DIABETESCLOSEUP

The Leading Source of Diabetes Business News

Ups and Downs **September 2008 • No. 83**

From the Editor

We often talk about the highs and lows in diabetes in reference to blood sugar levels, but they could also describe the current economic rollercoaster. For every positive, there seems to be a negative – for any given breakthrough in one lab, there seems to be a set back in another lab. Those thoughts come to mind in reviewing DCU this month as it was full of both positive and negative sentiment.

On the positive and inspired and inspiring end, we had an amazing interview with ADA 2008 Outstanding Physician Clinician Dr. Anne Peters. We are blown away, in particular, by her focus on improving care and treatment for underserved populations. This is by far the biggest need in diabetes today in our view. Such a focus was inspired by her experience in elementary school when Dr. Peters discovered the connection between illness, education, and poverty – a boy she wanted to teach to read kept missing class because he was sick – and that experience motivated her to treat the underserved today in East Los Angeles. Likewise, we had an informative conversation with Dr. Ken Moritsugu, former Assistant Surgeon General of the US and now Vice President of Global Strategic Affairs at J&J's Diabetes Franchise, about the new opening of JJDI in Beijing. This conversation was followed by our attendance at the JJDI opening in Paris last week – how the institute is inspiring healthcare providers in Europe, the Middle East, and Africa. The Institute itself, right in central Paris, is gleaming and shiny and there is a real buzz around it – just the place to inspire the hardest workers of anyone in diabetes, the healthcare providers.

Also on a positive note, September was also filled with new data releases that highlight the movement forward in diabetes therapies and technologies. At EASD 2008 we were encouraged by results released on the UKPDS legacy effect of early treatment (more on that in our EASD review next month) and the results from the JDRF continuous glucose monitoring (CGM) study. The original results of the UKPDS published in 1998 have had a huge impact on the treatment of type 2 diabetes in the past decade, and we believe the new results released at the conference will ensure that the UKPDS continues to significantly influence on the way diabetes is treated. The most important thing emphasized by Prof. Rury Holman was the legacy effect of intensive glucose control and intensive metformin therapy. The follow-up study demonstrated a 'metabolic memory' effect, showing that glycemic control can have a lasting effect even after A1cs and other metabolic parameters from all study arms have come together. These results should have a particularly positive clinical and commercial implication for the treatment of pre-diabetes and early intensive and/or combination therapy. We also think it should do a lot to promote the concept for patients to try to avoid cardiovascular disease at all costs.

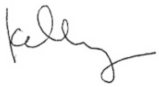
The results from the JDRF CGM trial were also landmark, demonstrating for the first time that CGM can clearly lower A1c by a significant amount in a six-month time frame in people that wear the sensors (on average, those who wore the CGM most frequently, adults, saw a 0.5%-plus reduction in A1c from an average baseline of 8.0%). CGM could provide several benefits for patients who are motivated, have

a good understanding of the basics of insulin therapy, have little fear of new technology, and have great access to education. While these results are encouraging, we also know that optimizing CGM therapy requires a robust clinical infrastructure and will benefit from greater ease of use (it's all about comfort level with the technology and being educated on knowing what to do with the numbers) - here's to further building.

On the downside, we were disappointed that the FDA seems intent on moving at a glacial pace for reviews on new drugs and is putting, in our view, unrealistic burdens on applications. Early this month, the New England Journal of Medicine published an incongruous editorial by Allison Goldfine, MD (Joslin Diabetes Center, Boston, MA). In her editorial, Dr. Goldfine defends the advisory panel's position in favor of cardiovascular requirements and proposes a specific integrated clinical development program with a separate pre-approval and post-approval component. Her proposal is for all new diabetes drugs to rule out an "unacceptable" level of cardiovascular risk in a pre-approval cardiovascular outcomes trial, followed by a longer post-approval clinical trial to more clearly establish cardiovascular safety or benefit. We remain concerned that the implementation of Dr. Goldfine's integrated trial design proposal could have wide-reaching negative consequences on the progress of drug development and creating better alternatives for patients – especially nearly ten plus million of them whose diabetes is out of control in the US alone. We worry about this proposal increasing up-front costs, detracting attention away from the microvascular complications, and delaying potentially beneficial drugs. Overall, it would be a negative for patients, healthcare providers, payors, and taxpayers. We worry that a combination of fear and timidity would stall the advancement of new products that could really improve diabetes care, treatment, and management.

Also on the downside, we know firsthand the economy is hurting patients. We have received hundreds of letters from diaTribe (our patient newsletter – see it at http://www.diatribe.us) readers about their pain associated with buying less medicine because they need to pay more for gas or food. This is a time of hard choices and that patients are bearing more upfront costs through higher deductibles and bigger co-pays is disturbing – and these are the patients that have insurance. It's not right.

Over the long run, we hope that the tide will turn and that positives will outweigh the negatives, but the pathway will never be direct or easy. That's research. That's science. That's diabetes. And that's life.



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/

- **September 14:** JDRF continuous monitoring trial receives big win — reported in Europe and published in the prestigious *New England Journal of Medicine*
- **September 9:** Check it out — Tour Now Then
- **September 9:** The modern man's guide — new men's health diabetes education campaign
- **September 9:** Sweet Home Alabama — "Does your conscience bother you?"
- **September 5:** Hitting the panic button — diabetes, Byetta, and pancreatitis
- **September 4:** Gila River Indian Community hopes water will wash out diabetes epidemic

Videowatch

See below for our favorite video since our last monthly newsletter. Check it out, Discovery Health is asking people for their stories about living with diabetes and what changes need to be made.

- "Life with Diabetes"
  http://www.youtube.com/watch?v=kWW40l4Yjd8&feature=dir

Coming soon in DCU…

We're very excited for the 20th Annual Scientific Meeting of the Obesity Society (formerly known as NAASO). The meeting is taking place in Phoenix from October 3-7 (see obesity.org) and is followed by the Third Annual Cardiometabolic Meeting taking place in Boston on October 15-18 (see cardiometabolichealth.org). We also can't wait for earnings season to start in mid-October. Stay tuned…

1. Quotable Quotes in Diabetes

"The focus on macrovascular outcomes has led us to forget about what blindness does to our patients and what kidney failure does to our patients. Let us not forget about microvascular outcomes."

— Steven Kahn, MB, ChB (University of Washington, Seattle, WA) reminding the audience of the importance of microvascular risk at the GSK symposium on GLP-1 mimetics at EASD 2008.

"If you treat patients early, you have extended benefit. You cannot wait to treat diabetes and should start treatment as soon as it is diagnosed. You will get added benefit by treating people early before waiting for them to get complications or waiting until glucose levels are extremely high."

— Rury Holman, FRCP (University of Oxford, Oxford, UK) commenting on the clinical implications of the legacy effect of earlier glucose control and metformin therapy seen in the ten year follow-up results from the UKPDS released at EASD 2008.

"There will be some who say glucose lowering is not cost effective, there will be some who say that the 7.5% target is adequate without saying for whom, there are those who will say that we should just focus on lipids and blood pressure, and there are those who will become famous for saying almost anything, but loudly."

— David Matthews, PhD (University of Oxford, Oxford, UK) reflecting at the end of EASD 2008 on the confusion generated by the "trial rollercoaster" (i.e., UKPDS, PROactive, UGDP, ACCORD, ADVANCE, etc.) in determining the best way to treat diabetes.

"We have not made much progress since Hippocrates (460-377 BC), the father of medicine, who observed that, 'Persons who are naturally fat are apt to die earlier than those who are slender.'"

— Eberhard Standl, MD (Munich Diabetes Research Group, Munich Germany) during the BMS/AZ symposium on SGLT-2 inhibitors at EASD 2008.

"Diabetes patients are at a 2-3 times higher risk of pancreatitis vs. the background population because they are more obese. In all of the exenatide studies, there was no signal of pancreatitis. However, once it goes on the market, statistically speaking, people on the medication will develop pancreatitis. At this stage it's difficult to assess if exenatide is related to a higher rate of pancreatitis, but I don't believe there's any evidence at this point that it is."

— Bernard Zinman, MDCM, FRCP, FACP (University of Toronto, Toronto, Canada) referring to the recent worry that use of GLP-1 mimetics leads to an increased risk of pancreatitis during the LEAD-4 results announcement at EASD 2008.

"I think [overdosing on DPP-4 inhibitors] would be a very poor choice for someone who wanted to do themselves harm."

— Mark Gorell, PhD (University of Sydney, Sydney, Australia) answering a hypothetical question about a suicidal patient taking 100 pills of a DPP-4 inhibitor and emphasizing the safety of DPP-4 inhibitors during his presentation at EASD 2008.

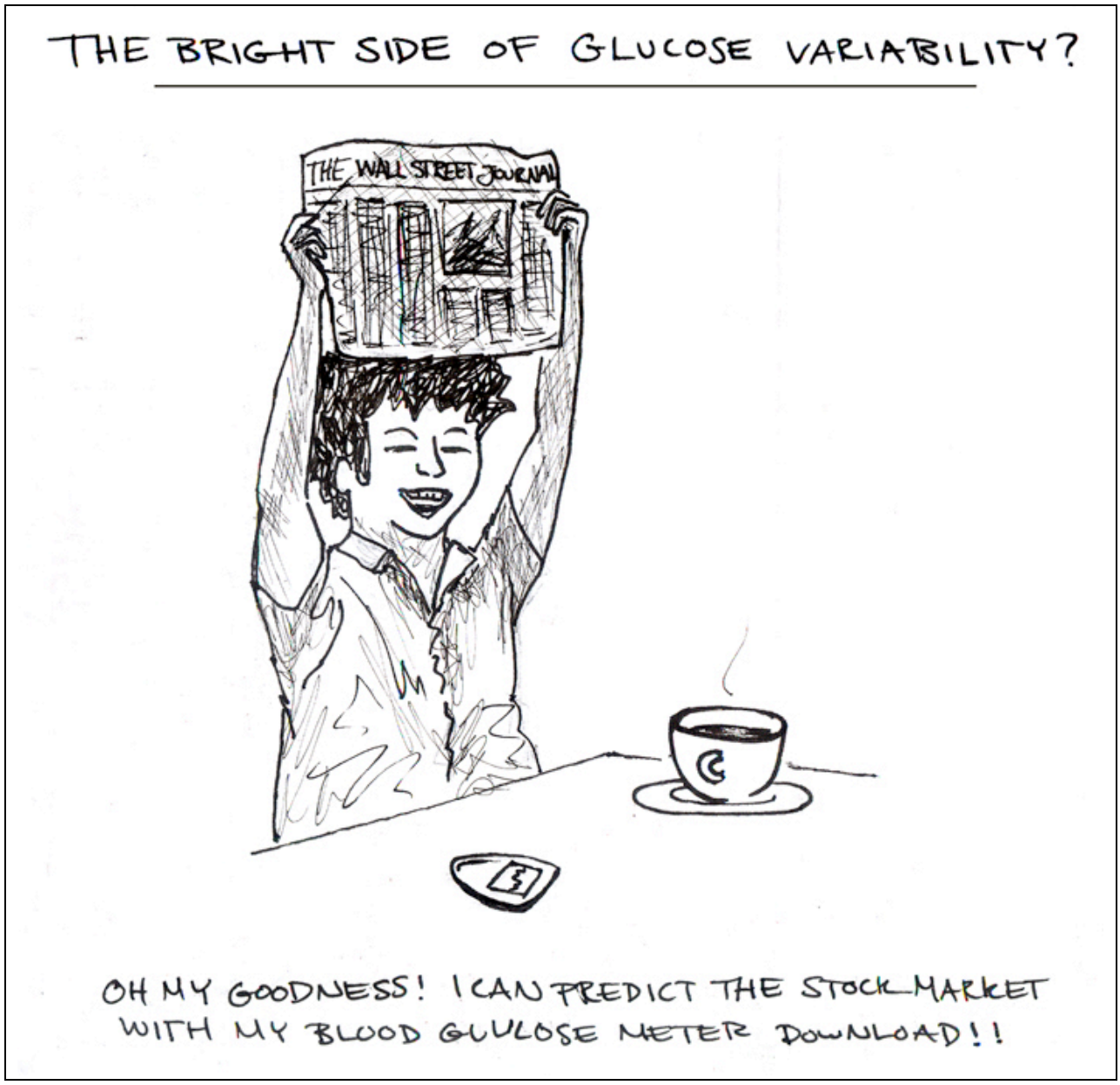
"One day we may be able to prevent obesity by a specific, short-term modification in early postnatal life wherein pre-conditioning for the development of obesity seems to be set."

— Thorkild Sørenson, MD (Copenhagen University Hospital, Copenhagen, Denmark) expressing his dream of early prevention of obesity at the Cleveland Clinic's Obesity Summit 2008.

"I think there will be a lot of advancements in the care of people with diabetes, but people have to remember there is not going to be a magic bullet to fix everything."

— Anne Peters, MD (USC Clinical Diabetes Program, Los Angeles, CA) commenting on the biggest changes in diabetes care and treatment during an interview with DCU.

2. diaTribe FingerSticks



— by Daniel A. Belkin

3. DCU Company Watch

- **EnteroMedics — Top-line data reported for EMPOWER:** On September 26, James Toouli (Flinders University, Adelaide, Australia) announced new data for two feasibility studies, VBLOC-RF1 and VBLOC-RF2. As a reminder, VBLOC therapy is a relatively new technique aimed at treating obesity by blocking the nerve signaling in the vagus nerve between the stomach and the brain. EnteroMedics' VBLOC therapy is delivered through a pacemaker-sized device using high frequency, low energy electrical pulses. In doing so, the therapy attempts to produce appetite suppression, feelings of fullness and corresponding weight loss. Dr. Toouli presented results from the ongoing

studies on VBLOC by focusing on two key co-morbidities of obesity: type 2 diabetes and hypertension. These results were presented at the 13th World Congress on Obesity Surgery of the International Federation for the Surgery of Obesity and metabolic disorders (IFSO).

The study found that VBLOC therapy resulted in significant improvements of A1c levels in patients (N=6) with type 2 diabetes. Patients had a mean BMI of 41.5 at the start of the trial. There was a statistically significant 1.3% reduction in A1c levels (from 8.7% baseline, p = 0.01) after one month of VBLOC therapy. This reduction was durable after six months with a mean A1c reduction of 1.7% (p = 0.03). We regard these data with interest although upon learning during Q&A that one of six participants had a drop in A1c from 12% to 8%, we are more interested in seeing a larger trial and learning more about variability in results. Regarding the other feasibility trial, we learned both systolic and diastolic blood pressure showed significant improvement (N=19).

In addition to the currently ongoing EMPOWER study, Dr. Toouli announced the initiation of a new feasibility trial for diabetes titled the ENABLE study. This randomized, double blind, placebo-controlled clinical trial will attempt to recruit 40 subjects at four study centers outside the United States. The study will evaluate the effects of VBLOC therapy at 1, 6 and 12 months. That trial is currently enrolling and the company expects enrollment to be completed before the end of this year. A larger trial will be great to see since the numbers for this one are hard to assess. Dr. Toouli said that comparable drugs on the market have only been shown to reduce A1c levels by 0.8% after 30 weeks; actually, recently-published data in *The Lancet* (initially announced in October 2007) showed Byetta prompting a 1.5% A1c reduction from a slightly lower baseline. Insulin of course has also shown greater response. One caller commented on the present troubled market and asked about the company's financial situation. CFO, Gregory Lea, answered that the company has "enough cash for 2009". Management also said it expects the CE mark by the end of the year. Sadly, for EnteroMedics, VP of Medical Affairs and Chief Medical Officer Dennis Kim recently left the company for Orexigen, where he is Senior Vice President, Head of Obesity and Metabolic Disorders.

