter Spek, EVP of pharma. Lantus sales for the quarter were €576 million (just under $900 million

USD using current exchange rate), which represents about 15% growth year-over-year and about 3% growth sequentially by our calculations. Overall, US sales of €328 million ($502 million, +26%) were the major driver for Lantus. European sales rose to €178 million ($276 million, +21), and sales in other countries grew to €70 million ($109 million, +52%). Lantus is now annualizing at $3.6 billion. Management is continuing its first-quarter commitment to make Lantus the leading global diabetes product before the end of 2009, a distinction currently held by Takeda's Actos. SoloStar, the new Lantus pen, was launched in Japan in June 2008 and continues to launch in various emerging markets. The slides showed that Lantus has a 52% share of "newly insulinized" patients, having stolen this share from NPH and other non-analog insulins.

The company did not announce rimonabant or Apidra sales. From our view, rimonabant's potential lies in combinations provided that safety can be established. Sales of rimonabant in the EU have been disappointing, but we believe Sanofi sees its promise in combinations with other oral drugs and eventually insulin – we are intrigued, at least conceptually, with the idea of a combination of AVE2268 (SGLT-2 inhibitor) and low-dose rimonabant, though we know significant work would have to go into demonstrating safety . Lilly's success with Humalog is one reason why Apidra hasn't managed to gain share in the short-acting analog market;, as usual, Apidra was not discussed during any part of the conference call and was not referenced in the press release.

On the pipeline front, management announced that Sanofi has begun phase 3 testing for its GLP-1 mimetic, AVE0010. The trial is investigating a once-daily injection of the new exendin-based GLP-1 mimetic as an add-on to metformin, sulfonylurea, or TZD treatment. This trial will also test AVE0010 against exenatide, and will include a monotherapy arm. Submission for FDA approval both as a monotherapy and in combination with a statin is scheduled for the second half of 2010,. A longer-lasting version of the drug is currently in phase 1. No updates were given on Sanofi's other two phase 2b molecules: AVE1625 (a CB1 antagonist) and AVE2268 (an SGLT-2 inhibitor). Notably, Sanofi has completed enrollment for ORIGIN, the 12,000-person Lantus cardiovascular outcomes trial expected to report in 2010 and CRESCENDO, the 17,000-person rimonabant cardiovascular outcomes trial. Enrollment looked slower on CRESCENDO than planned and results are now expected in 2011 rather than 2010.

- **Ipsen/Roche—Initiation of taspoglutide phase 3 trials:** On July 31, Ipsen released top-line data on positive phase 2 results presented at ADA 2008 for taspoglutide, the first once weekly GLP-1 analogue. Based on these results, Roche moved it into phase 3 clinical trials that were expected to start in 2H08. Based on this announcement, Ipsen will receive a payment of €6.7 million from Roche. In 2006, Roche acquired exclusive worldwide rights to develop and market taspoglutide except in Japan and France. As a reminder, the phase 2 studies looked at treatment of type 2 patients (n = 306) with taspoglutide for eight weeks. They were treated with either 5, 10, or 20 mg weekly, or 10 and 20 mg once every two weeks. At the end of the trial, the percentage of patients who had achieved A1c targets of 7% of less were 59%, 79 %, 81% in the 5 mg, 10 mg, 20 mg weekly arms, respectively; in the twice weekly arms, they were 44% and 63% for the 10 and 20 mg doses, respectively; only 17% of patients treated with a placebo reached the 7% target. Dose-dependent weight loss was also reported.

- **Bayer—Slow growth in 2Q08 compared to the rest of the field:** In a call led by CEO Werner Wenning, Bayer Diabetes Care reported global 2Q08 revenue results of €249 million ($388 million at today's exchange rate of $1.55 per Euro). This represents 2% growth, substantially lower than the 14% growth reported a year ago. From a competitive perspective, we note that on a reported basis, J&J and Roche grew 7% while Abbott grew 9%. Overall, Ascensia product sales of $243 million were flat on a reported basis of 0.8% growth (up 8.7% on a

currency-adjusted basis). Specifically, lackluster results for the Breeze system played a large part in this downturn. As a reminder, the Breeze meter, announced in September 2007, is large enough to hold a 10-disc set of strips enabling multiple blood-glucose tests without individual strip loading. Sales of the Breeze line fell 11%, while the Elite blood glucose meters dropped almost 30% (from a small base - they have been phased out). Contour sales were reported at €149 million ($233 million), reflecting 12% growth (22% with currency impact) – 1Q08 saw Contour sales up 21% (~28% on a currency adjusted basis). We have been impressed by the Contour meter's enhanced user customizability potential, which enables greater individualization of therapy.

- **Genaera—Interim phase 1 safety and pharmacokinetic data announced for PTP-1B inhibitor:** Unlike other PTP-1B inhibitors in development from Akros, Ceptyr/Lilly, Isis/Merck, and TransTech, Genaera is developing its PTP-1B inhibitor for an obesity indication. PTP-1B has been a well-validated drug target that has been recognized for over a decade, though development of PTP-1B inhibitors has been challenging. PTP-1b downregulates the insulin receptor, thereby decreasing insulin sensitivity; therefore, PTP-1B inhibition increases insulin sensitivity. In theory, it is a great target - increasing insulin sensitivity and causing significant weight loss. It may also have a positive effect on dyslipidemia through its indirect effect on apoprotein E (ApoE). It is not known why PTP-1B inhibition causes weight loss, but some have speculated that it is due to sensitization of leptin, an obesity hormone that is involved in long-term weight maintenance. Another explanation is that PTP-1B inhibition leads to less storage of fat in fat cells (adipocytes). We learned at ADA this year that PTP-1B knockout mice have significantly increased levels of P-CREB in white adipose tissue. This may lead to reduced insulin-stimulated glucose uptake in isolated adipocytes. This finding suggests that while PTP-1B sensitizes muscle and liver, it actually makes adipocytes insulin resistant and attenuates insulin signaling in adipocytes. IRS-1 is one of the insulin signaling kinases, which is reduced by 40% in adipocytes.

  Although PTP-1B is a well validated drug target, many attempts to develop PTP-1B inhibitors have failed. The problem is that phosphatases are notoriously non-specific. PTP-1B has a very similar catalytic domain to T cell protein tyrosine phosphatase (TC-PTP); therefore it has been difficult to find molecules that inhibit PTP-1B without also inhibiting TC-PTP. Another challenge has been making PTP-1B inhibitors soluble and potent enough for human use. The target enzyme is highly hydrophobic, and many PTP-1B inhibitors that were initially developed were highly insoluble and required large injection volumes. After a period in which many PTP-1B inhibitors such as Wyeth's ptp-112 were dropped, we are beginning to see a new set of PTP-1bs coming into human testing. Most of the PTP-1B inhibitors in development are twice-weekly injected antisense inhibitors (i.e. targeting the mRNA from which PTP-1B enzymes are made). Genaera's PTP-1B inhibitor is not an antisense inhibitor, and given the high failure rate of such PTP-1B inhibitors in the past, we will be looking closely at the side effects reported in upcoming clinical trials.

- **Human Genome Sciences—No mention of Syncria in 2Q08 earnings call:** During the call led by President and CEO H. Thomas Watkins, there was no mention of Syncria, a long-acting form of GLP-1 being developed with GSK. According to the website, a phase 2b trial was initiated in May 2007. No further updates about this drug have become available since that point.

- **Amgen—Update during 2Q08 earnings call:** The prepared presentation for the 2Q08 earnings call for Amgen on July 28, included a brief mention that phase 2a results for AMG222, the company's DPP-4 inhibitor, are expected in 2009. Two other diabetes drugs in Amgen's pipeline are still in phase 1: AMG 477, an antibody antagonist to the human glucagon receptor, and AMG 221, an inhibitor of 11-beta hydroxysteroid dehydrogenase type 1 (11ß-HSD1).

- **Sanofi-Aventis—Apidra approved for use in children and adolescents in Europe:** On July 24, the European Commission approved Apidra for use in adolescents and children younger than six years old. Apidra is Sanofi's rapid-acting insulin analog, which competes with Eli Lilly's Humalog and Novo Nordisk's Novolog. The approval was based on results from a phase 3 study that compared treatment with Apidra or Humalog in 572 children and adolescents with type 1 diabetes. The study showed non-inferiority of Apidra to the market leader Humalog. In the study, the mean A1c change was +0.10% (± 0.08) in the Apidra-treated group and +0.16% (± 0.07) in the Humalog treated group, a non-significant difference. Both groups also had similar post-prandial glycemia control.

- **EnteroMedics—Enrollment complete for EMPOWER pivotal study:** During EnteroMedic's 2Q08 earnings call on July 24, the company announced that it had a net loss for the quarter of $11.4 million attributed to the cost of multiple clinical trials and ongoing development of its VBLOC therapy. VBLOC therapy, administered by the company's Maestro System, uses high-frequency, low energy electrical impulses to intermittently block vagus nerve signals, thereby reducing appetite. As of June 30, the company's cash, cash equivalents, and short-term investments totaled $38.6 million. According to Senior Vice President and CFO Gregory S. Lea, the company has sufficient cash reserves to operate through 2009 and fund the EMPOWER study as well as the PMA submission to the FDA.

  Management said that the enrollment goal for the EMPOWER study has been achieved with approximately 450 subjects enrolled to date. This exceeds the company's original estimate of 220 to 300 subjects. According to top-line data, 300 Maestro Systems will be implanted over the next three weeks. The one-year study is being conducted at 15 sites in the US and Australia. EnteroMedics hopes to use data from the EMPOWER study to support a PMA for the Maestro System in mid-2009, targeting commercialization in early 2010.

- **BD—Strong results for 3Q08:** BD's Diabetes Care franchise reported strong FY3Q08 results in a call led by CFO John Considine on July 24. The division achieved revenues of $200 million reflecting 14% growth over FY2Q07 (8% excluding foreign exchange gains and up 7% sequentially. Diabetes Care, driven by pen needles, was once again pegged as one of the growth engines in this quarter. US sales reached $103 million, up 11.4% from FY3Q07 and up just over 6% from FY2Q08. Non-US sales came in at $97 million. This change reflects a 17.6% growth on a reported basis and 4.8% growth without the impact of currency factored in. Sequentially, international sales were up 7%. Last quarter, management had pointed to the loss of a contract with the VA last year as impacting US sales in Diabetes Care. This contract was reported to have been regained in FY2Q08 and this quarter's 11.4% US growth is concordant with management's FY2Q08 guidance of a return to ≥9% growth going forward.

