

DIABETESCLOSEUP

The Leading Source of Diabetes Business News

It's All Connected...

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From the Editor

“Slumdog Millionaire” has put India in the forefront of American culture, exposing audiences to some of the grim realities in this large, complex country – it has beauty and dynamism, but also poverty, violence, and corruption.

Well, it also has diabetes, and I got a first-hand look at how India is handling its diabetes pandemic, and a good deal more, when I attended the Diabetes Summit for Southeast Asia in Chennai, India, which took place November 27-30, 2008 and was organized by the World Diabetes Foundation (WDF) in collaboration with the World Health Organization (WHO), the South East Asia Regional office (SEARO), the International Diabetes Federation (IDF), and the World Bank. As it happened, I arrived on Nov. 26, the first day of the terrorist attacks in Mumbai, which killed at least 173 people. Fortunately, I flew into Chennai, but when I arrived at my hotel, security was already high, and I couldn't enter the hotel without going through what was like security in Heathrow – and a Sri Lankan minister ahead of me had seven bodyguards. As our world would have it, I found out about the bombings from a US DCU reader by BlackBerry, not by anyone in India.

Despite the heightened tensions and tragic attack, let me say that I felt very fortunate to have attended this meeting, in part because I got to conduct interviews with two extraordinary individuals in the diabetes field – Dr. Viswanathan Mohan, who runs Diabetes Specialty Centers across southern India as well as two research centers and Lars Sorensen, CEO of Novo Nordisk. These full interviews have been sent to our Closer Look subscribers and excerpts appear in this issue.

As most of you know, the increase in diabetes in India, virtually all type 2 diabetes, is staggering. An estimated 40 million Indians have the disease, only about half diagnosed, and only about half of those receive treatment. Indians have a genetic susceptibility, worsened by the kind of lifestyle changes – urbanization, increasingly sedentary behavior (especially by those with higher incomes), fast foods, weight gain, increased stress, etc. – that are increasing diabetes in the US and around the globe. But what makes India so different, and sobering, was the crushing poverty.

Of course we have poverty in our country, but it's not as prevalent. I realize that India is becoming an economic powerhouse, but right now, there are far more slums than millionaires. Things are bad in the US and Europe, I know, but the conditions and the trickle down in India were unimaginable to me before I saw them. Indians with diabetes have a real economic problem because they have to pay for supplies out of their own pocket, and it's estimated that patients with advanced diabetes can pay 25 percent of their income on treatment. And we're talking basic supplies. Glucose meters and strips, for example, are beyond the reach of most patients. In India, one checks blood glucose by going to the hospital. Armed with my pump and CGM and Symlin and glucagon, I felt incredibly fortunate and incredibly naive. What do I know about pain, really?

I had the opportunity to travel with Dr. Mohan in his van where he visited patients in the countryside, and one impression was how so many people felt resigned to their fate – if they didn't have diabetes already, they were going to get it (“I'll get it by the time I'm 50. We all will...” said one nurse), and complications seemed all but inevitable. If you ever needed to be convinced that prevention of disease and prevention of complications is our only salvation for diabetes, travel through India.

To Dr. Mohan's credit, he's doing some amazing things in terms of education and awareness. He has brought treatment and technology to people with diabetes in a way that we don't often see in the US – especially to those in rural India. He runs the largest practice for people with diabetes in the world, and he thinks big. Very big. As one example, he uses CGM on as many type 2 patients as he can – not full time use, but to diagnose problems early and to give the right therapy. The more well off patients subsidize the less well off patients, and he knows he's saving long-term.