- **Johnson and Johnson — Opening of JJDI in Paris:** J&J opened JJDI (Johnson & Johnson Diabetes Institute) in Paris on September 25. Once again, we were blown away by J&J's response to the threat of diabetes. JJDI-Paris is a gleaming, new state-of-the-art center, and we were lucky to speak to several healthcare professionals who had already gone through pilots in the new center and spoke encouragingly of the high degree of patient understanding that JJDI Paris showed in the new curriculum. Like at JJDI in Silicon Valley, the healthcare provider is at the heart of the center although patients figure prominently as well. Just noting the small, undoubtedly welcome detail of having child-sized tables and chairs for weekly meetings with newly diagnosed children and their parents. Overall, JJDI represents a long-term effort to arm doctors and nurses on the front lines in providing diabetes care through the latest information and practical skills to aid patients in living longer, healthier lives. In an interview on the JJDI Europe website (http://www.jjdi.eu), Dr. Ken Moritsugu says, "In short, some of the greatest barriers lie in communication and in health literacy—the acquisition and maintenance of up-to-date knowledge about diabetes on the part of the health professional, and the communication of this knowledge to their patients, so that those we serve hear, understand, embrace, and put into action the information and guidance we health professionals provide…"

  The opening of JJDI Paris was fascinating. Beyond tours of the new center, there was new data given from an intriguing survey authored by British powerhouse endocrinologist Dr. Anthony Barnett called "Diabetes: Tipping point or turning point?" (See Closer Look for a copy of our analysis of this report.)

- **XOMA — Update provided about anti-IL1 beta monoclonal antibody (XOMA 052):** On September 25, Xoma held its analyst day meeting focused on Interleukin-1 blockers. Steve Engle,

Xoma CEO, projected the diabetes market would make up 50-85% of the market opportunity presented by interleukin-1 based therapy (estimated at $7 billion to $12 billion) by 2020. Dr. Alan Solinger, VP Clinical Immunology, concluded the presentation by touching on the next steps for Xoma's IL-1 diabetes franchise. He mentioned finalization of dose regimens for XOMA 052 (monthly vs. every two months), evaluation of optimal beta cell preservation, as well as the positive effects of the candidate on other parts of the metabolic syndrome (CVD, obesity, hyperlipidemia, and hypertension).

On September 8 at EASD, Marc Donath, MD (University Hospital, Zurich, Switzerland) discussed the results from a phase 1 study for a single intravenous dose of the anti-IL-1 beta monoclonal antibody XOMA 052. This antibody has ultra high affinity for human IL-1beta and has a half-life of 22 days, allowing for once-monthly dosing. XOMA 052 utilizes the same strategy used in many anti-cancer monoclonal antibody biologic drugs such as Genentech's rituximab (rituxan), fusing an antibody against IL-1beta to the constant region of human IgG immunoglobin, which gives the antibody a long half-life and prevents rejection.

This phase 1 (n=48) dose-escalation study compared a single infusion of XOMA 052 to placebo. Six dose levels were included and for each dose level the six subjects were randomized to placebo (n=1) or active drug (n=5). They have completed the first three cohorts. Notably, baseline A1c was higher in the active drug patients (9.8%) than placebo (8.7%) and quite high to begin with, generally speaking. A1c dropped in a dose-dependent manner at day 28 ranging from -0.3% to -0.6%. Oddly, no beneficial effect was seen at the highest dose (1.0 mg/kg) – Dr. Donath said he was not sure why this was the case. The duration of diabetes was high in this group – 17 years – which may be a factor. In the 0.01 mg/kg and 0.03 mg/kg cohorts they looked at beta-cell function and saw improvements in glucose-stimulated insulin secretion at 28 days (+26% from baseline) and 91 days (+52% from baseline). A meaningful decrease in CRP was also seen at 28 days indicating improvement in systemic inflammatory status. Dr. Donath said that XOMA 052 could be a new therapeutic approach to type 2 diabetes by targeting inflammatory damage to beta cells. The next steps are to finalize the dose regimen, evaluate the ability to stop progression of diabetes, and to evaluate other aspects of the metabolic syndrome/diabetes. As a word of caution, while the side effects of powerful anti-inflammatory drugs are tolerated for diseases that are acutely debilitating, like severe arthritis, any increased risk of serious infection could make it very difficult to get this drug approved for diabetes.

- **Takeda – Submits Actos/DPP-4 inhibitor combo:** Takeda announced on September 24 that it has submitted an NDA application to market a fixed-dose combination of its DPP-4 inhibitor alogliptin (SYR-322) and pioglitazone (Actos) in the US. The NDA for alogliptin was submitted in January of this year, and it is awaiting approval in the US – we believe Takeda could hear back from the agency on this by year-end. As a reminder, Yashuchika Hasegawa, president of Takeda, had stated during the 1H08 earnings call his expectation that alogliptin would be on the market by the end of the year. If approved, the alogliptin/Actos combination will be only fixed-dose combination of a DPP-4 inhibitor and a PPAR available in the US. This combination therapy could be particularly interesting as Actos mechanistically works on insulin resistance while SYR-322 works on insulin secretion. As we noted in the June/July issue of DCU, the efficacy of alogliptin appears to be enhanced when it is used with Actos background therapy. In phase 3 results presented at ADA, alogliptin reduced A1c by 0.7% from a baseline of ~8.4% when used as an add-on to pioglitazone (relative to pioglitazone alone which produced an A1c drop of 0.5%). By comparison, the same dose of alogliptin was associated with an average A1c drop of 0.54% when used in monotherapy. If a lower fixed dose of Actos is used in the combination, the side effect profile would likely be better than Actos alone (less weight gain and edema, perhaps less association with congestive heart failure and fractures). We assume but aren't certain this would be a once-daily pill. Kudos to Takeda for striving to jump into the incretin wars

with both feet – in 2007, total incretin (Januvia franchise plus Byetta) sales were $1.4 billion, up from $470 million in 2006, and $75 million in 2005.

- **MannKind – Clearer picture of TI in phase 3, and a name emerges – Afresa!:** On September 16, MannKind released top-line data for its phase 3 study (N=565) comparing prandial Technosphere inhaled insulin (TI) with prandial insulin aspart (Novo Nordisk's Novolog) in patients treated with baseline insulin glargine (Sanofi's Lantus). CEO Al Mann later discussed the trial at length at the UBS Healthcare conference on Tuesday, September 23. Overall, the trial was positive in that it demonstrated significant weight loss, less mild-to-moderate hypoglycemia, and no effects on lung function. In other respects, the trial was disappointing: A1c results favored Novolog, and although the difference was not statistically significant, we had expected any edge in A1c reduction to go to TI; also, no information was provided on the rate of severe hypoglycemia in both groups. Post-prandial glucose results were a mixed bag (see below).

  From an average baseline of 8.5%, absolute A1c drops were 0.5% for Novolog and 0.25% for TI – we would have expected greater reductions though in part this is because Lantus is sub-optimized (meaning many patients come into a trial needing more Lantus than they are taking) in a trial like this. The TI group saw improvements in both fasting blood glucose and post-prandial glucose - we *were* very surprised even given likely sub-optimal Lantus dosing that this did not translate into a greater A1c drop. Specifically, fasting glucose declined to 140 mg/dL from 189 mg/dL in the TI group compared to a movement from 180 mg/dL to 160 mg/dL in the Novolog group. In several challenges, postprandial glucoses were 166-168 mg/dL in the TI group compared to 201-210 mg/dL in the Novolog group. We wonder what the three- or four-hour post-prandial results were – we think its possible clearance is too fast for TI. On the hypoglycemia front, fewer patients on TI experienced one or more mild-to-moderate hypoglycemic events (95%) compared to the proportion affected in the comparator group (99%) and although this was statistically significant, (odds ratio = 0.22; $p<0.02$), mild-to-moderate hypoglycemia is fairly accepted among type 1 patients as a "way of life," and we doubt most type 1 patients or providers would assess a difference of a 95% vs 99% chance of having a hypoglycemic event over a year as a significant difference. Disappointingly, no information was given during the conference call on the differences in severe hypoglycemia – we think payors really care about this measure for type 1 patients. On the safety front, TI did not affect lung function: although these results will need to be confirmed over a longer period of time before an effect on lung function can be firmly established. Notably, the TI group lost 4.3 pounds on average compared to a three-pound weight gain observed in those on Novolog. Overall, we certainly see the weight difference between groups as significant in the real world**.** Management said that more analysis is being done on the data to meet guidelines for reporting.

  Pfizer and MannKind announced a collaboration where certain Exubera patients who have a continuing medical need for inhaled insulin would be transitioned to TI. This agreement highlights Pfizer's attempts to distance itself from Exubera and focus on other areas of diabetes medications. Next steps are for MannKind to submit TI to the FDA, which is likely to happen either late this year (the original goal) or early next year. The company currently has $118 million cash in bank, and a $350 million personal credit line from Mann. That's a lot of credit.

- **Generex — Oral-lyn phase 3 clinical trial enrollment completed:** Generex announced on September 16 that it has completed enrollment for its phase 3 clinical trial of Oral-lyn, the company's prandial oral insulin spray. The study will look at 750 type 1 patients at centers in the United States, Canada, Bulgaria, Poland, Romania, Russia, and Ukraine. Given recent problems Biodel experienced with its VIAject data from centers in India, we can only say we hope for Generex's sake that the CRO (clinical research organization) is on a very tight leash. In the study, Oral-lyn will be compared to prandial injections of regular human insulin; the primary endpoint is change in A1c. Based on

previous trials of Oral-lyn showing similar kinetics to prandial regular insulin, we expect that efficacy will be similar to regular human insulin – we are interested in particular in more practical aspects of the oral insulin, such as how many puffs are needed, dosing, pricing, etc – these are the areas that could pose constraints, in our view, though as noted above, we do think the market would welcome practical alternatives. Whether or not they would be reimbursed is another question since they don't displace currently marketed insulins. In order to receive FDA approval, the company will look to demonstrate non-inferiority to regular insulin in phase 3. Oral-lyn has been approved in Ecuador and India. While there are clear questions about Oral-lyn in the real world, we are interested to see large-trial results.

- **Merck — Encouraging results for Januvia presented at EASD, including impressive pooled safety analysis:** One oral presentation and four posters were presented at this year's EASD conference examining the effectiveness of Januvia as combination therapy with other commonly prescribed diabetes drugs. The oral presentation (OP-73) showed two-year (104 week) data on initial combo therapy with metformin and sitagliptin. Type 2 patients underwent a 6-12 week diet/exercise run-in period and were then randomized to placebo 24 weeks/metformin 1,000 mg BID active therapy, sitagliptin 100 mg QD, metformin 500 mg BID, metformin 1,000 mg BID, sitagliptin 50 mg BID/metformin 500 mg BID, or sitagliptin 50 mg BID/metformin 1,000 mg BID. At 104 weeks, the A1c drop from a baseline of 8.5% for the five non-placebo groups was 1.1%, 1.1%, 1.3%, 1.4%, and 1.7% respectively- very strong results across the board. The proportion reaching A1c <7% ranged from 28% to 60%. We were very impressed with the trial design and execution – stratification analysis yielded quite strong results: average A1c drop was 0.9% for those with A1c <8% (mean 7.6%, n=123), 1.6% for those with A1c between 8% and 9% (mean 8.4%, N=146), and a very impressive A1c drop of 2.5% for those with A1c >9% (mean 9.7%, N=133).

  Merck continues to put together analyses to address outstanding questions, particularly on the safety front, where accumulating evidence, though still early, is notable. Poster #912 was a pooled safety analysis of 6,149 patients including 12 large double blind randomized phase 2b and 3 studies of 18 weeks to 104 weeks duration. This showed that Januvia/Janumet lead to fewer drug-related adverse events (4.8% less) because of less hypoglycemia – as at least severe hypoglycemia certainly adds costs to the system, even for some type 2s, and as severe hypoglycemia continues to be a condition feared by patients and providers, we thought this analysis was very smart to put together. We'll have more data in our EASD conference review this month.

- **Novartis — GALIANT study presented at EASD supports the clinical usefulness of Galvus vs. TZDs:** We were excited to see results for the head-to-head DPP-4 inhibitor/TZD trial announced. As a reminder, the GALIANT study investigated the effectiveness of Galvus compared to TZDs as add-on to metformin therapy in type 2 diabetes patients. In the three month study, Galvus was shown not only to be non-inferior to TZDs, but it was in fact superior to TZDs in reducing A1c with a decrease of -0.7% compared to -0.6% in the TZD group over the relatively short study period; we believe that the results would have been different however if the study had been extended, given that TZDs take longer to exert their maximal A1c lowering effects. Though the 0.1% difference in A1cs between the two groups may sound small, it's meaningful from the relatively low 8.0% baseline A1c and was shown to be significant at p=0.001. Notably, Galvus use was also associated with reduced weight, while TZD use was associated with increased weight (-0.58 kg [-1.23 lbs] vs. +0.33 kg [+0.73 pounds]). There were no significant differences between the two groups in terms of side effects, including hypoglycemia. This result is promising for Galvus, and the DPP-4 data that kept pouring in during this year's EASD was very positive for the class as a whole. We learned a great deal at EASD about Galvus – since it is not available or being pursued in the US, we hear less about it here, so it was nice to see updated data and hear thinking on the compound. To date, Galvus is approved in 18

countries and Eucreas (fixed dose once daily combo of Galvus and metformin) is approved in 10 countries. It seems safe to say based on Januvia franchise results that DPP-4 inhibitors are stealing share from most classes - this result is one of the most high-profile examples we have seen of a DPP-4 actually outperforming another oral drug in terms of A1c reduction in a head-to-head trial. That said, head-to-head trials can also be viewed as suspect. There's a precise science that goes into designing these types of trials to make the drug at hand look as good as possible – for example, through particular enrollment criteria or other aspects of study design. As noted above, we believe that the short study period and use of background metformin therapy (which is often found to be synergistic with DPP-4s) favored Galvus.

- **Amylin/Eli Lilly — 52-week DURATION-1 results compare once-weekly exenatide to twice-daily Byetta favorably – and no pancreatitis chatter:** On September 9, also at EASD, Dr. John Buse of the University of North Carolina discussed results from the 52-week DURATION-1 study in which all participants were put on once-weekly exenatide (Byetta) – the 30-week results were published earlier that week in *The Lancet* and these results were announced at ADA. Patients on the QW (once weekly) administration maintained a lowered A1c, a striking 2.0% drop, over the course of the entire study from a relatively low starting baseline A1c of 8.2%. Three quarters of patients achieved an A1c of under 7%, over half achieved an A1c of 6.5%, and approximately 25% achieved an A1c of lower than 6% - unprecedented for a therapy that causes no hypoglycemia and is associated with no weight gain.