- **Lilly—Robust sales of Humalog and Humulin:** On July 24, Eli Lilly reported continued strong growth for its insulin franchises. Humalog global sales rose to $437.9 million in 2Q08, reflecting 22% growth year-over-year, and Humulin global sales rose to $271.4 million for year-over-year growth of 12%. Sales of Humalog outside of the US increased to $188.4 million, a growth rate of almost 30%; clearly, favorable currency played a role, but the growth also appears to reflect increased demand overseas. US Humalog sales of $128.4 million grew 17% due to both increased demand and increased price. International sales of Humulin increased to $180 million, a 16% growth, driven by increased demand and favorable exchange rates, and domestic sales of Humulin grew to $91.6 million, a growth of 4% year over year. Management stated that for the first time since the launch of the Humalog Pen, endocrinologists prescribed more Lilly pens than Novo Nordisk pens for patients starting meal-time insulin. We were very surprised to hear this although we do think KwikPen has made a big splash for the company. Lilly's share of Byetta

revenues showed renewed strength. As noted below (see Amylin Company Watch on page 18), worldwide sales of Byetta rose to $194.7 million, a 25% increase. This quarter, Lilly recognized Byetta revenues of $101.2 million, representing a 27% increase year over year.

During the call, management characterized the advancement of its pipeline as a top priority. The company's website lists eight phase 1 diabetes compounds – none are specified except TT-223 (Transition Therapeutics' Gastrin) and glucokinase activator LY2599506 (partnered with OSI) – suggesting increased activity in early stage development. Three obesity programs are also in phase 1, as well as two unspecified phase 2 diabetes programs in addition to Lilly's in-house GLP-1 analog. Among later stage candidates, Lilly has exenatide once-weekly, which should be submitted shortly, and is in the midst of several important superiority trials; teplizumab, an anti-CD3 monoclonal antibody being developed with MacroGenics; and ruboxistaurin, a retinopathy medication, which has been submitted for review to the FDA, given an approvable letter, and we continue to await word on its status.

- **GSK—Looking ahead for Avandia and Alli:** GSK CEO Andrew Witty led a call July 23 to discuss GSK's second quarter performance and new strategic initiatives. Of interest to those watching diabetes, Avandia sales were roughly flat with last quarter at just under $400 million and although no turnaround was evident, no further global decline occurred, though sales declined slightly in the US. Avandia sales were £194 million ($386 million USD), down 44% from £349 million ($692 million) last year and up 0.02% from £191 million ($380 million) last quarter. Sales for the quarter in the US were £104 million ($194 million), down 50% year-on-year; in Europe sales were £49 million ($98 million), down 24% year on year; and in the rest of world sales were £41 million ($81 million), down 32% year on year. According to Witty, sales have appeared to stabilize, which he attributed to positive news in the past two months from ACCORD and VADT showing no link between Avandia and increased cardiovascular risk. See summary below for the last six quarters of sales:

2Q08	£194 million ($386 million)
1Q08	£191 million ($380 million)
4Q07	£231 million ($472 million)
3Q07	£253 million ($463 million)
2Q07	£349 million ($692 million)
1Q07	£414 million ($811 million)

Alli 2Q08 sales were £18 million ($36 million), up 50% from £9 million ($18 million) in 1Q08 but down 76% year-on-year from £76 million ($157 million). Alli was launched in 2Q07, and we are unsure about the future of this drug in light of the significant decline that has occurred over the past year. Overall, Pharmaceuticals and Consumer Healthcare declined 2% but grew 4% year-on-year from £5.7 billion in 2Q07 to £5.9 billion in 2Q08. The weak performance was attributed to competition from generic drugs and weak sales of Avandia in the US. When these two factors were excluded, growth was actually 13%.

No references were made to GSK's current diabetes drug candidates: 189075 (remogliflozin etabonate), Syncria, 376501 (PPAR-gamma partial agonist), and otelixizumab (TRX4, an anti-CD3 monoclonal antibody being developed with Tolerx). No preclinical new chemical entities (NCEs) were mentioned, nor was progress on the phase 2 study looking at the use of Sirtris's SRT-501 in combination with metformin or anything else about the Sirtris acquisition.

- **Merck—Extremely strong growth of Januvia and Janumet in 2Q08:** In a conference call led by CEO Dick Clarke, Merck reported strong worldwide second quarter Januvia franchise sales of $406 million, up 242% from $168 million a year ago and up 23% sequentially from $330 million last quarter. The franchise is now annualizing at $1.6 billion, continuing its remarkable ascent. Januvia sales were $334 million, up 130% year-over-year, while Janumet sales were $72 million, up 200% since 2Q07. US sales of Januvia were $262 million (up 91%) and US sales of Janumet were $67 million (up 100%). Sales of Januvia outside the US were $72 million (up 100%). Management pointed to recent launches in countries like Spain, Italy, Canada, and France as a key part of this growth. Janumet was recently approved in Europe, opening up 27 new European markets for the sale of this product. Januvia sales represented just over 80% of the total Januvia franchise – Janumet sales are strengthening, as are international sales, which were $77 million, or 19% of the total, up from last quarter's $50 million, or 15% of the total. These results continue the strong performance seen for both of these drugs since their release. Merck continues to benefit from its position as the only company with an FDA-approved DPP-4 inhibitor –as the benefits of a simple, "easy" drug continue, we see little short of safety problems stopping Januvia's continued growth. To us this also underscores clinician and patient (especially clinician) demand for drugs that have fairly benign side effects. Recent data presented at this year's ADA showed that Januvia use leads to a lowered frequency of hypoglycemia compared to sulfonylureas. This helps to reinforce the already well-accepted safety record of Januvia, and should help to bolster its continued growth, particularly given greater dissatisfaction expressed about SFUs at ADA. We believe the outcry over drugs that cause weight gain and hypoglycemia is greater now than in some time. This may reflect a latent worry that weight gain/hypoglycemia are the culprits for all of this circumstantial evidence pointing to increased cardiovascular risk with intensified therapy.

- **Amylin—Impressive sales of Byetta in 2Q08:** In a call led by President and CEO Daniel M. Bradbury on July 21, Amylin posted impressive Byetta sales of $200.3 million for 2Q08, up just under 20% from the same period last year. Total revenues, including collaborative income, were $222 million, matching analyst forecasts. Byetta sales reached $177.5 million, up nearly 17% - inventory levels were said to be the same as a year earlier, good news as this reflects true quarterly growth. Symlin sales reached $22.8 million, 50% growth year-over-year and 14% growth since last quarter. SG&A rose by almost $20 million to $111.1 million, and R&D expenses rose by about $4 million to $75.4 million. Net loss for 2Q08 were just under $65 million, compared to $45 million during the same period of 2007.

  Several market accelerators for Byetta were highlighted. First, management noted that a great deal of attention was given to Byetta during ADA 2008 - exenatide was featured in 159 different posters and presentations. Dr. Ralph DeFronzo, who gave the Banting lecture, advocated a change in the ADA algorithm and suggested initial triple combination therapy with metformin, TZD, and exenatide. Notably, Bradbury stated that the ADA is currently funding research that compares Dr. DeFronzo's suggestion with the current ADA algorithm. The results from ADVANCE, ACCORD, and VADT also benefited exenatide as the trend is now toward drugs that do not incur an increased risk of weight gain or hypoglycemia. All of these factors have contributed to an increasing dialogue in the medical community about treatments for type 2 diabetes and the benefits of Byetta, particularly following the FDA panel vote to require a long-term cardiovascular outcome study for all new diabetes drugs. Although nothing has been finalized yet, Bradbury mentioned that a post-marketing cardiovascular trial for once-weekly exenatide may be carried out.

Management affirmed that NDA submission for once-weekly exenatide was still expected by the end of the first half of 2009. Amylin has held a pre-NDA meeting with the FDA and management appeared to remain confident that its DURATION-1 clinical study would provide enough safety and efficacy data – we are very glad to see and hear this. Commercial batches of exenatide were manufactured and shipped for use in ongoing and planned clinical trials in 3Q08. Bradbury indicated that Amylin would accelerate its NDA submission if the results from ongoing *in vitro* studies and crossover studies are positive. Amylin continues to carry out superiority trials for once-weekly exenatide: DURATION-2 is a blinded 400 to 500 patient study comparing exenatide once-weekly against Takeda's Actos and Merck's Januvia as add-on to metformin background therapy. Results will be available in the first half of 2009. DURATION-3 will compare exenatide once-weekly to Sanofi-Aventis's Lantus as add-on to oral agent therapy. This trial will also enroll 400 to 500 patients, with results expected in the first half of 2009. DURATION-4 will begin later this year and will compare exenatide once-weekly monotherapy to metformin, Actos, or Januvia. We expect these studies to produce powerful data that will reveal once-weekly exenatide as a standout diabetes therapy.

An update on Symlin use indicated that total prescriptions of Symlin rose 5% quarter-on-quarter, presumably from SymlinPen and continued word of mouth. The SymlinPen now accounts for 60% of new Symlin prescriptions and 40% of total Symlin use. This is up from 1Q08 where the SymlinPen accounted for 39% of new Symlin prescriptions and 21% of total Symlin use. Data on the use of mealtime Symlin with basal insulin therapy was released at ADA 2008. Patients with type 2 diabetes were treated for 24 weeks with either mealtime Symlin and basal insulin or rapid-acting mealtime insulin and basal insulin. Patients treated with Symlin had improved glucose without weight gain or hypoglycemia (the results for this are in our ADA notes – if you do not have that handy please let us know).

In the INTO arena, a phase 2b clinical study was initiated to evaluate various dosings of pramlintide with metreleptin to treat obesity. This drug combination has been shown to reduce body weight by 12.7% over 24 weeks. The study will last six months and enroll approximately 600 patients; it should take around one year to complete. The results from this dose-ranging study will be used to support dose selection for phase 3 trials. Bradbury briefly mentioned that Amylin may seek financial or commercial partners for the development of its obesity-related drugs. As reiterated from 1Q08 notes, we would look for Amylin to think about companies like Amgen, J&J, and Wyeth (assuming they would look to re-enter obesity) with companies like Medtronic as perhaps outside possibilities (Medtronic has hinted before that it would consider a drug partnership at the right opportunity). While many companies would seem unlikely partners because of competitive drugs (Takeda, GSK, Sanofi-Aventis, BMS, AZ, etc.), one never knows what could happen – think about Medtronic's deals with J&J and Bayer last year.

- **Roche—Bid for Genentech and strong US sales in 2Q08:** On July 21 in a call led by CEO Severin Schwan, Roche discussed its results for 2Q08 as well as its recent bid to acquire publicly held shares in Genentech for US$89 per share, or just under US$44 billion. Currently, Roche holds 56% of all outstanding shares and plans to take Genentech private. Interestingly, one drug that Genentech is planning for phase 1 clinical trials is an anti-CD4 monoclonal antibody developed with Tolerx. Tolerx is already collaborating with GSK on a phase 3 anti-CD3 monoclonal antibody (otelixizumab) being developed for type 1 diabetes. CD3 is a molecule expressed by all T cells, and CD4 is expressed by a subset of T cells that are required for initiating and sustaining an immune response.