During a rural visit, I stayed in Dr. Mohan's van while he examined the eyes of his patients. He then downloaded the image and sent it electronically to his wife, who's an ophthalmologist, in Chennai. She could evaluate the image to determine if the eyes had any evidence of diabetic retinopathy or other eye disease. At one point, a woman of about 70, wearing a beautiful sari, stepped into the van for an eye exam. An interpreter told her that I also had diabetes, and we exchanged a knowing glance. The picture of her eyes was taken and sent off to Chennai. And then we waited. We waited for five minutes, and the tension built – would her eyes be okay, or was there a problem? And what was taking so long? I sat there nervous as well. I watched and my stomach knotted up, just like it does when I wait at UCSF for my eye results. They weren't my eyes, but I know that drill – that anxiety, and fear, wondering how your body part is going to fare, if it is going to betray you.

Finally, a loud voice came through a speaker. It was Dr. Mohan's wife calling in. She spoke in her native tongue, and I saw the old woman. A smile creased her face, her eyes were calm and bright. She was so happy she almost cried. She looked at me and I at her; I didn't understand a word, but I understood everything. I tend to be an optimist about diabetes, even in India, so that memory I'll always take with me. Godspeed, Dr. Mohan.

Sincerely,



Kelly L. Close

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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/:

- **January 20:** Help the FDA Help Us...
- **January 19:** Just What the World Needs: an ‘Excuse’ to Drink More Coffee!
- **January 18:** Type 1 Kids Lack Vitamin D
- **January 6:** Ask the FDA to Bring in More Diabetes Patient Input! Sign a Patient-Led Petition...
- **January 5:** The Future is Now — NYC is Again Ahead of the Curve, Implementing Electronic Health Records
- **January 2:** Five Simple Tricks to Keep You on Track in the New Year
- **December 31:** Don’t Faint — Bush Made the Nice List this Season
- **December 30:** Even the Experts Can Get it Wrong — the High and Low Tech of Healthcare Innovation
- **December 29:** Hooray for IHOP
- **December 27:** Obesity Tax Prompts Spirited Debate
- **December 17:** More on Why Childhood Obesity is Even More Dangerous Than We Thought!

Videos

Below is our favorite video in diabetes this month:

- Triabetes released this new documentary trailer, which does an outstanding job of articulating why their work is important (grab a Kleenex): <http://vimeo.com/2722286>.

Coming soon in DCU...

We're off to Austria at the end of January for the AIDPIT (Artificial Insulin Delivery Pancreas and Islet Transplantation) meeting. Then we're in New York City in early February for the 56th Annual ADA Postgraduate Course. Stay tuned...

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1. Quotable Quotes in Diabetes

Things that have not come to pass...

“I know, FDA has lots of guidances, but these will be in areas where we think the regulatory pathways could be improved or better defined, and we expect to learn something from outside experts in the open process of developing the guidances. They include new product guidances for obesity, diabetes, and cancer. In these critical areas, we think that new regulatory standards can reduce the time and cost of product development. That, in turn, should lead to more investment in much-needed new products.”

— Mark McClellan, MD (Brookings Institute, Washington, DC), FDA Commissioner 2002-2004, clarifying in a speech before PhRMA on March 28, 2003, that there would be improvements in FDA guidances for drug development. This view appears to contrast with the current regulatory environment, and it is worrying that drug development may be slowed by the recent FDA guidance on cardiovascular risk assessment for diabetes medications.

Global impact of the economic downturn

“This is a poverty problem. I was trying to make the point in my talk at WDF that this is a government responsibility, but we can’t wait until the governments assume that responsibility. It’s not without problems that private corporations are the donors and that profit-based companies are developing businesses based on [an impoverished population]. The government is not doing it, so we have to assume the responsibility or at least take some action.”

— CEO Lars Sørensen (Novo Nordisk, Bagsværd, Denmark) commenting during an interview with *Diabetes Close Up* on the problems associated with addressing diabetes and obesity in both developed and developing countries.

All hail insulin!

“Insulin is one of the body’s ways to protect you against the ravages of eating. If it is there at the right time, you are protected. If it isn’t there, then you aren’t protected. Diabetes is not the type of thing that kills you immediately; it is a progressive disease that hurts you a little bit all the time, and the damage accumulates over time.”