  Dr. Buse concluded from the results that there was durable glycemic improvement and he highlighted weight loss (average ~4 kg [8.8 lbs]) over 52 weeks with exenatide once-weekly. In those patients initially on exenatide BID regimens, further improvements in glycemic control and weight loss were seen when they were switched from exenatide BID to exenatide QW and the transition from exenatide BID to exenatide QW was not associated with any new or additional adverse events. On safety, there were no incidences of major hypoglycemia, and if the patient was not on a sulfonylurea, there were no minor hypoglycemic events. The largest complaint was local injection site irritation, which will be important to monitor. Ultimately we see Amylin raising the bar substantially for diabetes treatment for type 2 patients with this result - we think this study firmly establishes LAR as the therapy to beat. We look forward to hearing more patient and provider feedback on nausea and ease of use of the once-weekly shot. In our EASD survey of ~ 115 doctors recently published in *Closer Look*, 75% said that they thought, all else equal (an artificial construct, we realize) patients would prefer a once-weekly shot with a lower-gauge needle to a once-daily shot with a higher gauge needle. Generally, we heard very little at EASD about pancreatits - Dr. Buse noted that these cases were rare and should not overshadow the positive benefits of using exenatide to treat patients with diabetes.

- **BMS/AZ — Results from three phase 3 clinical studies with saxagliptin (Onglyza) reviewed at EASD:** Three of the six phase 3 clinical trials with Onglyza (the trade name for saxagliptin) were reviewed on Tuesday, September 9, by the always-precient Dr. Anthony Barrett (University of Birmingham, Birmingham, UK). The studies were on combination therapy of Onglyza and metformin, Onglyza with a sulfonylurea, and Onglyza with a TZD.

  The first trial looked at 1,306 treatment naïve type 2s (these are hard to find in a trial!) with baseline A1c of ~9.5%, a very high baseline but unsurprising given that patients were not on any treatment. Results presented for the study of Onglyza and metformin were as follows – note that the Onglyza and metformin certainly appear synergistic and we were surprised to see no further A1c drop with 10 mg vs 5 mg Onglyza:

	5 mg Onglyza + Metformin (N=320)	10 mg Onglyza + Metformin (N=323)	10 mg Onglyza (N=335)	Metformin (N=328)
Baseline A1c (%)	9.4	9.5	9.6	9.4
Change in A1c (%)	-2.5	-2.5	-1.7	-2.0
Weight loss (kg)	-1.8	-1.4	-1.1	-1.6
Reported Hypoglycemia	11.0 (3.4)	16.0 (5.0)	5.0 (1.5)	13.0 (4.0)

The most commonly reported adverse events were nasopharyngitis (common cold), headache, diarrhea, and hypertension with the greatest incidence coming from the 10 mg saxagliptin/metformin and metformin/placebo groups.

The second multi-center, international randomized double-blind placebo control trial compared glycemic effects of the Onglyza/glyburide vs. placebo/glyburide combination for N=768 type 2s with baseline A1cs of ~8.5%. All subjects had been on a sub-maximal dose of a sulfonylurea for at least two months. Subjects were randomized to one of three arms of the study of after a four-week lead-in during which subjects were placed on 7.5 mg of glyburide. Results presented for the study of Onglyza and glyburide:

	2.5 mg Onglyza + 7.5 mg Glyburide (N=248)	5 mg Onglyza + 7.5 mg Glyburide (N=253)	Placebo + Untitrated Glyburide (N=276)
Baseline A1c (%)	8.4	8.5	8.4
Change in A1c (%)	-0.5	-0.6	+0.1
Weight loss (kg)	+0.7	+0.8	+0.3
Reported Hypoglycemia	33 (13.3)	37 (14.6)	27 (10.1)

Adverse events reported included urinary tract infections, nasopharyngitis, upper respiratory tract infection, and influenza amongst others. Incidence was close to 75.0% in all groups, underscoring the high side effects taking a SFU. No clinically significant differences were reported between the groups. As seen in previous studies with sulfonylureas, weight gain was seen in all three groups (+0.7 kg, +0.8 kg, and +0.3 kg respectively). Interestingly, more weight gain occurred in the group that was treated with Onglyza. This result was commented on by Prof. Barnett who said that other combination therapies might prove to be more efficacious, and it was important to get the information on other drug combinations to determine what the best one for patients would be. Reported hypoglycemia was higher than in the previous study presented, which was expected as hypoglycemia is a known side effect of sulfonylureas. The two Onglyza groups reported 33 (13.3%) and 37 (14.6%) hypoglycemic events, compared to 27 events (10.1%) in the glyburide group. We don't really view 10% as very clinically different from 13-14%.

The design for the multinational TZD study was similar to the Onglyza and metformin study with (n=565) subjects with average baseline A1c of ~8.2%. Participants were on stable TZD therapy at least 12 weeks prior to screening for the study (30 mg or 45 mg Actos or 4 mg or 8mg Avandia). Results presented for the study of Onglyza and TZD:

	2.5 mg Onglyza + TZD (N=195)	5 mg Onglyza + TZD (N=186)	Placebo + TZD (N=184)
Baseline A1c (%)	8.25	8.35	8.19
Change in A1c (%)	-0.7	-0.9	-0.3
Weight loss (kg)	-1.3	-1.4	-0.9
Reported Hypoglycemia	8 (1.4)	5 (2.7)	7 (3.8)

According to comments we heard, head-to-head studies with the other three major DPP-4 inhibitors, Novartis' Galvus, Merck's Januvia, and Takeda's alogliptin are planned. Overall, in our opinion, the data from these four drugs appears to be relatively equivalent, so we're interested in seeing how Onglyza will differentiate itself from the other three. One difference is in the structure of Onglyza, which was designed to be highly specific for DPP-4. Whether or not this specificity will pan out positively or negatively in the clinical setting and what the implications would be remains to be seen, but if it can be proven, we imagine these marketing heavyweights will figure out a way to highlight it.

- **BMS/AZ — Efficacy and safety phase 2b results on dapagliflozin:** On September 8, James List, MD, PhD from BMS presented phase 2b data at EASD on dapagliflozin, the company's phase 3 SGLT-2 inhibitor. The 389-patient 12-week study tested five doses of dapagliflozin against placebo and 1,500 mg of metformin. A1c drops were in the 0.6%-0.9% with dapagliflozin vs. 0.18% with placebo and 0.73% with metformin, from an A1c baseline range of 7.7%-8.0%. FPG decreased by 16 mg/dl to 32 mg/dl in the various dapagliflozin groups vs. 5 mg/dl in the placebo group and 18 mg/dl in metformin group. Postprandial glucose also fell in a dose dependent fashion, with dapagliflozin showing more dramatic effects than metformin. Weight loss was 2.5%-3.4% of body weight for dapagliflozin vs. 1.15% for placebo and 1.67% for metformin (absolute weight loss values were not given). There was a suggestion of increased urinary tract infections (UTIs) though this was not statistically significant. We view SGLT2 results from both ADA and EASD as better than expected and look forward to seeing phase 3 results. Companies with these compounds may well have a new form of a low hassle drug. We can say more about this after seeing the drug tested in greater patient numbers over a longer period of time, but this 400-patient trial leaves us optimistic, knowing what we do about provider interest in relatively easier-to-learn and easier-to-teach drugs. We will be interested in seeing how this class combines with other classes.

- **Novo Nordisk — Liraglutide LEAD 4 data:** At EASD on September 8, Dr. Bernard Zinman (University of Toronto, Toronto, Canada) praised the robustness of the LEAD program before giving detailed results on LEAD 4, a 26-week, 533-patient trial that looked at liraglutide (1.2 mg and 1.8 mg) as add-on therapy to maximal doses of Avandia and metformin. Overall, LEAD 4 showed that liraglutide causes a significant decrease in systolic blood pressure (potentially meaning a reduction in CV risk), significant weight loss, improvements in beta-cell function, and the once-daily dose independent of meals decreases the complexity of treatment. A1c dropped 1.5% in both liraglutide groups vs. 0.5% in placebo from a baseline A1c of ~8.5%. Body weight fell 2.0 kg (4.4 pounds) for the 1.8 mg dose, and 1.0 kg (2.2 pounds) for the 1.2 mg dose, and increased 0.6 kg (1.3 pounds) in the placebo group. Beta-cell function as measured by HOMA-B and proinsulin/insulin ratio improved in the liraglutide groups compared to placebo. Beta-cell function improvement is always viewed as a positive, and we wonder if these benefits are sustained. If so, it would be positive for patients and possibly delay the deterioration of their beta cells. Dr. Zinman focused on the drop in blood pressure with liraglutide (about 6 mm Hg systolic) and suggested that this was very significant because we

know that decreasing SBP by 5.6 mm Hg reduces risk of death from CVD by 18% — we note that this fits with the general trend we've noticed at EASD of a focus on potential CVD benefits of incretins, post-ACCORD. Notably, Dr. Zinman suggested that from this result, liraglutide would have added value compared to other diabetes agents that only lower blood glucose.

Interestingly, nausea rates were 40% for the 1.8 mg dose, 29% for the 1.2 mg dose, and 9% in the placebo group– higher than in the other LEAD trials. Dr. Zinman reminded attendees that all the GLP-1 agonists cause nausea and that nausea is difficult to measure because of variability in reporting. Dr. Zinman attributed the higher nausea rates in LEAD 4 to the fact that patients were titrated to maximal doses of metformin, which also causes nausea. We note that there were 16 discontinuations in the 1.8 mg liraglutide group vs. none in the placebo group (which was also on maximal metformin dose), so it is unclear to us how metformin is playing a role unless it is producing a synergistic nausea effect with liraglutide – actually, we would have expected a higher nausea rate in the placebo arm – under 10% is positive given nausea rates of ~40% in studies like ADOPT. Nausea decreased over time as in other studies.

- **Sanofi-Aventis — Results from the ARPEGGIO trial show more psychiatric side effects with rimonabant:** On September 8, Priscilla Hollander, MD, PhD (Baylor College of Medicine, Dallas, TX) presented the results of the 48-week 366-patient ARPEGGIO trial, a 48-week study that looked at the effect of 20 mg rimonabant in type 2 patients not well controlled on insulin. The A1c drop was 0.89% (n=179) vs. 0.24% in placebo (n=187) from a baseline of 9.1%; 18.4% of rimonabant treated patients reached the A1c target goal of <7% vs. 6.7% in placebo. The largest A1c drop was in people with the highest baseline A1c. Rimonabant-treated patients also had a 3% placebo-subtracted reduction in insulin dose, and only 14% required rescue meds vs. 35% for placebo. Body weight change was -2.49 kg for rimonabant vs. +0.13 kg for placebo, and waist circumference was -2.95 cm vs. -0.33 cm; HDL increased by 3 mg/dl with rimonabant vs. -7 mg/dl placebo, and TG decreased 4 mg/dl compared to a 8 mg/dl increase with placebo.

  As with other rimonabant trials, psychiatric side effects were more common with rimonabant. Discontinuations due to adverse effects were more common for rimonabant (17% vs. 8% for rimonabant vs. placebo): anxiety was 14.0% vs. 5.3%, depression was 10.1% vs. 4.3%, insomnia was 7.8% vs. 3.2%, and discontinuations due to psychiatric disorders was 8.4% vs. 1.1% for rimonabant vs. placebo respectively. Notably, an audience member from Germany spoke up about his personal experience, saying that some of his patients don't respond (no weight loss) and some lose up to 20 kg on rimonabant and are able to go off insulin. Dr. Hollander concluded that ARPEGGIO supports the use of rimonabant for type 2 diabetes, though we believe that the CNS side effects will remain a concern for regulatory agencies. This drug could be extremely useful for patients if they could create a protocol that allowed for quick differentiation of those patients who will lose weight from those who will not as well as who will have the greatest chance of psychiatric side effects.

- **Roche — Concerning hypoglycemic results from an early phase 2 trial with RO4386920, a glucokinase activator:** Results from an early phase 2 trial of Roche's glucokinase activator (GKA), RO4386920, were reviewed by Chris Abbott of Roche on September 8. Glucokinase (GK) is an enzyme found in the pancreatic islet cells and the liver that acts as a glucose sensor and facilitates glycemia-dependent glucose uptake in the liver. In the pancreatic beta cells, it helps to control the secretion of insulin when blood glucose levels increase. In this safety and tolerability trial, RO4386920 was tested in 59 type 2 patients at a range of doses including five twice-daily doses and one once-daily dose. The trial was small - each of the six cohorts included eight active patients and two placebo patients. The drug was administered for six days. Both postprandial AUC and fasting glucose showed dose-dependent reductions from baseline, up to 35% and 32% from baseline, respectively – it's unclear what the baseline is. They found that the half-life is 8.1 to 11.2 hours.

Headache was the most common adverse event, but more concerning, 25% of the patients in the once-daily arm and 50% of the patients in the twice-daily highest dose arm developed symptomatic hypoglycemia, though it was not classified as severe. From what we understand of the mechanism, GKAs are a bit like sulfonylureas in that they stimulate glucose-independent insulin secretion, so we're not sure they offer particular benefit as a new class of drug. Impact on weight and A1c reduction would be the two obvious measures we'd like to see before coming to a more definite opinion about this drug class in general.

- **Amylin/Eli Lilly – Pancreatitis concerns with Byetta arise again:** In a conference call on August 27 led by Amylin CEO Daniel Bradbury and Dr. Donald Therasse, Lilly's VP of Global Patient Safety, the companies provided context for a recent FDA alert regarding pancreatitis and Byetta. The prepared portion of the call, in which management provided data about the alert and what it meant in terms of patient risk, was short. Management reviewed the recent FDA warning in reference to six new cases of hemorrhagic or necrotizing pancreatitis and severe complications of acute pancreatitis, that occurred in patients either taking or who had taken Byetta. According to management, the prevalence of these conditions in patients taking Byetta did not appear to be greater than in the general population, and the association was tenuous. Amylin and Lilly are continuing to pursue a comprehensive drug safety program, and they are in discussions with the FDA regarding safety information updates for Byetta. Overall, we do not see a cause for alarm because the evidence linking Byetta with pancreatitis remains tenuous according to experts including drug expert Dr. Harold Lebovitz of SUNY Brooklyn and Dr. David Orloff, head of MedPace. The Q&A was lengthy and focused on a possible expanded FDA warning for Byetta and what impact this warning could have on the timing of approval for exenatide LAR. Several prominent members of the diabetes medical community (i.e. Dr. Bernard Zinman, Dr. Anne Peters, Dr. John Buse, Dr. Jens Holst, and others) cautioned against drawing conclusions about GLP-1 drugs and pancreatitis. As Dr. Zinman stated at EASD, "Diabetes patients are at 2-3x higher risk of pancreatitis vs. background population because they are more obese. In all of the exenatide studies, there was no signal of pancreatitis. However, once it goes on the market, then people on the medication are going to develop pancreatitis. At this stage it's difficult to assess if exenatide is related to a higher rate of pancreatitis, but I don't believe there's any evidence at this point that it is. I think we should look at larger (insurance) databases and study this further – we can't just depend on MedWatch reporting." Amylin has previously used data from insurance company databases to show that pancreatitis incidence in Byetta patients is similar to that of the diabetic population generally.