  On the device side, Roche Diabetes Care posted sales up 7% for 2Q08 and had a nice turnaround in the US, where sales rose 9%. The Accu-Chek Aviva and Accu-Chek Performa were cited as

growth drivers in the US. Global sales for the half-year suffered from weak results last quarter – total sales came in at 1.482 billion CHF ($1.45 billion USD), which represents a 2% growth rate including currency effects and a 4% decrease operationally year over year. Putting these numbers into an industry perspective, Abbott Diabetes Care posted an approximately 2% operational growth rate for this quarter, and J&J reported just under 7% growth – we assume the competition overseas has made growth particularly difficult. Roche released one new diabetes product—the Accu-Chek Compact Plus—in April of this year, and three more products are expected in the remainder of 2008: Accu-Chek Inform II system, Accu-Chek Aviva Nano, and the Accu-Chek Active.

A pharma update from Pharma CEO William M. Burns noted Roche's plans to out-license R1579, its DPP-4 inhibitor. Roche had expected this compound to differentiate itself from other DPP-4 inhibitors by causing significant weight loss based on available clinical and preclinical data; however, the compound did not show weight loss in phase 2 trials. No further details were given; we suspect coming to market with a fourth "me-too" would be difficult and that resources are being invested elsewhere. As expected, management discussed the planned phase 3 trial for R1538 (taspoglutide), Roche's once-weekly GLP-1 candidate. Ipsen released the top-line phase 2 data on July 31 (initially presented at ADA 2008), and Roche said enrollment for the phase 3 trial will begin at the end of the year. Ipsen will receive a payment of €6.7 million from Roche. Notably, Roche also said that the phase 3 trial for CETPi, its dyslipidemia drug, is already recruiting. The phase 2 trial for R1439 (aleglitizar), a PPAR alpha-gamma dual agonist, is ongoing, and a go/no-go decision will be made in early 2009 following completion of the renal study (and presumably meetings with FDA). Sales of Xenical fell 16% year on year largely due to sales of Alli, an over-the-counter version marketed by GSK (which had a big launch but disappointing sales).

- **Biodel—Announces top-line phase 3 data for VIAject:** Biodel announced the completion of two of its phase 3 clinical trials for VIAject, the company's "very rapid-acting insulin." Unexpectedly, the company also released interim six-week data and announced that results of the full trial will be released in a poster presentation at EASD. Top-line data indicated that after six weeks of treatment, both type 1 and type 2 patients treated with VIAject showed significant differences compared to patients on regular human insulin (RHI) for weight gain, meal-time dose, and mild-to-moderate hypoglycemic events. For patients with type 1 diabetes, those treated with VIAject (n=102) had no change in weight while those treated with RHI (n=108) had an average weight gain of 1.4 ± 2.9 kg. In type 2 patients treated with VIAject (n=173), a weight reduction of 0.5 ± 4.7 kg was seen whereas in the RHI-treated patients (n=180) a weight gain of 0.8 ± 6.2 kg was seen. Notably, for type 1 patients a 34% reduction in prandial insulin dose during the first six weeks of the study was seen in patients treated with VIAject (n=102). A non-significant decrease was seen in RHI-treated patients (n=108). We were even more surprised by the results from the patients with type 2 diabetes. Those treated with VIAject (n=173) were able to reduce their prandial insulin dose by an average of 36% while patients treated with RHI (n=108) saw an average increase in prandial insulin dose of 15%. Out of 8,111 hypoglycemic event results in type 1 patients (just under one per day for 208 patients over 42 days), approximately 16% fewer events occurred in the VIAject group—3,691 events in the VIAject group or 0.86/event per day and 4,420 events or 0.99 event/day in the RHI group. Type 2 patients had 47% fewer events in the VIAject group compared to the RHI group—844 events in the VIAject group (0.11 event/day) and 1,594 in the RHI group (0.21 event/day). At first, we didn't understand why the trial had 208 type 1 patients and 353 type 2 patients rather than n=400 for each group, as we had expected; however in a follow-up call with Biodel, they clarified that not all of the data have been analyzed yet, explaining the n<400 for each group.

If VIAject is effectively weight neutral or causes weight loss, reduces prandial insulin dose, and results in fewer hypoglycemic events, it could have significant advantages over other diabetes drugs. We were very impressed by the fact that treatment with VIAject shows less weight gain and a reduction in hypoglycemic events. All three effects may well go hand-in-hand – with fewer post-meal lows due to insulin-on-board, diabetes patients may snack less frequently to "turn around" hypoglycemia, and weight gain would be reduced. These data are impressive and appear to be superior to data from the phase 3 trials of the currently available rapid-acting insulin analogs, which were also compared to regular human insulin (the FDA considers regular human insulin to be "standard of care"). We also await the publication of full six-month and one-year data as well as trials against other rapid-acting analogs before coming to any firm conclusions.

- **Private Company Roundup** (from Canaccord Adams meeting at ADA)**:**
    - **Elixir Pharmaceuticals (Paul Martin, Chief Medical Officer)—**This company emerged around discoveries made in the late 1990s about the relationship between aging, insulin pathways, and metabolism. Its late-stage candidates Glinsuna (mitiglutide) and Metgluna (mitiglutide combined with metformin) were in-licensed from Japan. Phase 3 data are expected in late 4Q08. Another important area for Elixir is its oral ghrelin antagonist and agonist programs. These programs are pre-clinical, but data presented at the annual meeting of the Endocrine Society in June 2008 demonstrated that in diet-induced obese mice the antagonist produced a significant decrease in white fat and liver fat. The ghrelin agonist program is intended for the treatment of gastroparesis, one of the autonomic complications of diabetes.
    - **DIObex (Keith Vendola, Corporate Development)—**DIObex focuses on preventing insulin-induced hypoglycemia. DIO-901 is in early development and uses low doses of glucagon to replace glucose stores and reduce hypoglycemia. Three phase 1 studies are complete with the final study honing in on an appropriate dose range. The company believes roughly $25 million will be needed for the phase 2 study (600 patients, commencement in 2009) and another $40 million for phase 3.
    - **TransTech (Stephen Holcombe, CEO)—**TransTech has a small molecule target program gleaned from Novo's jettisoned oral glucokinase activator (GKA) program. They are currently investigating two GKAs: TTP355 and TTP399 (pre-clinical development). In animal studies, TTP355 produced a reduction in glucose without spiking insulin. Some early patient studies are complete and show that TTP355 lowers glucose more effectively than metformin. Also in development are small molecule GLP-1R programs. The company has raised $110 million in private equity – mostly from MacAndrews. Other investors include Novo Nordisk and Cephalon. Holcombe believes that TransTech is widely known in the pharma community but barely known in the investment community.
    - **Tolerx (Chris Merrill, Director of Business Development)—**Tolerx approaches type 1 diabetes as an autoimmune disease and is looking at mediating immune system tolerance as a method of treatment. Two monoclonal antibodies are currently in clinical trials. The primary candidate is an anti-CD3 antibody (oteliximuzab) for type 1 diabetes. If it works effectively, it could lower the amount of insulin required over a lifetime as well as provide some beta cell protection. In phase 2 trials, insulin use decreased and some of the patients could have stopped taking insulin completely. Full dose optimization studies have been initiated – which has never been done with an anti-CD3 treatment. It is collaborating with GSK on oteliximuzab, and GSK gave the company $70 million upfront, which is enough funding until 2011, according to management. Tolerx is also working

with Genentech on an anti-CD4 monoclonal antibody (MTRX1011A), which was moved into phase 1 clinical trials in early August 2008.

- **GI Dynamics—**GI Dynamics offered an update on its EndoBarrier technology platform and plans to develop additional medical device interventions for type 2 diabetes and obesity that are reversible and mimic the effects of Roux-en-Y gastric bypass. The EndoBarrier is a two-foot long sleeve with a nitinol anchor that is delivered endoscopically in a capsule over a guide wire through the stomach into the intestine, where it ultimately self-expands. Placement is verified with a contrast medium and takes about 30 minutes with removal taking about 10 minutes. The sleeve prevents absorption of nutrients in the proximal small intestine. Early data in type 2s showed enough improvement in glucose control within a week of the implant to discontinue glucose medications. To date, the longest installation is 11 months, and the sleeve was removed because the sleeve anchor migrated (it was removed without surgical intervention). The company has raised roughly $40 million from top VCs ATV, Polaris, Domain, Cutlass, and JJDC.

- **Satiety—**Satiety's TOGa (trans oral gastroplasty) device endoscopically vacuums up a section of the stomach and staples a pouch to decrease the surface area of the stomach – this is another device that is intended to mimic Roux-en-Y gastric bypass. Eleven of the 50 patients in Satiety's phase 2 data pool have been monitored for a year, and excess weight loss of over 50% has been observed, compared to 30% for lap-band. No significant adverse events occurred in the phase 2 studies. A pivotal trial of over 380 patients is in the middle of securing IRB approval – we have heard very good things about this technology and eagerly await further updates.

- **OptiScan—**OptiScan offered a review of the hospital/ICU glucose monitoring market and the company's current status. The company noted that FDA approval was "imminent" but did not show any clinical data. As a reminder, OptiScan's inpatient continuous glucose monitor (also called OptiScan) is semi-invasive and draws blood every 15 minutes from a CVC or PICC venous line, which goes to an in-line centrifuge for testing. Daily blood loss is roughly 10 ccs. OptiScan anticipates a limited 2008 release and has modeled for 130 active accounts with $500,000 average sales per account in year one. The company anticipates raising money ($20 million) next year as it prepares for its full-blown commercial launch in the US. OptiScan has raised $59 million to date.

- **Luminous—**Luminous reviewed the hospital/ICU glucose monitoring market, the pressure to address poor glycemic control in ICUs, and its technology under development. The Luminous device uses near-infrared light to measure whole blood as it is flowing, so there is no need to process or extract blood. It can pull the blood out, test it, and put it back in, unlike the OptiScan, which uses mid-infrared light and thus requires blood to be drawn and centrifuged. Data suggest a strong accuracy profile. However, CEO Rick Thompson noted that the rate limiting step right now is patient enrollment in the pivotal trial which is due to begin this fall. We see one potential obstacle in the footprint of the device – it is big and consumes a lot of ICU real estate.

- **VeraLight—**VeraLight gave an update on its screening device for diabetes – one appropriate for a wide range of retail outlets or clinics. The idea is to place a non-invasive screening tool into as many mobile screening outlets, pharmacy labs, physician offices, etc. as possible to detect more patients in the early stages of diabetes (an estimated 50 million people fall into the "pre-diagnosed" category) and pull them into the treatment

loop before A1cs and other co-morbidities escalate. The device weighs eight pounds, is easy to use, and generates results in 60 seconds or less. It measures a predictive biomarker of diabetes that accumulates faster in individuals with pre-diabetes and diabetes. Current usage of this biomarker is very limited because it can only be assessed with a punch biopsy. VeraLight could offer an easy-to-access alternative. The company has completed a 20-site, 3,000-patient trial to create a calibration study. The pivotal trial is underway – 20 sites and 5,000 patients – with a regulatory submission expected by year-end. VeraLight believes only 300 installed devices can get the company close to profitability, but the expectation seems to be that a larger company will enter the picture to augment the opportunity.