— President and CEO Solomon Steiner (Biodel, Danbury, CT) pointing out the importance of insulin at the 27th Annual JP Morgan Healthcare Conference.

Fight for a healthier lifestyle!

“Why is it important to help the patients have a healthier lifestyle? Over 40% of all disease morbidity has to do with patients’ behaviors. The other part includes genetics, environment, and things that we can’t quite control as clinicians. By encouraging healthier lifestyles, we can clearly improve healthcare outcomes, reduce cost, improve services, and in some cases, generate new revenue.”

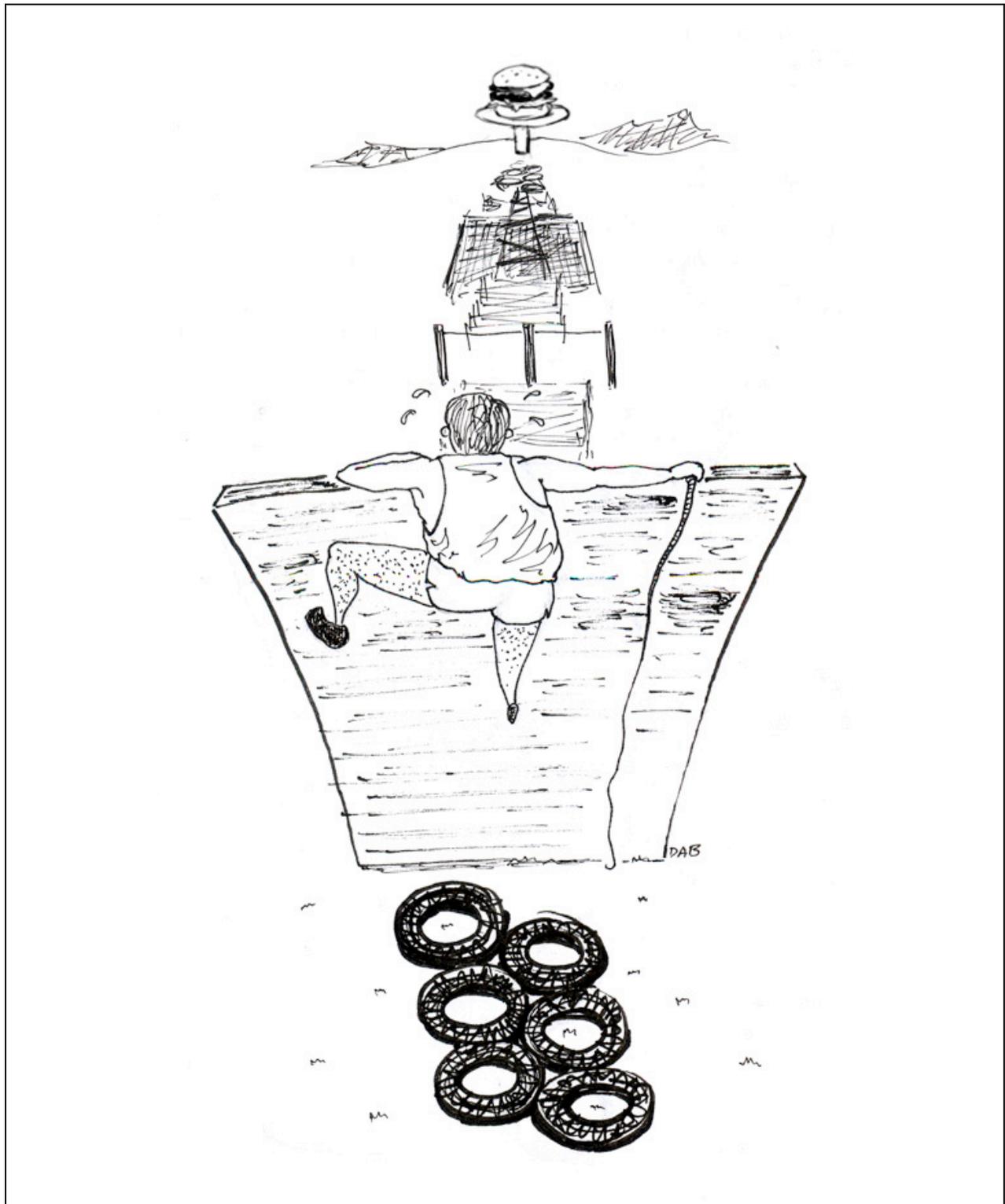
— Neal Kaufman, MD, MPH (DPS Health, Los Angeles, CA) talking about the importance of healthier lifestyles and how it can be aided by the Virtual Lifestyle Management Service (VLM) from DPS Health.