- **Metabasis — Qualitative overview given for MB07803:** On August 7, Metabasis reported 2Q08 results and discussed progress on MB07803. Management gave a very qualitative overview of top line phase 2a data for its second-generation fructose-1,6-bisphosphatase (FBPase) inhibitor, MB07803. This new class of drug works by inhibiting an enzyme involved in the production of glucose in the liver, thereby lowering glucose production and blood glucose levels. It works differently than a glucokinase activator because it is not involved in glucose sensing. The drug significantly lowered fasting plasma glucose at day 28 versus placebo, and was well tolerated overall. Unfortunately, no key data on this were provided beyond the "significant" characterization. The study was a proof-of-concept study with 105 patients who had mean fasting plasma glucose of 187 mg/dl and A1c of 8.2% at baseline. They reported statistically and clinically "significant" reduction in FPG versus placebo (p=0.0177). Regarding safety and tolerability, they noted a similar overall adverse event profile to placebo and normal fasting lactate levels with no hyperlacticemia reported. Metabasis hopes to present the full phase 2a results at the World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension in November in Barcelona. The phase 2b trial is expected to initiate in 2009, and the company plans to initiate a phase 1 drug/drug interaction clinical trial of MB07803 in combination with metformin.

On an annual basis, revenue for the quarter was down 56% at $0.7 million. Management attributed the decrease to the absence of licensing fees from a former collaboration with Idenix. Last quarter they attributed the 74% revenue drop to a similar issue with Schering-Plough. Net loss was reported at $11.5 million, down slightly (-3%) from last year's reported figure of $11.9 million. R&D expenses decreased almost 13% to $9.7 million mainly due to decreased clinical development costs for MB07803, MB07133, and MB07811 and stock-based compensation. The company reported raising $10 million through a warrant exchange and concurrent private placement. In 1Q08, Metabasis secured a venture loan from Oxford Finance and completed a warrant exchange transaction and concurrent private placement, raising a total of $15 million.

Private Company Roundup:

- **Alizyme —** On September 16, Alizyme announced that it would receive a $3 million milestone payment from Takeda following the company's decision to bring a phase 3 trial in Japan of cetilistat, a lipase inhibitor. This decision to proceed to a phase 3 program was based on positive results from the phase 2 study in which participants demonstrated significant weight loss and improvement in glycemic control over the six month treatment period.

- **Arkal Medical —** On September 24, with Thomas McNerney and Partners, Arkal secured $17.5 million in funding for its continuous glucose monitoring (CGM) system. According to top-line data, the CGM system being developed by Arkal circumvents current CGM problems, but further details were not forthcoming.

- **ConvaTec — Merger with Unomedical:** On June 27, Nordic Capital Fund VII and Avista Capital Partners announced the merger of Unomedical with newly acquired ConvaTec, formerly a Bristol-Myers Squibb (BMS) company. The sale of ConvaTec came as part of BMS's reported refocusing on their "next-generation Bio-Pharma strategy." Nordic Capital, a group of private equity funds, previously owned Unomedical, a company largely focused on single-use medical devices – notably infusion sets for diabetes. This merger announcement comes shortly after Avista, a private equity firm, and Nordic Capital jointly agreed to acquire ConvaTec, a wound therapeutics and ostomy care company, from BMS for $4.1 billion on May 2, 2008. The combined company has assumed the name ConvaTec and current ConvaTec CEO, David Johnson, has stayed on as CEO. The announcement noted $1.2 billion in 2007 net sales for ConvaTec (3,500 employees) and for the same period, DKK 2 billion ($422 million) for Unomedical (4,700 employees). Unomedical's infusion set business would appear to benefit from this merger by gaining access to ConvaTec's global operation while ConvaTec profits from Unomedical's expertise in infusion devices and some hospital care devices. Unomedical CEO, Henrik Brandt expressed optimism about new growth prospects for Unomedical through this merger. We note that ConvaTec touts its presence in 100 countries on six continents whereas Unomedical is more Euro-America focused so we expect geographic synergies as well. We see a growing interest in diabetes as core to the strategy of the resulting company and believe that Unomedical's business should continue to grow briskly as they are at the center of a business focused on intensively managed patients, a highly evolved and very profitable patient group.

- **Debiotech — Nanopump prototype announced:** On June 23, Debiotech, a Swiss medical technology company, announced their first prototype of a disposable miniaturized insulin pump, Nanopump, in partnership with STMicroelectronics, a semiconductor company. The Nanopump is reported to use microfluidic technology to enable precise control and delivery of low-volume fluids. The technology is based on the concept that at such small volumes, the properties of fluids change; these changes are said to be exploited for different applications. Details on the mechanics

of the prototype are scant and reports only indicate that the Nanopump can be mounted on a disposable skin patch to provide continuous insulin infusion.

Debiotech is pushing the Nanopump as a smaller, cheaper and more physiologic insulin delivery system compared to current durable and disposable pumps. The pump is noted to be less than a fourth the size of current pumps – the press release does not specify durable vs. disposable pumps but we assume they are referring to durable pumps. Additionally, they suggest that insulin delivery using microfluidic technology will better mimic physiologic insulin delivery. On that note, they also use the argument of lower manufacturing costs (hence product costs) given the usage of high-volume silicon-based processors manufactured by STMicroelectronics. This company entered into an agreement with Animas in October 2004 on development of needles based on Debiotech's Micro Electro-Mechanical System (MEMS) technology.

- **Diabetology Limited — Results from a 10-day study with an oral insulin formulation (Capsulin):** On September 8, Timothy Broke-Smith of Diabetology, presented phase 2 data on the company's oral insulin formulation, Capsulin. These capsules contain 150 units each and are taken twice a day for type 2 diabetes. They have a low 10% bioavailability, cause for concern in terms of pricing and dosing. The phase 2a study in type 1 patients included eight patients dosed one week apart with 150 or 300 units (effectively, 15 or 30 units – type 1 patients on average take 30-40 units per day). The insulin effect lasted about 1.5 hours. The phase 2 study in type 2 diabetes included 16 patients, and included data from a clamp. Group 1 had 150 units Capsulin vs. 12 units Actrapid (Novo Nordisk's Novolin), and group 2 had 300 units Capsulin vs. 12 units Actrapid. The patients then took oral 150 units Capsulin twice daily for 10 days. The clamp studies showed equivalency between 150 units of Capsulin and 12 units of Actrapid. During the 10-day study, there was a trend in reductions in postprandial glucose and there were drops in weight, and triglycerides. No severe hypoglycemic events were reported, which isn't surprising for such a small trial. Although the weight loss would be welcome, we're not sure that it would overcome other hassle factors – we would also be very concerned about pricing given the low bioavailability and we would cast reimbursement as a major question given what we believe would be little if any differentiation in a real-world trial.

- **Metacure — Electrical stimulation treatment during meal-time with Tantalus:** On September 8 at EASD, Bruno Guerci, MD, PhD (Hospital Jeanne-d'Arc, France) described a 19-patient study investigating the effect of Tantalus, a gastric motility inhibitor, in obese subjects with type 2 diabetes. The subcutaneous Tantalus system uses Gastric Contractility Modulation through electrical stimulation to slow gastric contractions and increase satiety. This study was not randomized and included 19 subjects who were not well controlled on oral agents; these subjects had a mean BMI = 38, average A1c = 8.0%, and average age = 53 years. The patients underwent implantation from June 2007 to January 2008 with the treatment phase lasting 24 weeks. Average weight loss over the 24 week period was 5 kg (mean weight was 114 kg, 109 kg, and 109 kg at baseline, three months, and six months respectively). Waist circumference values were 124 cm, 119 cm, and 118 cm at the three evaluation points. A1c fell from a baseline of 8.1% to 7.0% at six months, with 56% of the patients achieving an A1c <7% at six months. Roughly 48% of the change in A1c could be explained by the change in weight loss. Subgroup analysis showed that non-responders (n=5) had an A1c increase of 0.2% and responders (n=13) had an A1c decrease of 1.5%, suggesting that this therapy will only be affective in specific populations. Dr. Guerci said that this regimen is well tolerated and can potentially improve glucose homeostasis and induce weight loss in obese patients with type 2 diabetes. Mechanism-of-action studies are underway to look at the effect of Tantalus on glucose metabolism and gastric intestinal hormones.

- **VeroScience — Cardiovascular safety data for Cycloset (bromocriptine):** Anthony Cincotta, PhD of VeroScience described results from a subgroup analysis of a phase 3b 52-week cardiovascular safety study in 3,070 patients treated with Cycloset (bromocriptine), a central nervous system agent that increases peripheral metabolism. Patients with an average baseline BMI of 32, and A1c of 7.0% (quite low!) were randomized to once-daily Cycloset (n=2,054) or placebo (n=1,016). In a subgroup analysis of patients with A1c >7.5% (i.e. diabetes patients), Cycloset produced 0.6% to 0.9% reductions in A1c from mean baseline 8.3%. At 24 weeks the A1c dropped 0.6% for patients on any oral anti-diabetic (OAD), 0.6% for those on SU, 0.7% for those on metformin, and 0.7% for those on metformin plus SU – these results aren't bad for such a low baseline A1c. Interestingly, investigators reported that Cycloset reduced the primary CVD outcome by 42% - the primary outcome was a composite of MI, stroke, hospitalization for unstable angina, CHF, or revascularization surgery. In the ITT analysis, the hazard ratio (HR) was 0.58 for Cycloset (0.35-0.96) with 31 events in the Cycloset group (out of 2,054) and 30 events in the placebo group (out of 1,016) – basically the same number of events for a group twice as large. The hazard ratio for MACE (major acute coronary endpoints including death, MI, and stroke) was 0.45 (statistically significant). As a result, Dr. Cincotta suggested that Cycloset could be used to treat both micro- and macrovascular complications. We note that this study was initiated after the FDA gave Cycloset an approvable letter and asked for more cardiovascular safety data. This decision from the FDA may have occurred because bromocriptine was once used to block lactation after pregnancy, and this indication was pulled due to concerns about an increased risk of CVD. Presumably VeroScience plans to resubmit their data.

— by Kaku Armah, Kelly Close, Mike Dougan, Brendan Milliner, Melissa Tjota and Mark Yarchoan

4. DCU Dialogue with Dr. Anne Peters, ADA Outstanding Physician Clinician Award

In June, Dr. Anne Peters received what many would term the most prestigious award for a clinical endocrinologist – the ADA Outstanding Physician Clinical Award. Dr. Peters certainly deserves the title for her many contributions to the diabetes field. Dr. Peters is remarkable as she has worn many impressive hats, including her role as a top researcher in LookAHEAD and the JDRF artificial pancreas study; as an editor and author (she is on the editorial board of Diabetes Care *and author of the oft-cited* Conquering Diabetes*); as a top-ranked physician in the US treating diabetes; as a member of the American Board of Internal Medicine; and as a leader of two well-known diabetes clinics in Beverly Hills and East Los Angeles. The latter was begun so Dr. Peters could work with underserved populations - we applaud her efforts to bring good care to the people who most need it.*

Kelly Close: Dr. Peters, we really appreciate your taking the time to talk to us. To start off, can you give us a little background about your practice and about your philosophy on medicine?

Anne Peters: About my practice, I started seeing patients in 1989 at my practice in Beverly Hills and in East LA started in 2000. I have a team with a nurse practitioner and a dietician, and we co-manage anybody with diabetes who is referred to us. I have a program in Beverly Hills where I see people who have health insurance. Many of our patients have type 1 diabetes and are on insulin pumps, and we particularly enjoy managing women with type 1 diabetes during their pregnancy. It is a bit like a private practice even though it is administered through USC.

I also run the diabetes program at the Royal Comprehensive Health Center under the direction of the Department of Health Services for the County of LA. It is located in

East LA, which is one of the poorest parts of town. At first, it was designed as a pilot program to demonstrate that we could provide good care to an underserved population. It turned out to be a success, and the County continued to set up four other locations. We are really trying to unify care throughout the County of Los Angeles for the underserved, and we have worked together with the International Diabetes Center in Minneapolis to write the LA County Quick Guide to diabetes care.

Another thing I do is if a drug or technology that I think would be beneficial to patients in our healthcare system comes onto the market, I go to the LA County Department of Health Services Formulary Committee, and I try to get the drug on the formulary. My goal is to provide good care to all people who need it, rich or poor. Of course this is always done with an awareness of cost—with limited budgets decisions need to be made as to costs and benefits. However, the County has made a commitment to quality, which is important. We have the largest number of uninsured people with type 2 diabetes in the United States and therefore they stand the most to benefit from enhanced care. I try to advocate for patients in the County, and I have been encouraged by the County's willingness to try and improve life for patients with diabetes.

On the research front

Melissa Tjota: Could you tell us about some of the research you are involved in? We know you're a technology expert and also an expert on diabetes prevention.

Dr. Peters: Currently, I have an NIH grant as part of the LookAHEAD study, which is studying the effects of lifestyle on the treatment of type 2 diabetes. I also have the JDRF artificial pancreas project through which I am studying the benefits of continuous glucose monitoring in our East LA Clinic. I also have various small projects that are looking at how to improve health patterns in the East LA and South LA communities. I would rather find ways to prevent the disease than treat the disease.

Kelly: Congratulations on the JDRF study – it was great to see it put together so quickly and to be published in NEJM. What do you think are the most important lessons to come out of this study?

Dr. Peters: The JDRF study that was published was the one I am a part of, but I am a sub-study. It turns out that my patient data could not be included because my patients all come from an underserved population where they did not know the basics of carb counting and/or insulin dose adjustments. We had to follow a cross-over design in order to account for the learning that had to occur in all individuals as they entered the study. Our patients also have a varying degree of literacy and could not follow the standard directions for the study. We are still working on our part of the study, and we are hoping to be allowed to continue through this upcoming year to collect data on how we can use this technology in a less sophisticated patient population.

To me, the key points from the recently published study seem to be: 1. Wear the sensor! The best outcomes were seen in patients who wore the sensor constantly. I realize that many patients don't like the hassle of having two sites on their body that is attached to a device, but it is most helpful if patients rely on it for constant input. 2. The teen years are tough for having diabetes (we all knew that). Using the sensor or not did not make a difference in the adolescent group. It would be interesting to work with this age group to figure out what else, in combination with a sensor, could improve their outcomes.

Kelly: Can you comment on the LookAHEAD study as to when we might hear more? What are

you expecting to see?

Dr. Peters: LookAHEAD has published the one year outcomes and is starting to look at four year outcomes. The first year data showed that we were able to surpass our weight loss goals and that along with this expected improvements were seen. Improvements happened in patients from all ethnicities, and although quite resource-intense, it is wonderful to see that patients treated for their type 2 diabetes can lose weight and improve their one year outcomes. The real challenge is now to see how this weight loss can be sustained over time and if it translates to reductions in cardiovascular events. As a strong advocate for the benefit of lifestyle modification, (and leading a healthy lifestyle is important whether or not someone has diabetes) I am hoping we can prove its benefits.

Searching for a specialty, helping the underserved

Kelly: You mentioned earlier your practice in East LA. Did you know you wanted to serve underserved populations from the beginning?

Dr. Peters: Ever since I was a little girl, I've always been interested in helping the underserved. It's a long story, but I went to PS 40 in New York City when I was little and they had twin desks where they would sit a good student with one who was doing as well in school. I sat next to a little African-American boy, and my goal in school was to teach him how to read. Unfortunately, he was sick so much that he could never come to school, so I could never teach him to read and that is when I began to realize the effect illness had on education and poverty. At that point, I first decided that I wanted to work in underserved communities. I have always done volunteer work, and I try to give back to people who have less than I do.

Kelly: Did you realize when you first went into diabetes that it was so intellectually interesting?

Dr. Peters: No, I was not very surprised because I was at the University of Chicago, with several leading diabetologists. Dr. Arthur Rubenstein was my advisor and my mentor, and Drs. Ken Polonsky, Jonathan Jaspan and Steve Shoelson were there. For my senior year of medical school I worked in Arthur's lab doing radioimmunoassays and I also went and worked in Africa. I was in the right world for diabetes.