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

4. Dialog with AADE 2009 Educator of the Year: Janis Roszler, RD, CDE, LD/N

Janis Roszler was named the 2009 American Association of Diabetes Educators (AADE) Educator of the year. She is a well-known diabetes educator who is author of the "Dear Janis" column in Diabetes Positive! as well as a contributor to dLife.com, Onetouchgold.com, Diabetes Forecast, Diabetes Health, and Diabetes Living. Furthermore, she has written the following books: Sex and Diabetes, co-written with Donna Rice, Diabetes on your OWN Terms and The Secrets of Living and Loving with Diabetes, co-authored with William Polonsky and Steven Edelman. During the interview, she discussed her desire to bring more worldwide awareness and education about diabetes to people through mass media formats. She also gave tips on how educators could encourage their patients to instigate behavioral changes that would benefit their lifestyle and health.

Kelly Close: This is a really big honor for us to be able to speak with you, Janis, so thank you so much for taking the time this morning. To start our conversation, could you give us some background information on how you got involved in diabetes?

Janis Roszler: I didn't begin my career in diabetes. I started out as a registered dietitian and home economist. I wanted to go into private practice, so I started looking for a physician who could use my services. I worked with an internist for a while when an endocrinologist asked me to see his patients in his office. At that time, I had no particular opinion about working in the world of diabetes, but when I started doing it, I fell in love with the fact that a patient's behavior makes a difference, which isn't the case with most medical conditions. Diabetes educators and dietitians always try to motivate patients to take charge of their disease. Later, I developed gestational diabetes and now my risk of developing type 2 diabetes is quite high. Several years ago, my husband developed diabetes, so not only have I experienced diabetes during a pregnancy, but it is now in my family as well.

AADE 2008

Melissa Tjota: To start off with a little bit about AADE, how would you sum up the conference in one word? What did you feel was the major theme or point that was being emphasized throughout the conference?

Janis: My one word would be "international." During the pre-conference program, they held the International Diabetes Educators Conference (IDEC). It was the first time that AADE had an international piece, and personally, I made some wonderful international

connections. I am thrilled that we are starting to reach out to the world as diabetes is no longer a problem for the US alone.

Kelly: As a follow-up, it seems as if this meeting focused a great deal on prevention and pre-diabetes. Do you think we were learning more by having an international component?

Janis: The focus on pre-diabetes is still concentrated in the US. We know that there are around 24 million people with diabetes in the US, but what is more startling is that 57 million people have pre-diabetes. Once you see these astronomical numbers, you realize that we cannot just sit around and take care of the few who are diagnosed in our centers. We must reach out and educate everyone about the dangers of having pre-diabetes.

Melissa: Going back to AADE, are there changes you would wish to see in the conference next year?

Janis: I would like to see more classes that offer skills in using technology and different media to take the voices of the diabetes educators to the masses, so they can influence a greater population. We are trained to deal with individuals one-on-one, which is still the best way to educate people. The problem is that there are millions of people with diabetes, and only thousands of educators. The main hurdle right now is to find ways to take our voices beyond the face-to-face encounter with patients.

Melissa: Is there anything currently going on that is using technology and media to help CDEs spread more information to the diabetes community?

Janis: I was chosen as the AADE educator of the year to help spread that message to the different chapters and help members get connected. I hope to show them how to use different types of media to get their health messages out, including newspapers, magazines, radio, Internet, television and DVD's. AADE is aware that we need technology to help us do our job effectively and educate more people about diabetes.

Behavioral Changes in Patients

Kelly: Could you talk more about the behavioral end or issues with adherence? How do you reach out to encourage patients to change their behaviors?

Janis: I believe that it goes back to square one. As diabetes educators, we ask patients to engage in self-care behaviors that are necessary to improve their health. In order to do them successfully, most people need the support of family and friends. This is the piece that I focus on: relationships. If there is tension between a partner, a friend, or a spouse, it makes it more difficult to implement important self-care behaviors. As educators, we need to be aware of emotional stresses that may exist in a patient's world as these stresses can interfere with his or her ability to succeed.

Melissa: What do you think is the next step for CDEs in making sure that the behavioral piece is addressed?

Janis: I think we are starting to do that in a very significant way. Several years ago, when I first lectured at AADE about the emotional impact of diabetes-related sexual complications, the reaction of the audience was one of fear, discomfort, and shock. This year, a lot of CDEs told me that they had already started to implement that topic into their educational offerings. Today's diabetes educators do understand that behavioral issues can get in the way of successfully getting patients to self-manage their diabetes.

Diabetes educators tend to spend more time with patients than physicians who are on a

tighter time schedule. A lot of personal things often come out while we are speaking with a patient. We pick up on cues of stress, relationship issues, and other things. Diabetes educators are the first line that patients encounter, so we need to be a positive resource and help to direct patients in specific directions. It is key that we educate diabetes educators about the need for behavioral awareness and help them know what to do when someone indicates that he or she is having problems.

Kelly: How did you bring sex out of the closet in diabetes care? Should women get more attention in this realm in future years?

Janis: I just started talking and writing about sex and did not care that it made others uncomfortable. Sexual issues are too important to ignore. The research for women has lagged way behind men. We did not see any reliable studies on women until 2002! We recently discovered a connection between sexual complications in women with type 1 and the menstrual cycle. Who knows what else we can uncover? More health care providers are now aware that a diabetes/sexual connection exists for women.

Kelly: What about if the patients do not even know about the educators? Accessibility to educators is still difficult, so can you discuss access to education and what can be done to improve it?

Janis: I believe that is where the mass media comes in. I do a lot of work with dLife. They have a television show and educational website for people with diabetes. The public is becoming more computer savvy, so we should try to use it to our advantage to supply the public with reliable information. We need to have the information floating around in as many forms as possible. We need to get it into the American conversation.

It is important that we also get lifestyle information into schools because a quality health curriculum can lead to good health behaviors that promote diabetes health and pre-diabetes safety. Knowing how to become healthier should be as important as knowing not to drink and drive. Everyone needs to become aware of the importance of regular physical activity, sleep, healthy food choices, and portion control. We need to help people choose their foods wisely, maintain a healthy weight, and reduce their stress level. We need to get these lessons out to the general population as taking care of their health will ward off a lot of diseases, especially type 2 diabetes. If they already have diabetes, these behaviors can improve their condition. A person who does not have formal education can learn through osmosis by living in a healthier environment and a healthier culture.

Kelly: I think there is a lot of misinformation out there, but is the bigger problem that people actually do not have the information or that they don't understand how hard it is? I sense a frustration in both industry and people thinking about going into diabetes treatment, and they question why things are not moving faster.

Janis: One reason that I wrote my second book, "Diabetes on Your OWN Terms," is because I think that most patients receive the wrong messages. Many believe that there is only one way to care for diabetes. A lot of those messages come from lessons we have learned from clinical trials - that patients must employ a certain type of behavior to have the best outcome. Patients need to understand that they have many different behavior options to choose from. They can start with small steps and implement new health practices at a personal pace. For example, in the book I list what AACE and the ADA have as their target goals for blood glucose. The targets are significantly different, so I say, "Look at the range between the two. You could go somewhere in between if you

wish and still enjoy a significant improvement in your control. It depends on where you want to start."

Kelly: That really speaks to the individualization of therapy, but it flies in the face of patients who do not spend much time with their health care providers because they are limited in terms of reimbursement and so forth. Is it correct to say that you seem to be focusing on empowering the patient?

Janis: It is all about the small steps. As I mentioned earlier, I had gestational diabetes. For me, it made a difference to personally experience diabetes. Before I developed gestational diabetes, I had been teaching patients with diabetes in a very different way. I looked at the results from clinical trials then urged patients to meet those goals. I gave them the keys to meet those goals quickly and conveyed the message that they had no other options. When I developed gestational diabetes, my perspective changed dramatically because for the very first time, diabetes entered my personal world. I was glued to the clock. I had to check my blood at specific times and eat at specific times. My children were always worried about me because they saw how nervous I was about the results I would see on my meter. In other words, diabetes took over my life. For the first time, I felt that impact, and I decided that this was not the quality of life I wanted for myself. My diabetes ended after my pregnancy, but the experience motivated me to find a way for everyone with diabetes to enjoy a better quality of life. It was at this time that I decided people need to become aware of the fact that there are many levels of good behavior and health. The ideal is tight glycemic control; however, if you are not there, but have moved closer to that goal, that is fantastic. We need to encourage patients to do their best. And when they reach a personal target, they should feel very positive about this achievement and congratulate themselves. As you said, individualizing treatment is key because the person who takes a few steps in the right direction will live a better life.

But as you mentioned, there are time constraints and that is why we have to provide information in ways that are not necessarily face-to-face. The face-to-face timeframe is very limited, so it is difficult to get to everything that needs to be discussed. We need to provide patients with places where they can review topics and skills and pick and choose what they feel ready to do - they do not have to aim for perfection. There are people who can do it all. They have a good routine, check their blood glucose multiple times a day, and participate in regular physical activity. They have incorporated everything into their lives, and they are benefiting from it. But that is not everyone, and I do not want the person who cannot do that to feel that he or she is less of a success. Everyone can be successful in his or her own way and still benefit. It is difficult and challenging, but we should applaud everyone who tries to move their life in a positive direction.

Melissa: What are the key things you do to successfully motivate your patients to change their behavior?

Janis: I developed a plan called the Jump Start Pledge, which I use with patients and on my website, www.dearjanis.com. A Jump Start Pledge is a very small and doable behavior change that a person promises to do for a single week only. Behavior changes tend to be overwhelming. It is difficult to say, "From now on, I'm not going to do X, Y or Z." If you fail, you feel badly, which makes it even harder to change your behavior once you attempt to try again. So, the Jump Start Pledge is a smaller version that you try for a week. For example, if you want to cut back on your caffeine, and you drink nine cups of

coffee each day, you don't say, "I'm going to cut out coffee altogether." Rather, you say, "I'm going to cut back to eight cups of coffee and substitute one cup for decaf." This is the pledge you do for one week. At the end of the week, you have a choice - you can renew the pledge and continue renewing it until you feel ready to go to the next level, or you can change it to fit you better. When you carry out this tiny step, at the end of the week you have achieved success. Or if it did not work, it is not your fault because the pledge was not right for you at the time. This method takes away the guilt, and with patients that have diabetes, there is an enormous amount of guilt. Jump Start Pledges help you begin new healthy behaviors that can gradually become a natural part of your life.

Melissa: With the increasing emphasis on patient self-management, how do you feel that will affect the role of the diabetes educator?

Janis: I feel it will only increase the role of the diabetes educator because we help people implement the AADE-7, the American Association of Diabetes Educator's seven self-care behaviors. They are Healthy Eating, Being Active, Monitoring, Taking Medication, Problem Solving, Reducing Risks, and Healthy Coping.