More than just money...

“It is not only about the economy, but we also have to have more education, increase awareness of diabetes and obesity, and train more professionals in diabetes.”

— Viswanathan Mohan, MD, MPH (Dr. Mohan’s Diabetes Specialities Center, Chennai, India) commenting on improvements that needed to be made to increase diabetes awareness in India.

2. diaTribe FingerSticks



-by Daniel A. Belkin

3. DCU Company Watch

- **XOMA — Tough economic environment leads to a 42% workforce reduction:** XOMA, a biotech company focused on the development of therapeutic antibodies, announced a 42% workforce reduction on January 15. This translates to 144 employees who will lose their jobs and a \$3 million charge assessed to the company in 1Q09. These changes leave the company with 197 employees. CEO Steven Engle attributed the workforce reduction to the challenging economic climate and forecasted that manufacturing demand in 2009 will not meet expectations. Management reported that sufficient quantities of XOMA 052, an anti-IL-1 beta antibody targeting diabetes associated inflammation, have been made for planned phase 1 and phase 2 studies. As most of the layoffs were in manufacturing, we think that they reflect lowered guidance for XOMA's marketed plaque psoriasis and age-related macular degeneration medications. As a reminder at the RBC Capital Markets Healthcare Conference on December 10, 2008, management stated that 2Q09 is the target timeline for initiation of phase 2 clinical studies for XOMA 052, based on positive pre-clinical data on the use of XOMA 052 that showed increased insulin production, proliferation of insulin-producing islet cells, decreased islet cell death, reduction in peripheral insulin resistance and lower cholesterol levels. Obviously that data is extremely early stage, but this seems like a promising candidate and we are hopeful that development can continue to determine whether or not the compound is viable.
- **DexCom/J&J — Development agreement to extend internationally:** On January 12, DexCom announced an expansion to its development agreement with J&J's Animas that extends the development relationship internationally. The modified agreement grants Animas exclusive rights to DexCom technology going forward for integration into Animas pumps outside the US. This is very exciting from our view and underscores J&J's interest and commitment to CGM. The agreement significantly enhances DexCom's capital position as it includes a \$5 million payment on the first approval beyond the US, which we would look for in 2009. Given Animas' recent strength overseas and the increased interest in pump/CGM integration globally, we believe this agreement bodes well for both parties, especially if a patient-friendly application is created.
- **Galapagos/Merck — Strategic alliance to identify diabetes and obesity targets:** On January 9, Galapagos, a European-based drug discovery company, announced that it had entered into an alliance with Merck to identify therapeutic targets for diabetes and obesity. Details of the agreement were provided during a conference call with CEO Onno van de Stolpe and Senior VP Corporate Development Andre Hoekema. According to van de Stolpe, Galapagos will be responsible for early discovery, and if promising targets are identified, Merck has the option to license the programs at the candidate drug or phase 1 stage. Under this agreement, Galapagos will receive a €1.5 million (USD\$1.98 million) upfront payment; is eligible to receive up to €170 million (USD\$224.4 million) in milestone payments; and will receive double-digit royalties on worldwide sales. Clearly, if this results in a marketable compound, the early investment should have a robust ROI for Merck – no doubt the investment funds, even as low as they are, are quite welcome for Galapagos.