The downside of being a popular author

Melissa: We were wondering about your book *Conquering Diabetes*. It seems like you were ahead of the times because you were talking about pre-diabetes long before it became a common concept. How was the process of writing it for you and how has the reception been for it?

Dr. Peters: First of all, I did not want to write the book. I have always meant to write a book, but I wanted to do it when I was done practicing medicine. There was a story about me in the *New York Times* discussing diabetes prevention, and one of the editors from Penguin contacted me and asked, "This could be a great book. Would you be interested in writing one?" I told her that I was too busy with my patients to think about writing a book, and I declined the offer. Then my husband told me that "Penguin doesn't come calling very often to ask someone to write a book." So, I called them back and agreed to write the book. To be honest, my first instinct was right.

I wanted to write a book that would teach people how to be proactive and empower themselves in their own communities. What the book did was create a nightmare in two ways. One was that it made me too popular, and people wanted me on several television

and radio shows. It was a good way to advocate for people with diabetes, but it was not a good way to educate people with diabetes. I definitely believe in using the media to inform the public, but after writing the book, I felt that too much of the focus was on me and not on the cause. The second, much bigger issue, was that it caused an influx of people who tried to see me as though I was a cure. Diabetes is a process, and I can only help people who are able to come to see me and connect with me. I cannot properly take care of people who only communicate with me through e-mails and telephone calls. It made me sad because there were so many desperate people, and I could not say no, so I would ask them to let me help them find someone in their community. I prefer to focus on my immediate work and see my patients be successful, rather than deal with the media world that surrounds publishing a book.

About the feedback, I have gotten a great deal of positive feedback, and it has made me more aware of other great programs available across the country. It has encouraged me to do what I've been trying to do, which is to raise the bar and to improve access to care for everybody.

Reaching out to primary care doctors

Kelly: At ADA this year there was a lot of talk about individualizing therapy, and all of your work has shown the value of that through creating the county guide and teaching other doctors. Can you talk a little bit about the needs there?

Dr. Peters: I love teaching doctors. I want to seek out primary care doctors in each community and educate them on how to do a better job because that is how my skills are going to be best used. LA County was also thinking about a kind of diabetes expert on demand where specialists could talk with practitioners seeing patients on the Internet and provide more readily accessible care. I think there are all sorts of ways to use someone like me better, but it is really through the liaison with primary care that I can make a difference. For instance, Steve Edelman is wonderful, and he does a great job connecting with patients (as well as providers). I think I am pretty good at taking science and translating it to something that can be taught to primary care providers and used to enhance the provision of diabetes treatment.

Kelly: Could you tell us what you think are the most interesting research questions to you now?

Dr. Peters: The first area that I think is very interesting is the attempt to make a partially closed loop system, integrating sensors and pumps and allowing people to have more freedom from making constant insulin dosing decisions. Those of us who frequently deal with pumps and sensors can lead the way in terms of improving technologies and glycemic control in people with type 1 diabetes. In type 2 diabetes, the research that I am the most interested in is from the LookAHEAD study as well as the diabetes program I run in East LA. I know that with the right people, I can significantly improve outcomes in a given patient if they can be seen in our program, but once they graduate, they do not do nearly as well in controlling their glycemic levels.

I would like to integrate some sort of community-based system of peer educators or promotoras and figure out a way to sustain improvements. I believe that sustaining improved outcomes is one of the biggest issues in diabetes care. It is not just about getting someone to a specific target but making sure they keep that target for the next 20 years. The medical system as it stands currently is not going to be able to provide that level of care. That is why using novel approaches to providing long term care and

connection could be very helpful, and we have been working on this in my East LA clinic as well as in the South LA population. We know what we need to do, but how to do it in terms of the most effective utilization of is a big challenge. Prevention is also extremely important, but that is an entirely different issue given that so many patients with diagnosed diabetes aren't getting adequate care.

The biggest changes in care

Kelly: On to some big-picture questions! What has changed the most in diabetes in the last five years in your view? What has the biggest potential to change in the next five?

Dr. Peters: The biggest changes for type 2 patients and type 1 patients are different. In the type 2 realm, medications have been the great change in my practice. TZD's have played a large role in helping to maintain beta-cell function over time, and I have seen many patients of TZDs whose disease has not progressed over time, as would be predicted. Byetta has also been an important addition to treating type 2 diabetes. There will be a lot of ongoing interest in new GLP-1-related products such as long acting exenatide and liraglutide as they come on the market. People will also continue looking at novel ways of achieving weight reduction such as through gastric bypass surgery. My caveat with gastric bypass surgery is that we know that it works, but it is not practical on a large population level, and long-term risks and benefits are not known. So, there may be other ways of technology assisted weight reduction, particularly with minimally invasive surgical techniques.

For type 1 diabetes, the technologic improvements have been tremendous. The availability of analog insulins has made treatment much easier, and smarter pumps, especially in combination with sensors, have made achieving and maintaining tight control much more possible in my patients. As I stated above, the idea of developing a partially closed loop system for treating patients with type 1 diabetes would be very beneficial and will hopefully happen within the next few years. In terms of a "cure", however, the biggest changes may occur in the research lab rather than in immediate patient care. We need both a method to replace beta-cells in people with type 1 diabetes and a way to turn off the immune system so that the beta-cells aren't destroyed.

I think there will be a lot of advancements in the care of people with diabetes, but people have to remember there is not going to be a magic bullet to fix everything.

Melissa: Is pancreatitis from treatment with Byetta something that patients should be worried about? Has the media been responsible in getting the right news to patients?

Dr. Peters: Providing fair balance on medical news is often tough. Many times key points are missed, and patients panic. It is extremely difficult to know what the long-term risks to medications are because we do not do the sort of follow-up that would provide us such data, and the clinical trials done to bring drugs to market include relatively small numbers of patients. I am not convinced that Byetta causes pancreatitis—the rate of pancreatitis in people with type 2 diabetes are increased and in any drug safety data set, whether for Byetta or the TZD's or Januvia, there are reports of pancreatitis. Does this mean that the drug caused pancreatitis? It is hard to know because we only know the numerator, not the denominator, and therefore cannot calculate a rate. With Byetta, under FOIA (freedom of information act) I obtained the FDA data on side effects of Byetta and Januvia. Pancreatitis occurred with both drugs, and in most cases there was another cause for the pancreatitis. So I think that the rate of pancreatitis with

Byetta may not be much different than baseline rates, but I cannot know that for sure.

My general approach is to tell patients that all drugs have risks and newer drugs may have risks we don't know about. I tell patients to always let me know if they think they are having a reaction to a drug so we can stop it. I also try to use drugs only when necessary and discontinue them if they are not working or are unnecessary. When patients ask me what the worst side effect is to any given drug, I am honest and say "it could kill you," but I go on to explain that the disease the drug is treating is serious and worth the risk. In addition, I encourage all patients to read the patient package inserts so that they know what monitoring they need when on any given drug. Patients can minimize their risk by making sure they don't have any contraindications to the drug and then follow-up routinely for necessary testing.

Kelly: Some experts argue that type 2 diabetes – with its association with lifestyle and its impact on low-income populations – is less of a medical problem than a social problem. If that is true, what can health care providers do to confront the epidemic?

Dr. Peters: Type 2 diabetes is almost always an environmental as well as a genetic problem. In the poor communities where I work, individuals don't have access to healthy food in supermarkets or safe parks for walking. Many run out of food during the month, and I've heard of people selling food stamps to buy even cheaper food to feed their families. If having food at all is a big issue, people may be less likely to buy more expensive, potentially perishable healthy food, especially when cheaper, more filling, but less healthy food is readily available.

Through the Keck Foundation and a number of other grants, we have been working to understand our local environment and help make it healthier. The work I have done has been with Dr. Francine Kaufman and Children's Hospital Los Angeles. The premise of our projects has been that the communities need to be our guide to help them heal. We formed two community advisory boards in East and South LA, and at their suggestion, helped bring in farmer's markets, cooking classes, and grocery store tours to both areas. We are also working with schools to provide healthier meals and to start a high school to elementary school lifestyle mentoring program. These are small steps, but we are learning how to address issues of lifestyle change in underserved communities and will hopefully be able to help others embark on a similar process.

Kelly: What have you seen your Beverly Hills patients respond to the most in terms of diabetes care? East LA patients? How big a difference do resources make for someone with diabetes?

Dr. Peters: Patients respond most to not feeling judged and knowing that they have access to providers who care. In my Beverly Hills practice my patients email me all the time, sometimes daily, if they need me. It helps me help them, and I think it offers some comfort to my patients. In East LA we have care managers, nurses, and nurse practitioners who are available by phone and spend a lot of time talking with the patients and offering support and advice.

To have diabetes and not have access to health care turns a treatable disease into an incurable cancer. The patients I see in East LA have really suffered due to a lack of healthcare. Nearly every patient over the age of 24 already has significant diabetic complications. We have people in their 20's going blind, on dialysis, losing limbs. It is quite discouraging, especially since diabetes is a treatable disease but ONLY if patients

have access to care.

Kelly: Thank you so much, and we really appreciate your time and just salute you for everything that you have done and will continue to do to help patients with diabetes.

See www.closeconcerns.com for the full transcript of our interview with Dr. Peters.

— by Kelly Close and Melissa Tjota

5. In the News I: Anti-CD3 Therapy — Optimism for Tolerx's Immunotherapy in Type 1 Diabetes

After many failures in the field of immune-based interventions for type 1 diabetes, anti-CD3 monoclonal antibodies are arguably the first potentially preventive therapies that appear poised to change the landscape of type 1 diabetes. Two humanized anti-CD3 monoclonal antibodies are now in the later stages of clinical development after demonstrating in earlier studies that they can successfully reduce insulin requirements for newly diagnosed type 1 patients for at least 18 to 24 months. The two therapies in development are Macrogenic/Lilly's MGA031 (teplizumab, also called hOKT3g1 Ala-Ala) and Tolerx/GSK's TRX4 (otelixizumab, also called ChAglyCD3). The two therapies are unlikely to cure type 1 diabetes, per se, but they may blunt the decline of beta-cell function that is observed in type 1 diabetes, and they may even eventually be used as part of a preventive strategy before type 1 diabetes is diagnosed – perhaps in combination with other prevention strategies such as Diamyd's GAD65 vaccine (also in clinical trials). We recently had the opportunity to speak to Tolerx CEO Dr. Douglas J. Ringler about the company's ongoing phase 3 trial of otelixizumab called DEFEND, about his thoughts on the differences between otelixizumab and teplizumab, and about the potential implications of anti-CD3 therapy for type 1 patients.

- **Since the first serious attempts at immune-based interventions for type 1 diabetes in the early 1980s, the field of immune-based interventions and prevention strategies for type 1 diabetes has been wrought with failure.** Various interventions such as ketotifen, nicotinamide, dietary gluten elimination, and bacille and calmette–Guerin (BCG) were attempted but all failed to protect the insulin secreting beta-cells from attack by the body's immune system. Researchers did find that one immunosuppressant drug called cyclosporine could delay beta-cell loss in type 1 diabetes. Unfortunately, upon discontinuation of administration, beta cell destruction continued, so the effect was not durable. In addition, this drug is associated with many severe side effects, and for this reason it is not widely used at the time of diabetes onset; however the results provided some hope that a more specific immunosuppressant would eventually be successful.

- **Many researchers argued – and continue to argue to this day - that type 1 diabetes *should* be preventable.** These researchers point out that type 1 diabetes is actually a relatively "simple" disease: it involves a very selective immune system attack against a precise cell type (the beta-cell) in a very specific place. In part because of this common belief, immune tolerance has been funded aggressively through various organizations such as the Immune Tolerance Network (NIH) and the Juvenile Diabetes Research Foundation (JDRF). Anti-CD3 therapy is the product of these focused translational research efforts.

- **In separate earlier trials, both teplizumab (Macrogenic/Lilly) and otelixizumab (Tolerx/GSK) successfully reduced insulin needs in new-onset type 1 diabetes patients.** The phase 2 trial for otelixizumab showed reduced insulin requirements throughout the 18 month study period in 80 new-onset subjects, while teplizumab had similar success in 42 new-onset patients for its 24 month study period. The results from these earlier studies, which were announced in 2005, helped Macrogenics and Tolerx sign big partnerships: Macrogenics signed a billion-dollar partnership

with Eli Lilly to develop teplizumab, and shortly thereafter Tolerx followed with a $750 million partnership with GSK to develop otelixizumab. Both drugs have been granted orphan drug status by the FDA. Four year otelixizumab data has been collected by the Belgium study group that organized the original phase 2 study, but this data has not yet been published. However, we have heard anecdotally that many of the patients who received otelixizumab continue to show benefits to the present day.

- **Although the benefits of anti-CD3 therapy appear to be long lasting in many patients, anti-CD3 therapy is not a cure.** At the time that anti-CD3 therapy is currently administered, patients have already lost more than half of their beta-cells (20% beta-cell function is typical), and the benefits of anti-CD3 therapy may diminish with time. It was noted in the publication of the phase 2 study of otelixizumab that patients with more beta-cells at the time of anti-CD3 therapy initiation showed more benefits of the therapy. In patients with better-than-average beta-cell function in the study, the mean insulin dose of insulin at the end of the 18-month trial period for patients in the intervention group was 0.22 IU per kilogram per day, as compared to 0.61 IU per kilogram per day in the control group – a more pronounced benefit than in patients with worse-than-average beta-cell function at the study start. This underscores the importance of initiating anti-CD3 therapy as soon as possible.

- **Eventually, we believe that anti-CD3 therapy may be used as a preventive measure in high risk patients, and Dr. Ringler mentioned that the company hopes to start a prevention trial with otelixizumab either this year or next year.** Although many questions remain unanswered, we believe that it is possible that anti-CD3 therapy could delay the onset of diabetes by many years. Tolerx CEO Dr. Ringler was optimistic but cautious with regards to the use of anti-CD3 therapy in high risk patients. He said that the company hopes to begin a prevention trial as soon as this year, although the details of such a trial have not been worked out.

- **Anti-CD3 therapy is not without drawbacks, and questions remain about its efficacy, safety, and convenience.** To get a clearer picture of the safety and efficacy of anti-CD3, we look forward to viewing the results of the ongoing phase 2/3 trial of teplizumab and the phase 3 trial of otelixizumab. Convenience of anti-CD3 therapy leaves something to be desired; patients receive the therapy as an intravenous infusion that is given over the course of several days. Otelixizumab is currently given for a two hour period every day for eight days, although Dr. Ringler is optimistic that this time can be reduced. He told us, “we anticipate decreasing that in terms of the time of infusion considerably.” Teplizumab is administered over 14 days, although the dosing may also be adjusted with time. Even if the time of infusion is not reduced, we believe that this inconvenience is small in comparison to the potential benefit of the therapy. Another problem with anti-CD3 is that the infusions may cause a transient “reactivation” of existing infections including EBV, better known as “mono” in the US, leading to temporary flu-like symptoms. Importantly, the immune system reprogramming that takes place is very specific and not expected to impact the immune response to pathogens in the long term. An ongoing phase 2 trial called “TRX4 Monoclonal Antibody in Type 1 Diabetes” (TTEDD), sponsored by Tolerx and the JDRF, is further optimizing the dose of otelixizumab to minimize the reactivation of existing infections. In this regard, Tolerx has moved a dosing regimen identified in TTEDD into their phase 3 trial that in multiple subjects has not induced any reactivation of EBV while preserving the immunological responses important for durable efficacy.