Reimbursement

Kelly: Can you comment on reimbursement for a diabetes educator's time? Reimbursement is clearly aimed at primary care, but physicians do not have as much time with the patients.

Janis: Having more time with physicians certainly makes a difference, but unfortunately, most doctors do not have that time. Diabetes educators need to see people with diabetes and should receive appropriate reimbursement for their time. Quality education is worth every penny. Sadly, Medicare does not pay enough or offer an adequate number of visits for education. This makes it very difficult for that population to get the important self-care guidance they desperately need.

Kelly: We are also interested in reimbursement for things like e-mails and phone calls. What do you think about this issue?

Janis: I'd love to see reimbursement for other teaching pathways. We need to get important health information to as many people as possible, and we need to adequately compensate experts for their time.

Melissa: Becoming a CDE takes some time and there is definitely a need to increase their numbers. Is there any way of making the process to become a CDE faster, or can a subgroup of CDEs that focus only on pre-diabetes be developed? The pre-diabetes group would not require as much specialization as current CDEs, so do you think this may be a possibility in combating diabetes before it fully develops?

Janis: That is a great question. I do not believe that the road to becoming a CDE should be streamlined because it is a challenging certification that recognizes an extremely high level of education and skill. However, we could award interested educators with a basic certification that could be obtained more quickly. I love this idea, and I'm going to suggest it to AADE.

Kelly: Can you discuss prevention of complications and your thoughts broadly on this?

Janis: I believe that there is a lack of recognition of the power of education as a way to prevent complications. For example, to prevent amputations, a patient should learn how to

inspect his or her feet each day. Unfortunately, we do not have enough time to discuss every single topic. It is sad, but that is the way the system works; it is not prevention focused.

Diabetes Drugs and Devices

Kelly: Historically, there have been many side effects with diabetes medicine such as weight gain or hypoglycemia. Is there anything that you can say about what makes it easier for people to stay on drugs or new technology?

Janis: The greatest thing that has really made all the difference in the world is the glucose monitor. People are checking their blood sugar, and they are making decisions based on the patterns that they see. Once they know how to use the results, they have the opportunity to become their own physician, and can guide themselves. My favorite is the post-prandial test because people get very excited when they realize that they can look back at a meal and see what their food choices may have done to their glucose level.

As far as staying on medication, information is power. The glucose meter helps show people the role that medication is playing in their diabetes health. They also need to know that there are many medications options to choose from. If one drug doesn't work well, they should share their concern with their healthcare provider and ask if they can try something else.

Melissa: You were quite positive about the glucose monitor. Can you give us your view on CGM and furthermore the integration between CGM and the insulin pump?

Janis: The more information we have, the better it will be. I know that CGM provides a great deal of information, but most people are not comfortable wearing numerous gadgets on their body, so I hope we see a fully integrated CGM/pump soon.

Melissa: Are there any device areas or drug areas you feel need more improvement?

Janis: Depression medications really need a great deal of improvement because many have horrific side effects that make life very challenging for people with diabetes. For instance, some depression medications have sexual side effects and cause weight gain. If you don't feel confident and comfortable with your partner in an intimate setting, your discomfort can reverberate throughout your entire world and affect your ability to care for your diabetes.

As far as other diabetes medications, I am very disappointed that Exubera was not successful. I realize it may not have been the best product, but had it succeeded, it could have been the first step in developing a new way to take insulin. With its removal from the market, we lost an opportunity to go in a direction that would have increased convenience and ease of use for the patient.

Furthermore, I want to see alternate methods of insulin delivery come to the market as well as insulin that does not require refrigeration. There are too many individuals throughout the world who have no access to refrigeration who are suffering. We also need an accurate blood glucose testing system that does not require a blood sample. I want people with diabetes to go through their day without thinking about their diabetes.

Kelly: Can you give us your thoughts on new diabetes drugs and old drugs, specifically incretins and insulin? What can make insulin easier?

Janis: Incretins definitely have a place in glucose control and insulin action. Adjusting the ADA/EASD algorithm to reflect what we know about their importance would be a great idea. Each person is different and should have all care options available to him or her. For some patients, incretins make a superb first line option. Others may need to enter the diabetes world with oral medications because of their psychological resistance to injections. We have to be sensitive to a patients needs, both emotional and physical. There are 44% of patients not at goal in the US and only 23% are on insulin. Our understanding of how the body maintains its glucose balance continues to grow. The discovery of the action of incretins in diabetes control shows that we still have a great deal to learn. We are entering a very exciting time in diabetes history. About making insulin easier, I believe that we need to develop new delivery systems. People do not like taking shots or pricking their skin. If we can put insulin and incretins into capsules, patches, creams, pills or inhalers, more people would use them and reach their diabetes goals.

Kelly: There is a lot of evidence that sulfonylureas and metformin work well for some patients - also a lot of evidence that side effects prompt lower adherence. Do you have any opinions you could share on these classes?

Janis: Many people don't experience problematic side effects with these medications or have the ability to continue using them until the side effects subside. These are great medications, but we need even more options. I believe in making as many choices available as possible since each patient is different.

Kelly: What advice do you have for industry?

Janis: Everyone is looking for a cure, but until we get a cure, we need care. So far, industry has done a terrific job getting us to this point. We know that we have the brainpower to do much more, and I challenge everyone in industry to put on their thinking caps and brainstorm until we find the most effective way to treat people with diabetes. That is my challenge to industry.

Please keep the lifestyle needs of people who live with diabetes in mind. I am anxious to see how the single-dose Byetta works out because it will offer a dramatic improvement in the lifestyle of people who struggle with daily injections of that medication. Quality of life must always be a consideration.

Kelly: Janis, thank you again for your time, and we look forward to hearing more from you in the future.

— by Kelly Close and Melissa Tjota

5. Conference Pearls: Artificial Pancreas Meeting

July 21-22, 2008 • National Institutes of Health, Bethesda, MD • Towards an Artificial Pancreas: An FDA-NIH-JDRF Workshop

The excitement of the artificial pancreas (AP) project continues as we learn of the latest developments in pursuit of closed loop technology, and we are mindful of JDRF's continued financial support to complete this endeavor. Probably the most important take away from the meeting was that we should not allow our drive for perfection to stand in the way of progress, as even with current limitations, we are getting closer to being able to achieve significantly better glycemic control with the AP in development than we are manually with continuous glucose monitoring (CGM) and insulin pump therapy (CSII). The

immediate goals should be to reduce glycemic variability and significantly reduce hypoglycemic events. Researchers are taking two different approaches to reducing risk of hypoglycemia: auto shut-off of the pump when blood glucose is predicted to fall below 80 mg/dL, or use of calculated doses of exogenous glucagon as a counter-regulatory mechanism. Premeal priming boluses still seem to be necessary to avoid postprandial hyperglycemic blood glucose excursions. There is still some difference of opinion as to whether or not we should rely on interstitial glucose as opposed to blood glucose. Given that current CGM technology is not approved for dosing decisions, we may need to wait for more accurate sensors before we see approval of a closed loop relying on CGM technology.

Although the meeting was generally very positive about closed loop technology, Dr. Timothy Wysocki (Nemours, Jacksonville, FL) provided some balance by candidly addressing some of the potential psychological negatives associated with wearing and complying with the use of such a device.

We look forward to seeing increased accuracy in future sensors overcoming current hurdles, as well as more robust tests and observations under somewhat less controlled conditions in the laboratory and subsequent results of testing outside of the laboratory in real life situations.

- **Mr. Lawrence Soler from the JDRF explained in his introduction that the goal of the AP initiative is to accelerate the development of the AP**. Overall, the hope is to make it widely available to everyone who needs it and to increase the number of industry players because it will be better if there are more options. He noted that JDRF expects to spend ~$200 million on research this fiscal year, and Congress recently approved $300 million for type 1 diabetes last week. The results from the 450-patient JDRF CGM trial results will be available "very soon."
- **Closed loops with handheld devices are the next step**. Several researchers, including Dr. Stuart Weinzimer and Dr. Fouad Kandeel with the MiniMed closed loop system and Dr. Claudio Cobelli with the Navigator/OmniPod closed loop system remarked that next steps are clinical trials with smaller sensors, wireless transmission of data, and algorithm control via an ambulatory handheld controller rather than inpatient laptop controllers. We'll be excited to see 'real-life' data on closed loop systems.
- **Auto shutoff will offer improved safety for pumps and better glucose control for the artificial pancreas**. Dr. Buckingham presented an initial study he has performed to look at the feasibility and safety of basal rate shut-off as a method of avoiding hypoglycemia. The pilot study with 22 subjects used two different prediction alarms, where the basal rate was suspended for 90 minutes if both alarms detected impending glucose <80 mg/dL in the next 30 minutes. This had a 60% success rate, with no rebound hyperglycemia. An ongoing follow-on study is using five different prediction algorithms, with the basal rate to be suspended if three of them go off. During Q&A, Dr. Bill Tamborlane prompted Dr. Buckingham to point out that there is no harm in having an insulin pump that automatically turns off as a last defense if the glucose falls <60 mg/dL – in fact, this could help prevent hypoglycemia-induced seizures.
- **Pre-meal priming boluses are a hybrid step on the way to the closed loops**. Dr. Weinzimer has shown with his pediatric closed loop study with the MiniMed PID algorithm closed loop that glucose control on the closed loop is superior to traditional open loop systems, and use of manual pre-meal priming boluses improves prandial glycemic excursions but still results in post-prandial hyperinsulinemia after meals. He explained that pump users today have a basal rate so they're always safe, even if they forget to bolus, but they won't have as good control if they don't bolus. The hybrid loop is the same idea – you'll have better control if you use a priming bolus but you'll still have some closed loop control if you do not.