The Galapagos drug discovery platform is based on adenoviruses that introduce specific complementary DNA (cDNA) or small hairpin RNA (shRNA) constructs into cultured human primary cells. This step leads to a knock-in or knock-down of a specific gene allowing the researchers to study how it affects cell behavior. If a disease phenotype appears, high throughput screens are used to yield potential targets. Gene therapy has traditionally been a tedious development process due to inherent safety concerns, and we imagine that it will be a long time before clinical trials of any sort are initiated. We look forward to hearing about progress and next steps.

- **UnitedHealthCare — Expands reimbursement for CGM:** On January 6, UnitedHealthcare, one of the largest medical insurance providers in the country, released a new policy approving the

reimbursement of continuous glucose monitoring (CGM) in type 1 patients. According to the details of the policy, the long-term use of CGM for periods “greater than 72 hours” is now considered covered for those type 1 patients who experience hypoglycemia unawareness or have been unable to achieve optimal glycemic control. From our view, nearly any patient can prove they cannot achieve optimal control (even if their A1c is 7.0% or less), so we would assume that coverage approval will be widespread. Patients will, of course, still need to cover deductibles and co-payments. CGM use in people with type 2 or gestational diabetes is (explicitly) not covered by the company’s policy at this point. We await to see results from the study “Continuous Glucose Monitoring in Patients With Type 2 Diabetes” (<http://clinicaltrials.gov/ct2/show/NCT00529815?term=cgm&rank=3>) to see if this stance will change. United’s new policy parallels Aetna’s CGM policy revision released at the beginning of November 2008. While technically, Aetna’s policy went even farther in extending coverage to all people with type 1 diabetes over age 25, we are optimistic at this stage that coverage will be widespread with for United policyholders. Both insurance providers cited the recent JDRF CGM trial results as a major factor in the expansion of coverage, and we view this trial as a landmark in the CGM literature. We are very excited to see the trend toward increasing CGM coverage, and we applaud the success of the JDRF’s independent research effort in making this a reality. We expect that the increase in CGM reimbursement will be a critical factor in encouraging physicians and patients to adopt CGM use: the lack of widespread reimbursement has been cited frequently as one of the biggest barriers to adoption. That said, we still do view the weakened economy as a negative factor for patients. Additionally, we believe much better reimbursement for physician and educator time to assess and teach CGM will prompt better healthcare provider uptake. Ultimately, we certainly view this improved technology reimbursement as a major positive for CGM manufacturers Medtronic, DexCom, and Abbott and as a factor that will help lead toward better CGM uptake. Along with better healthcare provider reimbursement, easier-to-use and more patient-friendly technology should also help – look for that with all next generations emerging in the next year.

- **Alizyme – Japanese trial of cetilistat begun in partnership with Takeda:** Alizyme, a small biopharmaceutical company based in Cambridge, UK, announced on December 22 that its partner Takeda initiated a phase 3 trial in Japan for cetilistat (ATL-962), a candidate compound for the treatment of obesity and associated comorbidities like type 2 diabetes. Cetilistat is a lipase inhibitor (similar to orlistat, Roche’s Xenical/GSK’s Alli) that blocks fat digestion and absorption, consequently reducing caloric intake. The initial partnership agreement was reached in September 2004 and included a milestone \$3 million payment from Takeda in September 2008 upon the decision to move the drug into phase 3. According to the company’s website, the FDA has recommended that Alizyme file for a separate diabetes indication. Previously, compounds had to have a significant weight-independent effect on glycemic control to be considered for diabetes indications, but the February 2008 FDA guidance changed this requirement and said that drugs could be considered for diabetes indications regardless of whether the improvement in glycemic control was weight-loss dependent or independent. Although cetilistat may not be the most efficacious drug, it has thus far demonstrated a favorable safety profile and tolerability that is similar to orlistat, which we believe patients and providers will view favorably.
- **Biocompatibles/AstraZeneca – GLP-1 development announced in collaboration with AZ:** On December 22, the medical technology manufacturer Biocompatibles announced product development and option-to-license agreements with AZ for the development of a novel GLP-1 analogue developed by Biocompatibles’ CellMed subsidiary. According to the agreement, AZ will fund pre-clinical, phase 1, and phase 2 trials with a payment of up to €8.8 million (USD\$12.2 million), and CellMed will manage the trials. The option-to-license agreement gives AZ the exclusive option to license Biocompatibles’ patents during the course of the development program. If the company chooses to exercise this option, it would pay a fee of €25 million (USD\$34.5 million) and assume