- **A phase 3 trial for otelixizumab in new-onset type 1 diabetes patients called “Durable-Response Therapy Evaluation For Early or New-Onset Type 1 Diabetes” (DEFEND) is ongoing, and Dr. Ringler reported to us that enrollment is progressing well.** The study investigators hope to enroll a total of 240 subjects, randomized to either otelixizumab or placebo at a ratio of 2:1 (160 subjects randomized to otelixizumab, 80 randomized to placebo). The primary

outcome of the study is mixed-meal stimulated c-peptide levels at one year, though other measures such as A1c and average blood glucose will be collected at months 6, 12, 18, and 24. A similar phase 2/3 trial of teplizumab called "The Protégé Study" is also ongoing and should be completed in March of 2010. Although Tolerx CEO Dr. Ringler would not provide us with an estimated time of BLA submission for otelixizumab, we believe that it could be submitted as early as 2011 or 2012.

- **When asked what he considers to be the biggest advantage of otelixizumab over teplizumab, Dr. Ringler spoke eagerly about the elimination of carbohydrate in the Fc binding region of the otelixizumab antibody.** He said, "I think the greatest difference is in molecular structure…Otelixizumab is the only CD3 antibody that has been changed in the Fc binding region to eliminate all carbohydrate." Without delving deep into the science, removing carbohydrate in this region of the monoclonal antibody could in theory reduce the rate of adverse reactions and improve efficacy. We await confirmatory clinical data, and without a head to head trial with teplizumab, this difference may not be demonstrated clinically. Ultimately, we believe the compounds' respective abilities to delay type 1 diabetes will be the most important factor when patients choose between the two.

- **Despite our optimism about anti-CD3 therapy, we caution that it is unlikely to be a cure, even if it is eventually used before the onset of type 1 diabetes.** Instead, it may delay the onset of type 1 diabetes by months or years – still a tremendous advantage, as it may mean developing diabetes as a teenager or even as an adult, rather than at age five. The advantages of anti-CD3 therapy may be compounded by combining it with antigen-specific agents, such as Diamyd's GAD65 vaccine, which is currently in later-stage clinical trials. Mouse models have thus far indicated that an insulin-related peptide vaccine could actually work synergistically with anti-CD3 therapy, although no such human trials have been conducted. For all this promise, however, type 1 patients will likely need to rely on insulin for many more years to come.

— by Kelly Close, Melissa Tjota, and Mark Yarchoan

6. In the News II: JDRF CGM Trial Shows Strong User Results

The JDRF released the results of its CGM trial in a special session at the beginning of this year's EASD annual meeting. The JDRF trial is, in our view, a landmark trial as it demonstrated for the first time that CGM can significantly lower A1c in a six-month time frame — health insurers and national health services please take note. In addition, the results of the JDRF study seem to point out some "requirements" for the success of CGM therapy: patients must be motivated, have a good understanding of the basics of insulin therapy, and have little fear of new technology. They need to be taught to react to trends in glucose and not exact numbers because CGM systems suffer from a certain amount of inaccuracy. In addition, it is critical that patients be able to call upon the resources of a team of health workers who are willing to change their preconceived notions about diabetes and to invest the time necessary for optimal use of the CGM device. We look very forward to seeing one-year data from this important trial at ADA 2009.

- **The primary phase of the study lasted six months.** Patients in the 'SMBG alone' group remained on their standard blood testing regimen (at least three tests per day). Patients in the "SMBG + RT-CGM" group were given a CGM device and instructed to use it as a supplement to standard blood glucose testing. Patients in the CGM group were allowed their choice of the Abbott, DexCom, or Medtronic CGM systems, and they could switch between them during the course of the study. Patients were given instruction on how to manage their glycemic control, and CGM patients were given additional training on optimal use of the device. Patients had a clinic visit at 1, 4, 8, 13, 19, and 26 weeks, and follow-up by phone at 3 days and 2, 6, 10, 16, and 22 weeks.

- **In adults, there was significant improvement in both primary and secondary outcomes with CGM use.** After the 26 week study, there was a -0.5% decrease in A1c in the CGM group from baseline and a tiny 0.03% increase in the control group, combining in a highly significant between-group difference of 0.53%. Significant differences were seen in the secondary outcomes as well with 35% of adults in the CGM group reaching a target of 7.0% compared to about 10% in the control group, 25% in CGM versus 5% in the control achieving a relative drop of ≥10%, and 47% versus 10% seeing an absolute drop of ≥0.5%.
- **In children (8-14 years) there was a significant improvement in secondary outcomes but not in the primary outcome of A1c.** There was a -0.37% decrease in children using CGM compared to a -0.22% decrease in controls, and the difference was not significant. In the secondary outcomes, 15% of CGM children and about 10% of controls achieved the glycemic target of <7%, about 15% of CGM versus about 10% control saw a ≥10% relative drop, and about 30% versus about 15% saw a ≥0.5% absolute drop. Only about 50% of children used the technology six days a week or more – we would like to see the sub-analysis of children who wore it continuously.
- **In adolescents (15-24 years), there was no significant difference in either the primary or secondary outcomes between the two groups.** Only about 30% of the adolescents and young adults wore the CGM continuously so we believe data in this group is difficult to study though there seems to be a clear message that adolescence is hard (we knew that) and that there are hurdles – probably many educational – for them to embrace a complex product.
- **There was no significant decrease in the rate of severe hypoglycemia between the two groups.** The rate of severe hypoglycemia tended to be slightly lower in the CGM group, with rates per 100 patient years hovering around 20. In the adult group, there was a non-significant trend toward increased severe hypoglycemia in adults, explained by the existence of a single identified outlier with six severe hypoglycemic events in six months. When the outlier is excluded, then hypoglycemia is comparable across the control and CGM groups. We would have expected hypoglycemia to be lower in the "treated" groups and believe that may be shown over a longer time period – severe hypoglycemia is not so common, especially among very well controlled patients.
- **As noted, the magnitude of the A1c benefit of CGM therapy was related to the number of days per week spent on CGM, with more frequent users seeing more improvement across all three age groups.** Thus, we don't see success associated with particular age groups as much as we see success tied to inclination to wear the device. Of particular importance is the finding that adolescents using CGM for at least six days/week improved their A1c by 0.5%, in line with results seen in the other age groups. Children who used CGM for the same period had an even bigger decrease of about 0.7%. Notably, overall, near-daily use of CGM was associated with similar treatment outcomes in patients of all ages.

— by Jenny Jin and Brendan Milliner

7. In the News III: JJDI Opened in Beijing

After the opening of the J&J Diabetes Institute in Beijing during the Olympic Games in July, we had the chance to sit down with Dr. Ken Moritsugu, Vice President of Global Strategic Affairs at J&J's Diabetes Franchise. Dr. Moritsugu has a wide range of experience, including his role as former Assistant Surgeon General of the United States. His perspective on the global state of diabetes is an incredibly valuable one, from our view, as he understands patients, healthcare providers, payors, and bureaucratic figures. We were lucky to speak with him about the recent opening of Beijing's JJDI as well as more broadly on the state of diabetes today.

- **Dr. Moritsugu on the scope of the diabetes pandemic:** When we look at the problem in the United States, you know that there are 24 million people who have diabetes. In addition to those 24 million, there are 57 million people who have pre-diabetes. If you add those two numbers, you come up with 81 million people, out of a population in the United States of 300 million people. Taking that number to the global population gives you an estimated 245 million people with diabetes from a total world population that is skirting seven billion people now (~6.8 billion people). That is a significant number, and those 245 million are projected to increase to 420 million by the year 2025.

- **Dr. Moritsugu on diabetes in Asia:** In Asia, diabetes is a particularly huge problem in India and China. Both countries have over 40 million people with diabetes and a significant number with pre-diabetes. Diabetes is a global issue, and that is why Johnson and Johnson wants to help be a part of the solution by establishing branches of the Johnson and Johnson Diabetes Institute. Obviously, the health system in the United States is not the same as the health system in China, and the local issues are different in China, Tokyo, and France where we are opening or have opened our four JJDIs at this point. We have been extremely pleased with the reaction and the acceptance of the JJDI in China. We had an opening, a dedication of the Johnson and Johnson Diabetes Institute in China, and the director general of China's CDC as well as other top level professionals were in attendance.

- **Dr. Moritsugu on some differences between Asian countries and the US in diabetes care:** At the opening session of the JJDI in Silicon Valley, we presented results from a survey of health professionals in which we found that a great number of patients with diabetes were being identified not by endocrinologists but rather by frontline community providers. This situation differs from the one in China where it is highly hospital-based and there are a number of major tertiary care hospitals, and you see that they are very interested in moving from a central hospital-based diagnosis and treatment model to community hospitals as a first step. Without anticipating where I think they are going - I don't want to presume that - but I think that they do appreciate the fact that the diagnosis, treatment, and monitoring of individuals with diabetes has got to be done at the local level. That is one major example of how in the United States, we have a different approach with a different system.

- **Dr. Moritsugu on the roundtable discussion held in China during the 2008 Olympic games:** The message was clear that everyone appreciated the importance of diabetes in China. Everyone fully agreed on what was important: to identify and to treat individuals. Everyone also saw the need to have good, up-to-date information available and disseminated to health professionals as well as to empower patients to take care of their chronic illness. These were all in tune with the approach that we have taken with the JJDI and specifically with the JJDI in Beijing. I think there was a universal embracing of the need for education and the appreciation that the JJDI was going to be part of the solution in helping China address this problem.

- **Dr. Moritsugu on diabetes education in China and the reimbursement situation:** There is an absolute need for more trained diabetes educators in China because the current system relies on nurses being the diabetes educators in China. Increasing the number of individuals who are trained as diabetes educators is one of the reasons and one of the areas that the Chinese professional societies, as well as the Chinese government, are eager to see the Johnson and Johnson Diabetes Institute assist them with. I mentioned before that while the JJDI may be global in scope, it is local in implementation, and we have local opinion leaders helping us identify certain needs, and helping us to develop a curriculum that addresses those needs. On reimbursement, that is an issue at the governmental level and that is where I believe that there is an increasing awareness of the need to compensate more diabetes educators in order to address the increasing numbers of people with diabetes in China. For example, that is the reason why individuals would go to a hospital for diagnosis and for treatment because while you are in the hospital, then there is reimbursement. Outside the

hospital, there isn't universal reimbursement for something like strips. This is where we are working together with the local key opinion leaders to be able to address the issue of patients understanding what they need to do as well as raising the awareness of the professional associations and the government on the benefits of SMBG and pump use.

- **Dr. Moritsugu on the perception of diabetes in China, patient-centered approaches to diabetes care, and chronic care healthcare models:** I think it depends upon the health care system within which individuals are being treated. In China, it is a physician-driven healthcare delivery system, and I'm not certain whether or not empowering patients has been as great a focus as it has been in the US. I think the message that we left in China through JJDI is not only do we need to help China in terms of increasing the number of diabetes educators as well as individuals who can treat diabetes, but that we want to share with them the whole concept of empowering patients in a chronic care model.

  I don't want you to think that I believe that we have the answer to chronic care here in the US. If anything, we need to move to a greater appreciation of the impact of chronic care on chronic disease. Diabetes, in my opinion, is simply the tip of the spear. We must improve the empowerment of individuals to help them take better care of themselves. We are not there yet, even in the United States. There is still a huge focus on the acute care system. For example, when you break a bone or get an infection, you go to a doctor or a health professional to get it fixed in one visit. The individual is less involved in the actual cure, but in the chronic care model, the individual is intimately involved in the day-to-day management and mastery of disease. That is a challenge to us here in the US, and it is part of the curriculum input in our JJDI here in Silicon Valley.

  Dr. Moritsugu on transferrable knowledge: We have learned a few lessons, most importantly: "if you build it they will come." JJDI Silicon Valley opened on the 29th of February 2008, and we began our first classes on the 3rd March 2008 with a single solicitation to the three target audiences – physician assistants, nurse practitioners, and diabetes educators. We have an annual capacity - once we are fully ramped up - of approximately 2,500. Within the first few weeks, we had nearly 3,500 individuals registered. Right now, we are sitting on a waiting list that we have been able to wiggle down to about 3,700. At this point we have been able to put about 700 individuals through Silicon Valley including offering everyone who comes through here the two-day course and the opportunity to wear an insulin pump for 24 hours. This experience provides a real insight to the health professionals about what they are attempting to communicate to the patients they serve.

- **Dr. Moritsugu on next steps for JJDI:** Right now it is still too early to be able to look at that kind of an outcome analysis from JJDI courses. We have not captured that information, and at this point, it is not on our radar screen. However, there may be investigators out there in the general public who may look at their own practice and analyze metrics themselves. I think that people who attend JJDI have left with an enthusiasm about wanting to truly make a difference, and I would not be surprised if we see these kinds of analyses generated not by us, but by those who are actually on the frontline in practice. In terms of the next step, I think what it really comes down to - and I can say this for China, for Tokyo, for the US, and for Paris – is it still boils down to what is needed at the local level. I believe that through the JJDI we are putting into place leaders for the institute as well as a panel of key opinion leaders who will continue to assess need, which will show different local needs, whatever they may be. We are not prescribing to any region what has to be done; rather, we are trying to find out what needs to be done, so we can be responsive and supportive towards that end.

  When I look at the United States, we look at the overwhelming response to a single solicitation and we are over capacity. What does that mean? Does that mean that we need another site(s)? We have only approached the first group: physician assistants, nurse practitioners, and diabetes educators. What

about the primary care providers? What about the endocrine fellows? What about endocrinologists? For all of these, we are here as the platform to address the needs of the local areas.

See www.closeconcerns.com for the full transcript of our interview with Dr. Moritsugu.

— by Kaku Armah, Melissa Tjota, and Kelly Close

8. Conference Pearls: AADE 2008 Annual Meeting

August 6-9, 2008 • Washington, DC • http://www.diabeteseducator.org

As always, this year's AADE was a whirlwind review of the state of diabetes care today. This year, the conference emphasized individualizing therapy – we had heard this theme at other conferences recently, including ADA, but it was particularly relevant here as diabetes educators are the healthcare providers who are primarily responsible for sitting down with patients and going over treatment plans. Key themes and highlights from the conference are below:

- **Continuous Glucose Monitoring (CGM) and Pumps:** On CGM, Jennifer Block, RN, CDE (Stanford University, Palo Alto, CA) said, "Nothing has taught me as much about diabetes and what it looks like for each individual than CGM." She noted that CGM is not easy to use, but that the benefits (short- and long-term) are well worth the effort. Block asked, "What are we seeing in CGM patients?" She answered: 1. Changes in meal behavior, 2. better appreciation for the effects of different types of foods, and 3. fewer carbs with breakfast. CGM also increases the use of pre-bolusing 10-15 minutes before a meal - especially before breakfast. She stressed the need for increased patient education about insulin action profiles as well as other glycemia-related medications like Symlin. Christine Zaveson, RN, RSN, CDE, PHN (Biggs Gridley Memorial Hospital, Gridley, CA) was also incredibly positive about CGM and felt it was a major advance in the management and treatment of diabetes.