- **Dr. Edward Damiano presented data from bi-hormonal (double pump) closed loop studies he has performed with diabetic pigs, which suggest that good control can be achieved with insulin and glucagon**. Interestingly, he said that he did see a bit better performance in his pig studies in the efficacy of Lilly's glucagon over Novo Nordisk's, but this observation has been limited to doses that are much smaller than the standard rescue dose described in the product labeling. He is now conducting a 27-hour closed-loop human clinical trial on adult subjects with type 1 diabetes at Massachusetts General Hospital (MGH) with Drs. David Nathan and Steven Russell . They are sampling IV glucose values every five minutes with the GlucoScout, using Deltec pumps, and have an algorithm (that they tested in their pig studies) that controls insulin and glucagon infusion every five minutes. They are also testing the Guardian, Navigator, and DexCom concurrently. Dr. Damiano reaffirmed, based on his experiences with his son with type 1 diabetes, that a counter-regulatory hormone will be necessary to achieve tight closed-loop control, given the delays in interstitial glucose sampling and insulin absorption. During the panel discussion, Dr. Sherwin agreed that glucagon is a good way to avoid hypoglycemia but expressed concerns with the size of the device that would be necessary to achieve this.
- **Dr. Claudio Cobelli discussed two ongoing studies at the University of Virginia and at the University of Padova, Italy with the Navigator and OmniPod closed loop**. He said there is excellent overnight control with the algorithm with no rescue carbs or hypoglycemia. There are margins for improvement during breakfast, however. He noted that *in silico* experiments accelerate the development of closed-loop control algorithms by bypassing animal trials and enabling the initiation of clinical trials more quickly. In turn, the accumulation of clinical data refines the available data for computer simulations going forward – the *in silico* models are held at JDRF and available to other researchers as well.
- **Dr. Boris Kovatchev explained that *in silico* experiments allow us to test the robustness of control algorithms and accelerate the development of closed loop**. The current simulator has 300 subjects and has been accepted by the FDA as a substitute to animal trials for studies meeting certain criteria, e.g. including a population that is covered by the population of simulated "subjects". It can be used by anyone in the JDRF consortium. It includes simulation of all three CGMs and two insulin pumps: the OmniPod and Deltec Cozmo. Dr. Kovachev said that it is intended to allow testing of algorithms in extreme conditions, for example, the complete discharge of a pump. Various meals can be tested. Some audience members, including Dr. Tamborlane, seemed concerned about the model during Q&A and questioned its ability to simulate real patients. His main concern appears to be that the requirement to even go through a simulator was slowing down approval to do carefully controlled CRC studies in human subjects that would tell a lot more than a simulation can. However, in speaking to him directly, he let us know that he thinks that this is becoming less of a problem. Dr. Francis Doyle jumped in and commented that the point of the tool is not to be a perfect simulation of real life, but as long as it's sufficiently challenging, it can challenge the algorithm, which is how engineers can learn to improve their algorithms.
- **Dr. Aaron Kowalski stated that his takeaways from the sessions on closed loop clinical trials were**: 1) closed loop control with subcutaneous sensing is possible and better than open loop control, and that in fact, the open loop control in these trials was probably better than normal control in real life anyway, and 2) that this field has been held up significantly by shooting for perfection. There are significant sequential things we can do, such as turn off a pump when someone is low, or control basal rates, and Dr. Kowalski stated that he believes progress will be in incremental steps. He urged participants not to be delayed by trying to achieve perfection.

- **Dr. Robert Sherwin stated that we need controlled trials to show that the closed loop reduces hypoglycemia in the outpatient setting**. It's unrealistic to think we'll totally avoid hypoglycemia. The hope is that we can reduce it statistically. To that end, he proposed that hypoglycemia should be quantified with a composite index: 1) number of severe hypoglycemia events, 2) the percent of time spent <50 mg/dL, and 3) the area under the sensor curve for hypoglycemia excursions <70 mg/dL. The general consensus during Q&A is that we should not quantify hypoglycemia by symptoms because symptoms may increase with better control (less hypoglycemia unawareness).
- **Dr. Sherwin's criteria for a successful closed loop would be**: for patients with A1c >7%, a significant reduction in mean BG measured by a sensor and/or A1c, reduction in frequency and severity of hypo, and restoration of symptom awareness. For patients with A1c <7%, no worsening of mean BG measured by a sensor and/or A1c, reduction in frequency and severity of hypo, and restoration of symptom awareness.
- **Similarly, Dr. Weinzimer argued that closed loop is a clinical intervention and should be judged by clinical endpoints**: mean BG, time in target, reduction of postprandial excursions, and minimization of hypoglycemia. Statistical measures such as variability and high and low blood glucose indices are best used to refine algorithms – they should not be used to approve the devices.
- **Dr. Kovatchev emphasized the importance of glucose variability as a measure of success** – frequent hypoglycemia and hyperglycemia represents a failure even if A1c is acceptable. He explained that there are two primary dimensions to glycemic control: 1) time within target range, and 2) the acute risk of glucose fluctuation (measured by the Low Blood Glucose Index introduced in 1997). Thus, an evidence-based metric for assessing glucose control should include both of these dimensions. Dr. Weinzimer similarly pointed out that glucose variability matters – in the DCCT, patients with the most glucose variability had the highest risk of hypoglycemia.
- **There was some debate about the use of interstitial vs. blood glucose values**. Dr. Steven Russell argued that we should monitor blood glucose (not interstitial glucose) every 10 minutes to get the full picture of glucose dynamics, whereas the other speakers were generally optimistic about the ability of interstitial glucose to replace blood glucose as CGM becomes more accurate and we learn more about how to use it. In response to a question about which fluid he would sample if there were no cost or technical concerns, Dr. Sherwin answered that he would use blood glucose, not because it's a better marker of the brain, but because it gives faster information so the algorithm can respond faster. The rest of the panelists seemed to agree when he said, "I would want something that told me I was low before the brain actually got low. The advantage of blood makes sense, but I don't think it's so critical that it will prevent us from closing the loop."
- **Much work needs to be done before we can move to outpatient studies**. Dr. Russell listed five likely steps in clinical trial progression: 1) inpatient feasibility trials, 2) inpatient efficacy and fault tolerance trials, 3) bridging portable implementation trials, 4) closely monitored outpatient trials, and finally 5) pivotal home use trials. Currently, all of the trials being described are inpatient feasibility trials. So far, none of the systems under development have moved beyond the first step. Dr. Russell emphasized the importance of challenging the algorithm with things like big meals and exercise during step two, and using a supervised diabetes camp-like setting for steps three and four before performing true outpatient studies. In the panel discussion, the speakers agreed that exercise is a big problem because it changes insulin sensitivity – closed loop algorithms may need to react differently during times of exercise.

- **Behavioral scientist Dr. Timothy Wysocki gave a generally cautionary talk on all of the behavioral aspects that may prevent successful adoption of the closed loop**. In particular, beyond the fact that patients may not choose to use it, there are issues with patient selection, declining frequency of use over time, variability in adherence, and possibly decreased quality of life (alarms, increased responsibility, etc.).
- **Dr. Kowalski opened the second day of the meeting by saying that he strongly believes the first step toward the AP is a pump that shuts off when patients get low**. "I feel very passionately that we should not lose focus on near-term potentially significantly impactful movement in this field such as insulin pumps that turn off when people are low and automated basal control in the near term." The next step, said Dr. Kowalski, is an automated semi-closed loop and it needs to come a lot faster. After that we will drive to more and more automation, to a fully closed loop. Some possibilities include insulin plus glucagon, use of pramlintide, and applications in new onset diabetes and islet transplant patients.
- **Dr. Nelly Mauras gave an excellent overview of the effects of exercise- and insulin-induced hypoglycemia in children type 1 diabetes**. Notably, the counterregulatory responses to hypoglycemia are severely blunted - glucagon and cortisol do not rise during nighttime hypoglycemia, whereas rises in the level of epinephrine and growth hormone do not prevent hypoglycemia. Interestingly, pre-exercise blood glucose (<120 mg/dL) is the best predictor of exercise and post-exercise nighttime hypoglycemia. Dr. Mauras concluded that in designing closed loop systems, in addition to functional alarms warning for hypoglycemia, algorithms need to be tested that automatically decrease but do not disconnect insulin infusions during and immediately following exercise, and possibly that also automate concomitant glucagon infusions during the night following exercise. These algorithms should be tested for adolescents and even young children. She said she'd like to see if counterregulatory responses could be restored with closed loop control.
- **Dr. Howard Zisser presented some overseas data on the MiniMed Long Term Sensor System (LTSS), a combined pump and sensor that is implanted like a pacemaker**. The sensor lasts about one year and the pump must be filled with U400 insulin every 90 days. It sounds like there are significant engineering issues with this device, including large size, sensor delay, and invasiveness. Nonetheless, Dr. Zisser quoted one of his patients who said, "With the implantable insulin pump, I often forget that I have diabetes." Dr. Buckingham also commented that at his Diabetes Camp, 40% of children aged 8 to 18 years say they would prefer an implantable pump to an external pump.
- **Dr. Buckingham described the rationale for a new DirecNet/TrialNet study to look at the effect of metabolic control on the progression of type 1 diabetes**. This is a three-year study that will look at the effects of two years of intensive vs. conventional control in 108 new onset type 1 subjects aged three to 45 years. Intensive control includes three days of inpatient closed loop therapy (MiniMed Closed Loop system with PID algorithm) at diagnosis followed by outpatient sensor-augmented pump therapy. The primary outcome measures will be the difference between groups in C-peptide levels. Secondary outcomes include A1c, insulin dose, hypoglycemia, time in euglycemia, glycemic variability, etc. We note that this is somewhat similar to what the ORIGIN trial is studying in type 2 diabetes patients, though on a much more aggressive level.
- **Dr. Kenneth Brayman, a transplant surgeon, described the drawbacks of islet cell transplants and then postulated that there may be potential for a combined beta cell transplant/closed loop treatment for type 1 diabetes**. The idea is that closed loop control may reduce the number of islet transplants needed to avoid hypoglycemia and prolong islet

survival. This hypothesis was supported by *in silico* model testing. It will be interesting to see if this can be validated in human studies. Ideally, a fully functional closed loop would obviate the need for islet transplants, but we imagine that they could be a bridging step for achieving better control on hybrid systems.

- **During the first roundtable discussion, panelists agreed that a well-structured algorithm could be used for all patient subtypes** (children, ICU patients, transplant patients, etc.) as long as the parameters are fine-tuned to the individual. Dr. Kowalski asked panelists what they would like to see in the long term. Dr. Buckingham said: dual or triple chamber pumps with glucagon and Symlin, and devices that reduce surface area/weight such as a single insertion pump/sensor, integration with cell phones, etc. Dr. Zisser mentioned faster acting insulins (VIAject, microneedles, etc.) or anything that decreases delay time at the sensing or insulin delivery end of the equation.
- **Dr. David Klonoff emphasized that compatibility is key for a closed loop system**. The hardware must be interoperable between systems of different type, model, or manufacturer as well as resistant to electromagnetic interference. The software must perform flawlessly. The system must be designed to respond to non-glucose physiologic data. Telemedicine input must become incorporated into the system. We agree that compatibility will be key, though it has been elusive for BG meters and CGM so far - Dr. Klonoff said the Diabetes Technology Society is working on developing standards for this.
- **Dr. Jeffrey Joseph gave a dynamic overview of the need for better, less time-consuming glucose monitoring techniques in the hospital**. At Thomas Jefferson Hospital alone, 32,000 Accu-Chek measurements are taken every month, yet 10% of patients on anti-hyperglycemic medications experience hypoglycemia in the hospital. A real time CGM system on the general floor would be a great adjunct to fingersticks. Dr. Joseph mentioned the Nikkiso STG022 (Japan) and Glucostator (Germany), two AP devices currently available, as well as the VIA blood chemistry monitor for glucose (International Biomedical). The OptiScan and GluCath System (Glumetrics) are under development; Dr. Joseph said he was especially excited about the GluCath because its sensor works better in the hypoglycemic range.
- **Dr. Heather Pidcoke explained that despite intensive protocol implementation, it has been difficult to achieve ideal euglycemia range among the DOD's trauma patients**. Thus, the DOD is currently doing a three-phase multicenter trial on the AP. First they are evaluating FDA-approved products (GlucoScout) at seven participating institutions and hope to eventually move to a multicenter trial of open loop control. They expect 12,000 patients and 2,400 ICU admissions. Interestingly, Dr. Pidcoke said that they are testing DexCom's device in large animal models and are interested in talking to makers of other non-FDA-approved products for animal testing.
- **Dr. Cobelli spent some time explaining the rationale behind *in silico* testing again**, emphasizing that models are not real life but that an algorithm that doesn't work in *in silico* subjects will certainly never work in real subjects – it sounded like he was responding to the criticism of *in silico* testing we heard on day 1. He said that they plan to use *in silico* testing to look at islet transplantation and closed loop control, study the effects of counterregulation and exercise, and test the effect of dual chamber pumps with pramlintide. Dr. Cobelli called initial model data with pramlintide "very interesting" because it delays glucose entry into the system, but unfortunately ran out of time before he could discuss the data.
- **CLINICIP is a reproducible/standardized algorithm-based approach to intensive insulin infusion in the medical ICU based on blood glucose samples** (>2 hours between

samples). Dr. Hovorka showed data indicating that it is safe (0.004 hypos per 24 hours) and produces good control (>50% in target). He said that a commercial product is in development.

- **Biofouling is the accumulation of proteins and cells on the sensor surface and clogging flow**. Dr. William Reichert said that the problem with biofouling is the inability to predict whether a given implanted sensor will perform reliably or fail catastrophically. Dr. Reichert's recommendations for dealing with biofouling are to: 1) take a staged, multi-pronged approach to affect surrounding tissue, possibly with multiple layers of drug; 2) apply techniques that integrate the sensor into the tissue bed rather than "easy in/easy out" approaches, such as textured surfaces and fully implantable systems; and 3) apply modern imaging biology to sensor research so that we can see what is happening in vivo in real time.
- **During the final roundtable discussion, Dr. Klonoff, Dr. Cobelli, and Dr. Joseph all agreed that the sensor is the main barrier to the artificial pancreas right now. Dr. Klonoff suggested that the solution will be to use redundant sensors**. Dr. Reichert said that there's probably no way to avoid short-term (one to two day) inflammation and sensor drift, so calibration will be necessary during this period, but it may be possible to reduce it in the three to seven day range. Dr. Sherwin expressed concern that the 80 to 110 mg/dL range is too strict for in-hospital control. He believes it may be easier and safer to maintain in the 80 to 130 or 140 mg/dL range. Dr. Pidcoke agreed but said that going above 150 mg/dL is probably harmful, based on data from an unpublished VA study she has seen.

— by Kaku Armah

6. In the News: Perception of Diabetes in America

In collaboration with Novo Nordisk and the National Changing Diabetes Program (NCDP), Gallup surveyed the national public (n=2,015) on their attitudes and perceptions of diabetes. The hope is that with these results, future strategies can be developed to increase public awareness of diabetes. The goals of this study were to determine the following:

- *Knowledge, perceptions, and attitudes of the seriousness of diabetes as compared with other chronic diseases*
- *Knowledge of diabetes risk factors*
- *Perceptions of personal and family diabetes risk and actions to reduce risk*
- *Attitudes about diabetes prevention and self-care*
- *Attitudes toward public policy regarding diabetes prevention and treatment.*

In general, only 19% of adults follow diabetes news "very closely" with 36% following it "closely." According to the results from the poll, most adults do realize diabetes is a serious health condition that can be accompanied by multiple complications like neuropathy, nephropathy, retinopathy, blindness, and cardiovascular disease. However, it is still difficult to change people's behaviors, and greater steps need to be taken to teach the public about preventative measures that would stave off the development of diabetes. At the moment, there are around 42 million people with impaired fasting glucose or impaired glucose tolerance. People should start thinking about preventative measures because of the long period of glucose intolerance that precedes the development of diabetes. Furthermore, screening tests can identify people at high risk, providing a potential window for preventative therapy.

- **Most adults consider diabetes to be a serious health condition.** Overall, 94% of respondents considered diabetes to be serious at a national level with 46% considering it very serious and 48% considering it serious. They also agreed that it was increasing rapidly with 47%

strongly agreeing and 46% agreeing. Cardiovascular disease and cancer have traditionally dominated public perception of serious diseases, but according to the poll, 71% considered diabetes to be either more serious (15%) or as serious (56%) as heart disease; 69% considered diabetes to be more serious (20%) or as serious (49%) as stroke; 57% believe diabetes is more serious (14%) or as serious (43%) as cancer; and 57% see diabetes as more serious (22%) or as serious (35%) as AIDS. Both people with and without diabetes consider it to be a grave disease. Among people without diabetes, 71% disagreed with the statement "Diabetes doesn't concern me because I don't think I'll get it." We were pleased to see that people polled recognized diabetes as a serious health concern because historically public awareness of the severity of diabetes has not been as high as it has been for cardiovascular disease and cancer.

- **Many people agree that diabetes can have life-altering effects.** Of people without diabetes, 48% strongly agreed and 42% agreed that, "having diabetes would dramatically affect the way I live." Among those with diabetes, 41% strongly agreed and 42% agreed with this statement.

- **The majority of respondents have been tested for diabetes.** Encouragingly, 81% of respondents stated that they had blood work done to test for diabetes or high blood sugar when they visited their healthcare provider. Unfortunately, 71% did not recall the name of the test (i.e. blood glucose, A1c, fasting blood sugar, etc.). Out of those tested, 18% of African Americans, 8% of Caucasians, and 10% of Hispanics were told they have diabetes. In addition, 24% of African Americans and 17% of Hispanics were told they were at high risk for diabetes. In this group, 20% felt it was likely they would develop diabetes, 51% believed it was somewhat likely, and 27% thought it was not likely. Overall, approximately 23% of adults surveyed either have diabetes or are at high risk for developing diabetes. Among those without diabetes, 47% felt that they could be at high risk for diabetes, and 33% felt it was very likely (5%) or somewhat likely (28%) they would develop diabetes at some point in their lifetime.

- **Behavioral changes are difficult to institute and not all follow healthcare professionals' advice.** Most respondents received advice from their physicians, but many also got advice from a nutritionist (30%), a dietitian (22%), a nurse or nurse practitioner (21%), or other healthcare professional (22%). Among respondents, 79% said they were following advice to lose or control weight, 70% have increased physical activity/exercise based on physician recommendations, and 84% are working to reduce the amount of fat or calories they consume.

- **Most respondents were aware of obesity and weight as risk factors, but were less aware of race and ethnicity as risk factors.** When asked who was at risk for developing diabetes, 52% cited being obese or overweight with 32% putting family history as a risk factor. However, relatively few were aware that race and ethnicity were also risk factors: 11% knew being African American, Hispanic, or Native American increased risk for diabetes. Awareness was more prevalent amongst African Americans and Hispanics. People need to be made aware that weight and obesity are not the only risk factors that can lead to diabetes. For instance, Asians do not typically fit this category, and many Asians who develop type 2 diabetes are not necessarily over-weight.

- **In general, adults realize that severe complications can accompany diabetes but some confusion persists.** About nine in ten respondents knew that circulatory problems, blindness, amputation, and foot problems are complications of diabetes. Eight in ten adults knew that kidney disease, high blood pressure, and cardiovascular disease could be caused by diabetes. However, 20% incorrectly believed that cancer was a complication of diabetes, and 30% incorrectly believed that lung problems could result from diabetes. Interestingly, although most

adults know the various complications that can result from diabetes, hurdles still need to be overcome in order to get people to start preventative measures and stave off the development of this disease.

- **The general public (83%) believes there are things that can be done to prevent diabetes.** The most cited preventative measure was good nutrition and eating a healthy diet, which is what 56% of adults reported; 27% answered that a combination of exercise and diet could prevent diabetes, and 20% believed maintaining a healthy weight was important to prevent diabetes. The Diabetes Prevention Program (DPP) demonstrated that in people with prediabetes, there was a 31% risk reduction in developing diabetes when treated with metformin and a 58% risk reduction in developing diabetes when lifestyle changes were made. Lifestyle changes can have a huge impact on the prevention of diabetes, and more attention needs to be given to getting people to exercise and eat well.

- **Changes need to be made in the way healthcare is approached in schools and the workplace.** Physical education has been cut from many school programs, but 45% of adults strongly agree and 51% agree that schools should have a mandatory physical education program. Moreover, 40% strongly agree and 54% agree that there should be classes that educate children on healthy lifestyles. Going hand-in-hand with this suggestion, 32% strongly agree and 57% agree that schools should educate children specifically on preventing diabetes. In the workplace, the majority (81%) agreed incentives should be given to people who engage in healthy behavior while 17% disagreed. In theory, this point makes sense because employers save a great deal of money when their workers are healthy – not only by saving on medical costs but also by increasing productivity. According to a report compiled by the ADA in 2007, there were 15 million workdays lost, 120 million workdays with reduced performance, 107 million workdays lost to unemployment disability, and 445,000 cases of unemployment disability as a result of diabetes.

- **Disagreement exists over how to fund population wide diabetes interventions.** The survey asked the respondents about whether or not tax dollars should be used to educate the public about how a healthy lifestyle can prevent health problems, particularly diabetes: 21% strongly agreed, 56% agreed, and 22% disagreed on this point. The percentage of those who agreed significantly dropped when asked if taxes should be raised to support medical care for diabetes: 8% strongly agreed, 33% agreed, and 55% disagreed. Interestingly, people would be more inclined to raise taxes to fund preventative measures such as helping communities fund park paths and trails for walking: 15% strongly agreed to this plan, 45% agreed, and 38% disagreed. On the research side, it was split approximately in half with 51% supporting an increase in taxes to support medical research in diabetes and 46% disagreeing.

- **Physicians are the key source of information for people with diabetes, but the Internet is becoming another primary source of health information:** 68% of the public believes that current educational resources are adequate with 27% thinking they are inadequate. Overall, the physician is the most cited source of information (51%) with the Internet (41%), television and radio (39%), and magazines and periodicals (37%) cited as additional resources. The physician plays an even more prominent role for those with diabetes as 72% chose the physician as their source of information versus 30% choosing the Internet. Among those at high risk for developing diabetes, only 56% chose a physician as a source of information while 47% chose the Internet. As mentioned by Janis Roszler, “The problem is that there are millions of people with diabetes, and only thousands of educators. The main hurdle right now is to find ways to take our voices beyond the face-to-face encounter with patients,” and she points out technology and mass media are among the key tools to educate (see page 24 for more details).