- **Self-Monitoring of Blood Glucose:** William Polonsky, PhD, CDE (University of California, San Diego, CA) gave a particularly popular talk in which he jokingly revealed six "secret" strategies used by healthcare providers to discourage patients from SMBG. 1. be vague about SMBG recommendations; 2. never ask for, look at, or comment on results; 3. don't explain the results or let patients know how to understand them; 4. hide your own discomfort; 5. be controlling ("Explain that the patient must use SMBG results to restrict his/her sinful lifestyles"); and 6. focus on the worst number using the "red circle approach." He compared these methods of discouraging SMBG use to a new weight loss strategy where patients are told to weigh in once a day, lose weight if they are heavy, write down every number, and bring them into the doctor's office even though the numbers won't be discussed. He then moved onto a more serious discussion of how to enhance SMBG in patients including making it meaningful to patients; making use of the Noah's Ark Principle (highlighting change is the focus); looking at the patient's results; congratulating effort, not numbers; challenging self-worth interpretations; providing guidance in interpretation; and providing guidance in promoting action. He said that SMBG is not about judging or identifying mistakes but instead should focus on gathering data and learning together what does/doesn't work. Dr. Polonsky recommended promoting action instead of paralysis. The lecture room was packed, and the listeners relished the humor from Dr. Polonsky. Later in the conference, Andrew Drexler, MD (Gonda Diabetes Center, Los Angeles, CA) and Guillermo Umpierrez, MD (Emory University, Atlanta, GA) debated the role of SMBG in type 2 diabetes patients not on insulin. The opinion of the audience clearly favored testing ("How can you figure out where to go if you don't know where you are?" wondered one educator).

- **Diabetes in the Hospital:** CDC data identified a 234% increase in the number of hospital discharges that listed a diabetes diagnosis from 1980 to 2003. Multiple studies have shown hyperglycemia as a marker of poor clinical outcomes. David Baldwin, MD (Rush Medical Center,

Chicago, IL) called for improved follow-up and documentation of care for undiagnosed patients with in-hospital hyperglycemia. According to Carol Manchester, MSN, APRN, BC-ADM, CDE (University of Minnesota, Fairview, MN) in 2002, diabetes related hospitalizations totaled 16.9 million days, and $40.3 billion was spent for inpatient hospital care (ADA website 2006). She pointed out that Medicare will cease covering costs incurred as a result of a hypoglycemic or DKA events that were caused by hospital staff, and hospitals will have to absorb these fees – a great move in our view as greater focus should be put on inpatient management. We note though that one potential drawback could be that hospitals will treat hyperglycemia as conservatively as possible. We will be reporting on this change shortly.

- **ACCORD:** We were disappointed to report bad news on the ACCORD front: confusion in the field has started to rear its ugly head, as one audience member demonstrated when she said that her doctor told her to "let all the patients ride over 7%" after reading the trial's result. The overall message that came out of the ACCORD session was that an A1c below 7% was indeed "bad," but only for "ACCORD-like" patients, and CDEs were advised to watch out for these (older, sicker) people and set A1c targets in the 7.0-7.9% range. Let's hope that this message is clearly understood and that ACCORD doesn't create more microvascular complications. This is the first time we had actually heard advice to set levels over 7.0%, and we found this surprising and disappointing since while clearly ACCORD did not show macrovascular benefit for A1cs below 7%, the microvascular benefits hadn't disappeared the last time we checked.

- **Diabetes Pharmacotherapy:** Richard Pratley, MD (UVM College of Medicine, Burlington, VT) highlighted the confusion among doctors regarding the use of the type 2 treatment algorithm, and advocated rapid changes in treatment regimens, the use of combination therapy earlier in the disease progression, and the use of incretins. Edward Horton, MD (Harvard Medical School, Boston, MA) pointed out that adherence to prescribed drugs is not optimal for patients with type 2 diabetes; when looking at all drugs, the percent adherence is a measly 35%. Better treatments that address the complete metabolic needs, particularly preserving or restoring beta cell function, are needed. We have noticed that while many of the talks reviewed the current treatments available for type 2 diabetes, the speakers continually advocated for better treatments. The focus in the field seems to have shifted from simply lowering A1c to actually preventing macrovascular complications and the progressive loss of beta cell function.

- **Obesity, Prevention, and Diagnosis:** Obesity, the driver behind the increase in type 2 diabetes in pediatric and adult populations, was much discussed throughout this conference, but we noted a lack of concrete, actionable plans for how to reduce it. We have yet to see the results of the Diabetes Prevention Program implemented in a real-world setting. Here's to hoping that better obesity treatments will be available and better public policy decisions will be made to help stem the tide of "diabesity" in future years.

- **Healthcare System and Reform:** Mark McClellan, MD (Brookings Institute, Washington, DC) gave an impassioned speech about the current economic state of the healthcare system. He highlighted that 75% of spending is related to chronic disease, so prevention is the key. However, changing funding strategies can no longer be the sole solution as changes need to be made so that healthcare is delivered to improve quality, reduce errors, and increase prevention. Healthcare costs are increasing 3% faster than income, and within the next decade they will account for 16% of the GDP – wow, remember when it was 10% and we thought that was high? 12%? 14%? Robert Ratner, MD (Georgetown University Medical School, Washington, DC) emphasized that the prevention of type 2 diabetes should be feasible if preventive measures are instituted for the ~42 million people that have IFG or IGT. We couldn't agree more on the focus of this group, especially because of all the worry about the "tsunami" of diabetes complications coming in the next couple of decades.

- **Pregnancy and Pediatric Populations:** The conference closed with an inspiring speech by Francine Kaufman, MD (University of California, Los Angeles, CA) who gave a vivid overview of the threat posed by diabetes for children around the world, explaining the extent to which health care workers are seeing an unrelenting increase in the prevalence of both type 1 and type 2 diabetes in children worldwide. Children with diabetes have been found to be at a much higher risk for complications of the disease than was previously thought. A study in Australia found that of young type 1 patients with an average A1c of 8.5%, 16% have hypertension, 27% have peripheral neuropathy, 61% have autonomic neuropathy, and 20% have retinopathy. Other studies have found that children who have had diabetes for an extended period of time often have begun to develop arterial narrowing and dyslipidemia. Ninety-two percent of type 2 children have two or more independent risk factors for CV disease, compared to only 14% of type 1s.

- **Psychosocial Factors:** William Polonsky, PhD, CDE (University of California, San Diego, CA) said that, in a study with over 700 participants, more than a third agreed strongly that the long-term complications of diabetes couldn't be avoided. We find this very disturbing and believe that we need an educational push not only to inform people about the seriousness of diabetes, but also to spread the word that diabetes is eminently treatable and, with the proper management, does not have to be a debilitating disease. Patrick Lustman, PhD (Washington University in St. Louis, St. Louis, MO) focused on the correlation between depression and diabetes. Depression is an independent risk factor for type 2 diabetes, with a 37% increased risk. Dr. Lustman suggested that depression has the effect of adding another layer of insulin resistance, which he felt explained the link between diabetes to obesity, hyperglycemia and disease progression. Nearly one quarter of all cases of obesity are attributable to the association with mood disorder! We have been writing more of late about behavioral problems associated with diabetes, and we believe much more work needs to be done on this front.– We also feel that this further supports the need for much more (reimbursed) time for patients and HCPs.

— by Kaku Armah, Dana Lewis, Brendan Milliner, Melissa Tjota and Ellen Ullman

9. Literature Review: Assessing the Cardiovascular Safety of Diabetes Therapeutics

Goldfine, A.B. (2008) New England Journal of Medicine: 359(11), 1092-95.

http://content.nejm.org/cgi/content/full/359/11/1092 (free full text)

The September 11 issue of the New England Journal of Medicine contains a controversial editorial by Dr. Allison Goldfine, head of the section on Clinical Research at the Joslin Diabetes Center, regarding the role of cardiovascular outcome studies in diabetes drug approval. As a reminder, the FDA Endocrinologic and Metabolic Drugs Advisory Committee (of which Dr. Goldfine is a member) recently voted 14 to 2 in favor of requiring all new type 2 diabetes drugs to demonstrate cardiovascular safety through a hard outcomes clinical trial, even in the absence of concerning cardiovascular signals (for an in-depth review of this meeting, please refer to our "July 1-2 FDA Advisory Committee Panel Meeting").

In her editorial, Dr. Goldfine defends the advisory panel's position in favor of cardiovascular requirements and proposes a specific integrated clinical development program with a separate pre-approval and post-approval component. Her proposal is for all new diabetes drugs to rule out an "unacceptable" level of cardiovascular risk in a pre-approval cardiovascular outcomes trial, followed by a longer post-approval clinical trial to more clearly establish cardiovascular safety or benefit. This proposal closely resembles the hybrid pre-approval "screening" trial/post-approval "confirmation" trial program introduced by Dr. Steven Nissen at the FDA Advisory Committee meeting. Dr. Goldfine does not provide an opinion on what level of cardiovascular risk should be tolerated by the pre- and post-

approval trials, and she suggests that the clinical trial requirements might be individualized based on a particular drug's molecular mechanism and pre-clinical data.

We believe that Dr. Goldfine's suggestion of individualization is important; drugs with pre-clinical cardiovascular signals should be treated differently than drugs with no such signals. Nonetheless, we remain concerned that the implementation of Dr. Goldfine's integrated trial design proposal could have wide-reaching negative consequences on drug development. Transitioning to an integrated trial design will certainly require significantly higher up-front costs from a regulatory as well as clinical development perspective, and we believe that the increased attention placed upon cardiovascular outcomes will distract attention from microvascular endpoints. Too, delaying novel drugs in an era where more alternatives are clearly needed (payors estimate adherence for current diabetes drugs at about 50% in aggregate) is a negative for patients, healthcare providers, payors, and taxpayers, in our view, since this contributes to lower adherence and likely more long-term complications. We believe such a new standard for diabetes therapeutics, with its increased regulatory hurdles, would deter future investment in diabetes research programs.

- **Dr. Goldfine begins her editorial by recognizing the need for new drugs to treat type 2 diabetes, and suggesting that the continued approval of diabetes medications on the basis of lowering glycemia is merited.** She explains that although there are eight new classes of diabetes therapies on the marketplace (metformin, alpha-glucosidase inhibitors, thiazolidinediones, glinidines, GLP analogues, amylin analogues, DPP4 inhibitors, and bile acid sequestrants), type 2 diabetes is a chronic disease and additional safe and effective agents are needed. Additionally, she recognizes that although diabetes and cardiovascular disease are associated, they are separate diseases and therefore it is appropriate for drugs to be approved to treat diabetes only. We agree entirely with these points, although believe they could have been highlighted more clearly in Dr. Goldfine's editorial. For example, it may have been helpful for readers who don't follow diabetes closely to have statistics supporting the need for new diabetes drugs, such as the fact that nearly half of diabetes patients in the US are not at goal (A1c<7.0%). Otherwise, some may feel, as was posited during the meeting (see "July 1-2 FDA Advisory Committee Panel Meeting") that "there are already ten drugs, why are more needed?" as was questioned during the session. She doesn't address the improvements in side effect profile that might be beneficial – some current drugs cause weight gain, hypoglycemia, gastrointestinal problems, etc. that can contribute to poor patient adherence.

- **Pointing to the ACCORD study and Dr. Nissen's meta-analysis of Avandia, Dr. Goldfine contends that approved diabetes agents might impart greater cardiovascular risk than was previously appreciated.** The explosion of treatment options for type 2 diabetes has resulted in improvement in microvascular complications (i.e. retinopathy, neuropathy, and nephropathy), but it has yet to yield compelling reduction in macrovascular complications, most notably cardiovascular disease. Dr. Goldfine notes that most longitudinal evidence suggests that improved glycemic control in the era of novel agents and combination therapy has resulted in improved metabolic control, reduced end-stage kidney disease, and reduced vision loss. Such effects were notably seen in studies like the UKPDS, which recently presented results at EASD 2008 showing a legacy effect with treating early-on to improve glycemic control – and showing macrovascular benefits. (As she rightly points out, cardiovascular disease remains the number one cause of illness and death in diabetic patients. During the Claude Bernard lecture at EASD 2008, Dr. Ralph DeFronzo stated that 80% of deaths among patients with diabetes results from cardiovascular disease.)

- **Dr. Goldfine advocates for an integrated trial design for all phase 2 and phase 3 pre-approval trials, which could improve assessment of cardiovascular risk.** Specifically, she suggests that an independent blinded adjudication committee should monitor cardiovascular events for diabetes drugs, and that there should be standardization of data collection and analysis. This

proposal is similar to that put forth by the FDA Endocrinologic and Metabolic Drugs Advisory Committee in their recent meeting. Under current FDA approval expectations, the procedures and data collection methods of phase 2 and phase 3 trials may have some variation in measuring adverse events. We believe that an integrated trial design may offer companies improved scalability of clinical development as well as more longitudinal safety data for both early phase and NDA filings. Such benefits, however, may never exceed the costs associated with conducting post-approval trials that are expected to maintain the methodological rigor of pre-approval RCTs.

- **More controversially, Dr. Goldfine argues that the FDA should require all new diabetes drugs to rule out an "unacceptable" level of cardiovascular risk in a pre-approval cardiovascular outcomes trial, followed by a longer post-approval clinical trial to more clearly establish cardiovascular safety or benefit.** Dr. Goldfine argues that companies may benefit from the ability to detect unfavorable cardiovascular risk profiles prior to approval by discontinuing the drug development early on. This possibility may be beneficial for firms with regards to the opportunity cost of late stage development, marketing, and brand costs associated with the withdrawal of approved drugs. Alternatively, just as pre-approval studies are underpowered to demonstrate clinical benefit, they are also underpowered to show population level cardiotoxicity since chance may explain cardiovascular events in a small, early group of patients. This point was a significant question the FDA Advisory Committee had to take into account because such a trial would require thousands more years of patient data. As such, the use of early-stage pre-approval data may result in discontinuing clinical development of viable drug candidates.

- **Dr. Goldfine does not provide specific recommendations as to what sort of hazard ratios would have to be ruled out in pre-approval trials.** Interestingly, she suggests that the clinical trial requirements might be individualized based on a particular drug's molecular mechanism and pre-clinical data. This is somewhat of a departure from the clinical trial requirements discussed by the FDA Endocrinologic and Metabolic Drugs Advisory Committee, which advocated more of a one-size-fits-all model. Although we agree with Dr. Goldfine's belief that clinical trial requirements should be individualized based on a particular drug's molecular mechanism and pre-clinical data, we are concerned that any sort of cardiovascular endpoints trial will significantly harm diabetes drug development. We calculate that even ruling out a relative hazard ratio of 1.333 (meaning 33% more likely to cause cardiovascular harm than another drug) might require approximately 5,000 participants followed for five years (assuming a population with a baseline 2% per year rate of cardiovascular disease/myocardial infarction/stroke). We believe that the FDA has tools to assess cardiovascular risk based on preclinical and mechanistic information, and only drugs with a cardiovascular signal should undergo a cardiovascular outcomes trial.