- **Greater steps need to be taken not only to make the public aware of diabetes and the accompanying complications, but to also encourage beneficial lifestyle changes.** If changes are not made to the way we live today, serious problems will develop in the future. As Dr. John Andrew Sapala recently said at the AADE 2008 conference, "Surgeries and drugs can do a lot to improve one's condition, but the best medication is a healthy lifestyle. The most important medicine that we take today is what we put in our mouth: food."

— by Melissa Tjota

7. In the News: Children With Diabetes—Friends for Life 2008

July 23-27 • Orlando, Florida • http://www.childrenwithdiabetes.com

We recently attended the 2008 Children With Diabetes—Friends for Life conference held July 23-27 in Orlando, Florida. Session topics included introductions to relatively new technologies like continuous glucose monitoring (CGM), practical reviews about how to use monitoring and pumps to address difficult care decisions, and discussions of current research on islet transplantation and immunomodulatory agents. Events for children of all ages were run concurrently with the sessions.

We were pleased to note that parents of type 1 patients, or at least the particular subset of these patients who were in attendance, seemed to be extremely well informed about the management of their child's diabetes. Most audience members were familiar with CGM technology, even if their child was not using it, and understood how to deal with common insulin delivery. Few parents had considered the use of Symlin, and there was a great deal of confusion about islet transplantation and immune modulation. Parents seemed disappointed by the lack of a clear path to a "cure," but they were optimistic about current research.

Speaker highlights from the conference:

- **Dr. Peter Chase presented data suggesting that the prevalence of type 1 diabetes is increasing at a rate of 3-5% each year.** An unpublished study in Finland demonstrated that antibodies indicating a predisposition for diabetes are present in children as young as three years of age. He encouraged participation in the TrialNet studies as a way of helping to define the epidemiology, natural history, and risk factors of type 1 diabetes. He also cautioned patients against taking animal research out of context, pointing to the need for definitive clinical research.

- **Dr. Norma Kenyon of the Diabetes Research Institute suggested that islet transplantation, particularly encapsulated islets used in combination with immunosuppressive therapy, has the potential to drastically change the course of diabetes.** According to her data, most of the approximately 700 patients who have had a transplant saw a reduction in insulin requirements. However, because of the severe side effects of immunosuppressive medications, she did not recommend transplants for anyone under 18. She also mentioned that the Institute has begun its own drug discovery program to investigate pathways of interest that it feels have been ignored by the pharmaceutical industry.

- **Drs. Eda Cengiz and Edward Damiano presented some interesting data regarding the development of closed loop systems.** Dr. Cengiz has seen encouraging results in an inpatient setting with an automated insulin delivery system, and Dr. Damiano showed data from his prototype insulin/glucagon combination closed-loop system.

- **Dr. Bruce Buckingham gave some practical suggestions about how to deal with common situations in diabetes management using a pump and CGM.** The most important thing to take away from this session in our view is that many patients do not know how

to deal with difficult treatment decisions, and they could benefit from additional training with their pump and/or CGM device.

- **Very few parents of children with type 1 have considered using Symlin to control their child's diabetes or improve their glycemic variability.** Dr. Kim Kelly spoke about the importance of glycemic variability; this alternative measure of glycemic control is coming more and more into the public eye. Of particular note was Dr. Kelly's recommendation that type 1 patients who are having trouble controlling variability consider the use of Symlin. Of the audience members, nearly all parents of children with diabetes, almost no one had considered using the drug.

— by Kaku Armah, Brendan Milliner, and Melissa Tjota

8. Conference Preview: EASD Annual Meeting

September 7-11 • Rome, Italy • http://www.easd.org

From what we've seen of the program, EASD 2008 looks to be another stellar conference with plenty of new research to be gleaned in the oral sessions as well as a number of fascinating symposia to attend, both in the official program and the corporate-sponsored and non profit organization-sponsored satellite program. See below for our list of the most cutting-edge corporate symposia (on late stage pipeline drugs), our favorite general sessions for each day of the conference, and our top seven picks for oral presentation sessions. See you in Rome!

Satellite Symposia:

- **Saturday 16:00-18:00 Sheraton Roma Hotel—Merck** is sponsoring a session on obesity which will include an update on taranabant, the company's CB1 receptor antagonist.
- **Sunday 10:00-12:30, 14:30-17:00 Spallanzani Hall—GSK** is sponsoring two sessions on Sunday: a morning symposium on long-acting GLP-1 mimetics with a focus on its candidate albiglutide, and an afternoon symposium on TZDs with a focus on combination therapy.
- **Sunday 10:00-13:00 Guilia Hall—Amylin** will be holding a morning session on neurohormonal strategies for diabetes and obesity – we're excited to hear about INTO here.
- **Sunday 10:00-12:30 Iustina Hall, 14:30-16:30 Domizia-Euphemia Hall—BMS/AZ's** two Sunday sessions will focus on DPP-4 inhibitors (saxagliptin) and SGLT-2 inhibitors (dapagliflozin), respectively.
- **Sunday 14:00-17:30 Baebiana Hall—D.G.M.P. srl** is sponsoring several sessions focused on type 1 on Sunday, including an afternoon session on diabetes technology.
- **Thursday 14:30-16:00 Celcus Hall—Servier** is sponsoring a presentation of the ADVANCE study trial results. While the data have already been previously released at ADA in June, it will be interesting to hear the international interpretation of the study findings.

Official Symposia:

- **Monday 16:30-17:30 da Vinci Hall—Oral antidiabetic agents and recent endpoint trials**: We look forward to hearing about the ADVANCE trial, followed by a UK-focused lecture on "glycaemic control: how intensive?" We worry that in the wake of ACCORD the answer will be 'not very', but hope that this session will prove otherwise.

- **Tuesday 9:00-10:30 da Vinci Hall—Balloon debate: Step 2 of the EASD/ADA therapeutic algorithm: Are all drugs equal?** The title of this session sounds almost like a leading question! Four eminent speakers will debate the merits of sulfonylureas, TZDs, insulin, and incretins, respectively. This is a session not to be missed.
- **Wednesday 9:00-10:30 da Vinci Hall—UKPDS 30 year data and Veteran Affairs Diabetes Trial**: We're very interested in hearing the newest from the UKPDS follow-up, as well as a critical evaluation of the results of the VADT trial initially presented at ADA (the microvascular results of the trial will be presented at EASD for the first time).
- **Thursday 9:00-10:00 Morgagni Hall—Michael Berger Evidence-Based Medical Debate: Preventing type 2 diabetes—lifestyle versus drugs**: The age-old question will be debated by Dr. Paul Zimmet (drugs) and Dr. Nick Wareham (lifestyle). Our opinion continues to be that for now lifestyle is the best in theory but drugs are easier to implement in practice.

Oral Presentations:

- **Monday 10:45-12:15 Riva Rocci Hall—OP 3 Continuous glucose monitoring system**: This session will include presentations on the use of CGM in pregnancy as well as data on the GlucoDay system.
- **Monday 14:45-16:15 da Vinci Hall—OP 7 Novel oral agents for type 2 diabetes:** This will include talks on novel insulin sensitizers, dapagliflozin, glucokinase activators, and more.
- **Tuesday 10:45-12:15 da Vinci Hall—OP 13 DPP-IV inhibitors:** Two-year sitagliptin data, vildagliptin in renal impairment patients, alogliptin combinations with glyburide and insulin, and saxagliptin + metformin initial therapy data will be shown here.
- **Tuesday 14:45-16:15 Riva Rocci Hall—OP 21 Incretins: action and secretion:** This is a more basic science oriented session on GLP-1 and other incretin research.
- **Wednesday 10:45-12:15 da Vinci Hall—OP 25 GLP-1 based therapies:** Sanofi-Aventis' AVE0010, exenatide once weekly, and liraglutide data will all be shown here. Notably there is also a session on the surgical treatment of non-obese diabetic patients.
- **Wednesday 14:45-16:15 da Vinci Hall—OP 31 Insulin and analogue treatment:** This includes a talk on closed-loop control for the device enthusiasts, as well as presentations on detemir, insulin initiation, and basal-bolus regimens.
- **Thursday 10:15-11:15 Morgagni Hall—OP 38 Prevention of type 2 diabetes:** This session will include discussions of the STOP-NIDDM (alpha glucosidase inhibitors) and ACT-NOW studies (pioglitazone) on diabetes prevention.

— by Jenny Jin and Melissa Tjota

9. Diabetes Comings and Goings

- **Quentin Roach** has been named Senior Vice President and Chief Procurement Officer of Bristol-Myers Squibb.
- **Dan Troy** was named Senior Vice President and General Counsel for GlaxoSmithKline.
- **Donald J. Kellerman, PharmD,** was appointed Senior Vice President, Clinical Development and Medical Affairs at MAP Pharmaceuticals.

- **Andreas Fibig** was appointed Chairman of the Board of Management of Bayer Schering Pharma.
- **Randall Moreadith, MD, PhD,** was named Senior Vice President of Drug Development and Chief Development Officer of Nektar Therapeutics.

10. Stock Chart

	22-Aug-08	22-Jul-08		2-Jan-08		22-Aug-07		IPO		Market Cap
GSK	46.39	48.55	-4%	50.17	-8%	51.48	-10%	-	-	121.52B
NVO	57.96	62.73	-8%	63.8	-9%	54.57	6%	-	-	42.07B
AMLN	26.58	28.57	-7%	36.95	-28%	49.83	-47%	14	90%	3.65B
BIOD	18.19	15.95	14%	22.65	-20%	17.66	3%	15	21%	430.51M
OREX	11.76	8.49	39%	13.94	-16%	14.02	-16%	12	-2%	403.63M
PODD	13.59	15.42	-12%	23.42	-42%	16.99	-20%	15	-9%	376.55M
MNKD	3.29	2.93	12%	7.86	-58%	9.01	-63%	14	-77%	334.26M
DXCM	6.37	7.67	-17%	8.95	-29%	9.19	-31%	12	-47%	189.05M
HDIX	9.77	8.09	21%	8.45	16%	9.35	4%	12	-19%	172.23M

The performance of health care stocks is often independent from the business cycle and this past month is another good case in point. The credit markets are under severe stress, the banking sector is gasping, and the markets are nervous ... but not so nervous that stocks like OREX (up 39%), HDIX (up 21%), and BIOD (up 14%) couldn't post solid returns. That said, it wasn't all rosy as some stocks paid the familiar price for appearing to disappoint investors. Health care is likely to remain a safe haven for the foreseeable future, but the prevalence of fear and desperation on the Street suggests that companies seen as disappointments will be heavily punished, while companies posting good (and especially better-than-expected) news may see outsized rewards.

Diabetes Close Up is a newsletter distributed eleven times per year highlighting notable information and events related to the business of diabetes. Subscription information can be found on our website www.closeconcerns.com. This newsletter is put forth as an unbiased commentary on the industry and is not meant to serve as a recommendation to buy or sell (or hold!) any stocks. Companies that are current purchasers of Close Concerns' healthcare information include Abbott, Alkermes, Amylin, Bayer, Becton Dickinson, Biodel, DexCom, Insulet, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, and a number of private companies.