- **Dr. Goldfine mentioned that careful consideration needs to be given to including high-risk patients in the proposed preliminary cardiovascular-event-driven trial.** In order for the preliminary trial to be brief but still include a sufficient number of cardiovascular events to permit evaluation, it would need to be performed in high-risk patients. These high-risk patients include patients with diabetes and a history of myocardial infarction, bypass grafting, or stenting. Such patients, however, are very vulnerable to metabolic changes and other unknown adverse events. Thus, inclusion of such patients in initial randomized, controlled trials should be undertaken in consultation with the FDA to ensure that the likelihood of preclinical data demonstrating cardiovascular safety is balanced with the ethics and reliability of such data. While we agree that subjecting high-risk patients to additional cardiovascular risk is unethical, we believe it is important to remember that existing trial frameworks include drug safety monitoring boards, which are empowered to prevent trial subjects from being subject to any additional harm even when adverse drug events are noticed prior to trial completion. Furthermore, we believe that a more effective means to ensuring effective trial design

while maintaining the highest ethical standards, is to utilize active surveillance for adverse events during a trial rather than to exclude patient populations that may tremendously benefit from therapies in development. In short, more trials with patients already at risk for CVD seems like a bad idea given what we learned from ACCORD.

- **We are surprised that the idea that drugs for diabetes should prompt cardiovascular benefit has even been raised as an idea.** Dr. Goldfine writes, "Since, as the advisory committee agreed, it is sufficient for a diabetes drug to improve glycemia to be considered to have clinical merit, clinical trials could be designed to rule out an unacceptable increase in cardiovascular risk rather than be required to demonstrate cardiovascular benefit." Why the idea of "required to demonstrate cardiovascular benefit" is in consideration is unclear to us.

- **In summary, Dr. Goldfine summarized the Endocrinologic and Metabolic Drugs Advisory Committee position as favoring utilization of glycemic reduction as the primary clinical endpoint of importance, but with increasing attention and potentially radical reformulation of the clinical development process to assess cardiovascular safety in diabetes therapeutics.** Such a transformation may create more reliable longitudinal data, however, we believe that a transition to new, integrated trial frameworks would construct cost barriers and expectations for outcomes so high that companies will be discouraged from developing a wide array of future diabetes therapies. This would be a lose-lose for patients and healthcare providers and payors and taxpayers, the latter two of whom bear the brunt of the costs of complications from diabetes – $56 billion was spent on this in 2007 alone.

— by Kelly Close, Melissa Tjota, and Mark Yarchoan

10. Conference Preview I: The Obesity Society's Annual Scientific Meeting

October 3-7, 2008 • Phoenix, AZ • http://www.obesity.org/

The Obesity Society's Scientific Meeting begins Friday in Phoenix with the annual pharmacotherapy update – this is one of our favorite parts of the meeting every year and although we don't yet know the speakers, there are certainly many drugs and drug combinations to discuss.

On Saturday, there are several highlights in the multi-track program. First, we'll hear the "Key Lecture" focus on mechanisms of Leptin action – this could be instructive if it offers further learning that we can use to develop our thinking on Amylin's INTO program. Next is an oral symposium on the treatment of pediatric obesity, followed by another oral session on obesity and disability, sure to be a hot topic. Closing the day, you may want to choose between one oral symposium on physical activity levels and weight loss and the clinical professional practice symposium on weight management strategies.

On Sunday, there will be a briefing on antipsychotic drugs and obesity – we hope this will be of interest as we try to learn more on Vivus and Orexigen and larger companies with endocannabinoid receptors – specifically Merck and Sanofi. Later that day hear from experts on the metabolic effects of bariatric surgery – listen for Dr. David Cummings in particular, who knows more than we can imagine on this topic.

On Monday, there will be a talk on using evidence to treat overweight and obesity – we know there isn't too much evidence, so we worry this one might be less interesting than it sounds. Adipokines are currently a hot topic and there is an oral symposium later that day that sounds very good. At the same time as the session on adipokines are sessions on early-life risk factors for obesity and then a session we definitely won't miss, one of smart use of obesity drugs, with a whole slew of experts including Dr. Lou Arrone.

On Tuesday, the other hot topic, inflammation, will come up at a symposium called "Fat in the Fire" – this will be interesting to hear and Dr. Allison Goldfine is on the panel – she's author of a recent editorial paper in NEJM that we found quite unsettling (see page 32 for details). At the same time is another symposium on bariatric surgery that we're excited to see – in particular, to hear Dr. Harvey J. Sugarman speak.

We'll be back with a report on this conference in not too long – and we hope to see many of you in the land of the sun! For those going, check out our list of top sessions below.

Pre-Conference Session: Friday, October 3

- **(1:00-4:00pm) Pharmacotherapy Update.** *Speakers TBD.*

Day 1: Saturday, October 4

- **(10:15-11:15am) Key Lecture: Mechanisms of Leptin Action and Leptin Resistance.** Harvey Grill, PhD and Martin Myers, MD, PhD.
- **(1:45-3:15pm) Oral Symposium: Treatment of Pediatric Obesity.** Sarah E. Barlow, MD, MPH; Denise Wilfley, PhD; Robert Berkowitz, MD; and Thomas Inge, MD, PhD.
- **(1:45-3:15pm) Oral Symposium: Obesity and Disability.** Tamara B. Harris, MD; Dawn Alley, PhD; and Walter J. Rejeski, PhD.
- **(3:30-5:00pm) Oral Symposium: Physical Activity Levels and Obesity.** John M. Jakicic, PhD; Anne McTieran, MD, PhD; Robert Ross, PhD; and William L. Haskell, PhD.
- **(3:30-5:00pm) Clinical Professional Practice Symposium: Enhancing Weight Management Strategies.** Judy Loper, PhD, RD; Greg Hottinger, MPH, RD, LDN; Michael Scholtz, MS, CFT, CSCS; and Julie Schwartz, MS, RD.

Day 2: Sunday, October 5

- **(8:00-9:00am) Oral Symposium: Antipsychotic Drugs and Obesity.** Mai A. Elobeid, PhD; John W. Newcomer, MD; Marilyn Ader, PhD; and Kishore M. Gadde, PhD.
- **(3:45-5:30pm) Oral Symposium: The Metabolic Effects of Bariatric Surgery.** Phillip Schauer, MD; Bruce M. Wolfe, MD; David E. Cummings, MD; Francesco Rubino, MD; and Mary Elizabeth Patti, MD.
- **(3:45-5:00pm) Oral Symposium: Building Evidence for Environmental and Policy Solutions to prevent Childhood Obesity.** Mary Story, PhD, RD; Marlene B. Schwartz, PhD; Patricia Crawford, DPH, RD; Robert C. Whitaker, MD, MPH; and Roland Sturm, PhD.
- **(3:45-5:00pm) Clinical Professional Practice Symposium: Weight Management for Life Stages.** Robert F. Kushner, MD; Angelo Pietrobelli, MD; Arya M. Sharma, MD, PhD; Matthew W. Gillman, MD; and Caroline M. Apovian, MD.

Day 3: Monday, October 6

- **(10:00-11:00am) Clinical Professional Practice Symposium: Using Evidence to Treat Overweight and Obesity.** Rebecca S. Reeves, PhD; Christina Biesemeier, MS, RD; and Nancy Cooperman, MS, RD.
- **(3:45-5:00pm) Oral Symposium: Adipokines.** Claire M. Steppan, PhD; Barbara B. Kahn, MD; Evan D. Rosen, PhD; John C. McLenithan, PhD; and Robert V. Considine, PhD.

- **(3:45-5:30pm) Oral Symposium: Early-Life Risk Factors for Obesity.** Matthew W. Gillman, MD; Suzanne Ozanne, PhD; Dana Dabelea, MD, PhD; Linda Adair, PhD; and Nicolas Stettler, MD, MSCE.
- **(3:45-5:30pm) Clinical Professional Practice Symposium: Smart Use of Obesity Drugs.** Peter D. Vash, MD, MPH; Richard A. Lutes, MD; Louis J. Aronne, MD; and Frank L. Greenway, MD.

Day 4: Tuesday, October 7

- **(11:00am-12:45pm) Oral Symposium: Fat in the Fire: Inflammation and Obesity.** Susan K. Fried, PhD; Allison B. Goldfine, MD; Andrew S. Greenberg, MD; Anthony W. Ferrante, MD, PhD; and James B. Meigs, MD, MPH.
- **(11:00am-12:45pm) Clinical Professional Practice Symposium: Bariatric Surgery.** Harvey J. Sugerman, MD; Bruce M. Wolfe, MD; Edward H. Livingston, MD; and Phillip R. Schauer, MD.

— by Kelly Close and Melissa Tjota

11. Conference Preview II: Cardiometabolic Health Conference

October 15-18, 2008 • Boston, MA • cardiometabolichealth.org

This time of year we always look forward to learning more on obesity, with the NAASO meeting (Obesity Society) in the works. Another meeting that excites us just as much is the annual Cardiometabolic Health Conference, which takes place, as always, in Boston from October 15–17. Chaired by the powerhouse team of Dr. Jay Skyer of the University of Miami, Dr. Dick Nesto of Harvard, Dr. Bob Eckel of the University of Colorado, and Dr. Christie Ballentyne of Baylor, there's lots of great learning in store here.

First of all are three sure-to-be-great keystone talks. On Thursday, Dr. Richard Kahn of the Joslin Clinic will be speaking on new insights on mechanisms of insulin resistance, while on Friday, Dr. Paul Ridker of Brigham and Women's Hospital in Boston will speak on the evolving role of biomarkers for cardiometabolic risk reduction, and on Saturday, Dr. Peter Libby of Harvard will speak on mechanisms of atherosclerosis.

Other not-to-miss sessions on Thursday include Dr. Harold Lebovitz of SUNY Brooklyn on gut hormones and their impact on metabolic control, Dr. Alice Lichtenstein of Tufts University on what should be recommended to patients to reduce cardiometabolic risk, and Dr. Bob Eckel chairing a session on integrating (and ostensibly creating) a successful obesity management practice - in that session, we'll hear from Dr. Lou Arrone of Columbia University on what to do when diet and exercise alone fail.

Friday might be the day with the most surprises as on tap will be new data on obesity in a "Late Breaking Clinical Trial Data session" – wow! We don't know what that focus will be yet but we'll be there. Following this will be a session with noted experts Dr. Marty Abrahmson of Joslin and Dr. Silva Arslanian of the University of Pittsburgh, who will be discussing clinical controversies in the treatment of type 2 diabetes. Whew! Dr. Peter McCullough of University of Washington will present on the kidney as a potential cardiovascular risk equivalent, followed by what is sure to be an intriguing panel of experts talking about simultaneous management of dyslipidemia, hypertension, and type 2 diabetes– this should be great learning on individualized therapy, which is a new, important theme that's come out of this year's meeting. Dr. McCullough has done some amazing work on the best ways to treat chronic care – don't miss this session.

Saturday look for Dr. Bob Eckel of Colorado State University to talk about hypertrygliceridemia – this is yet anther topic we've been hearing a lot about lately and we hope to learn more about the latest thinking on clinical management. Dr. Dick Nesto of Harvard Medical School will also talk about screening the patient at higher cardiometabolic risk – this one should be most interesting, with a focus on assessing the latest technologies and their utility in practice.

Also on Saturday, to close the meeting will be a panel discussion on clinical controversies in lipid management – here we'll get the scoop from Dr. Bob Eckel, Dr. Henry Ginsberg, and Dr. Nancy Houston Miller.

In addition to multiple sessions of note, there are six corporate symposia that we term "can't–miss":

1. *Management of Obesity, Type 2 Diabetes, and CVD Disease: A role for CB1 Blockade? (Sanofi-Aventis)*
2. *Targeting the Pathophysiology of Type 2 Diabetes: The Emerging Role of Incretin-Base Therapies (Novo Nordisk)*
3. *Integrated Neurohormonal Therapy: An Emerging Approach for Cardiometabolic Risk Reduction (Amylin)*
4. *Incretin Mimetics and Cardiometabolic Risk Reduction: Targeting Diabetes, Obesity, Hypertension, and Dyslipidemia (Amylin/Lilly)*
5. *Comprehensive Cardiometabolic Risk Reduction: New Approaches to Targeting Type 2 Diabetes, Lipids, and Hypertension (Daiichi-Sankyo)*
6. *From Pipeline to Practice: The Role of DPP-4 Inhibitors in Achieving Glycemic Control (Takeda)*

See you in Boston!

— by Kelly Close

12. Diabetes Coming and Going

- **Bill Arthur** was named Vice President of Business Development at Insulet Corporation. Prior to this appointment he was President and COO of SpectRx.
- **Amy Erbskorn** left Abbott Diabetes Care where she led continuous monitoring commercialization.
- **Dennis Kim** was recently hired as Senior Vice President, Head of Obesity and Metabolic Disorders at Orexigen. He was formerly Vice President of Medical Affairs and Chief Medical Officer of EnteroMedics.
- **Christine Poon**, Vice Chairman of the Board of Directors and Worldwide Chairman, Pharmaceuticals Groups at Johnson & Johnson, plans to retire on March 1, 2009.
- **William Tamberlane** is the founding member of the scientific advisory board formed by MicroCHIPS. He is head of pediatric endocrinology at Yale University.
- **John Timberlake** is the new President and Chief Commercial Officer of Valeritas.
- **Christ Viehbacher**, former GlaxoSmithKline executive, was appointed as the new chief executive at Sanofi-Aventis.
- **Scott Ward** of MAP Pharmaceuticals recently joined the company's Board of Directors.
- **Denny Ware** joined the Board of Directors at Pelikan Technologies after having most recently served at President and CEO of Kinetic Concepts Inc. (KCI).

- **Gregg Zegras** was appointed as Chief Operating Officer of the integrated media network of LifeMed Media company dLife.
- **Vyteris** announced the formation of a Scientific Advisory Board composed of Russell Potts, Ph.D., chairperson; Richard Guy, Ph.D. (University of Bath, Bath, UK); Randy Mrsny, Ph.D. (University of Bath, Bath, UK); and Stephen Silberstein, M.D., FACP (Jefferson Medical College, Philadelphia, PA).
- **This isn't really a "coming or going" but we thought we would report that science powerhouse Adam Heller, PhD,** received the 2007 National Medal of Technology and Innovation. Dr. Heller was co-founder of TheraSense, which developed new approaches to glucose measurements that eventually led to Abbott's Freestyle Blood Glucose Monitoring System and the Freestyle Navigator Continuous Glucose Monitoring System.

13. DCU Stock Chart and Final Thoughts

	30-Sep-08	29-Aug-08		28-Mar-08		28-Sep-07		IPO		Market Cap
GSK	43.46	46.97	-7%	42.28	3%	53.3	-18%	-	-	111.77B
NVO	51.2	55.56	-8%	66.73	-23%	60.52	-15%	-	-	38.38B
AMLN	20.22	21.98	-8%	27.99	-28%	50	-60%	14	44%	2.75B
BIOD	3.35	17.87	-81%	10.55	-68%	17.04	-80%	15	-78%	84.97M
OREX	10.79	11.63	-7%	10.19	6%	13.21	-18%	12	-10%	360.38M
PODD	13.92	14.34	-3%	14.66	-5%	21.75	-36%	15	-7%	391.51M
MNKD	3.85	3.25	18%	5.66	-32%	9.68	-60%	14	-73%	395.22M
DXCM	6.19	6.88	-10%	4.07	52%	10	-38%	12	-48%	183.42M
HDIX	9.68	10.31	-6%	7	38%	9.58	1%	12	-19%	172.93M

It's been quite a difficult month for diabetes stocks – there are literally no stocks that are up versus a month ago though we note that half our portfolio is up versus six months ago. One sobering note is that versus a year ago, all the stocks are down double digits except HDI, which is the only stock up even a little. An even more sobering note – all stocks are below their IPO prices except Amylin, which went public in 1992.

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