financial and management responsibility for the development program. This compound is still in early development (initiation of the first set of clinical trials is expected in 2010), and we look forward to seeing how it will differentiate itself from the other GLP-1s under development. Unlike the DPP-4 inhibitors, which do not appear to differ a great deal in terms of mechanism of action, we have noted differences between the GLP-1 analogs, and we would assume that AZ would only move forward on developing this compound if evidence emerged indicating dramatically better efficacy or markedly improved tolerability. Although professing excitement about CellMed's drug as a marketable therapy is premature at this stage, we appreciate seeing innovation happening despite the negative influence (in our opinion) of the new FDA guidelines on cardiovascular risk assessment for diabetes medications. However, the GLP-1 drug class may ultimately be cardioprotective (only outcomes trials will prove this), which may be prompting continued investment in the field for early stage drugs.

- **Wyeth/Thiakis — Wyeth acquires Thiakis and moves ahead in obesity drug development:** On December 19, Wyeth acquired Thiakis, a private biopharmaceutical company focused on treatments for obesity and metabolic disorders. According to the deal, Wyeth will first pay Thiakis \$30 million, and future payments totaling up to \$120 million will be made for milestone developments of Thiakis's lead drug candidate TKS1225, a synthetic version of oxyntomodulin, which started phase 1 studies in March 2008. This naturally occurring hormone is produced in the small intestine and acts on the hypothalamus as a satiety signal. Early studies by Prof. Steve Bloom, founder of Thiakis, demonstrated that administration of oxyntomodulin led to a reduction in food intake as well as an increase in energy expenditure and physical activity. Overall, oxyntomodulin produced a decrease in body weight and adiposity. A specific oxyntomodulin receptor has not yet been identified, but the hormone is believed to exert its effects through the GLP-1 receptor. Considering the recent worry over drugs that act on the brain, we will be curious to see whether TKS1225 has any psychological side effects. As is well known, these side effects were what ultimately led to the demise of the CB1 antagonist class — Sanofi-Aventis's rimonabant (Acomplia) and Merck's taranabant — a few months ago. So far, the main adverse side effect shown has been nausea occurring when high levels of plasma oxyntomodulin were achieved. High nausea rates are certainly a negative for drug uptake; more information on nausea should come after dosing studies.
- **Merck — Pipeline updates given at the annual Business Briefing:** Merck held its annual Business Briefing on December 9, during which Dr. Peter Kim, President of Merck Research Labs, provided a number of interesting updates in the company's diabetes and obesity pipeline. Overall, Merck appears to be strengthening its focus on patient and healthcare provider convenience by emphasizing combination compounds and once-daily dosing. Dr. Kim shared that three compounds have entered phase 3 at the end of 2008 including the fixed dose combination of sitagliptin (Januvia) with pioglitazone (Takeda's Actos), which has an anticipated FDA filing date of 2011; extended release Janumet (enabling once-daily dosing) with an anticipated FDA filing date of 2011; and a Januvia and simvastatin (MK-0431D) combination with an expected 2010 FDA submission date. Trials for the latter two compounds will officially begin in 2009. These compounds bode well from our view in terms of likely efficacy and safety (nothing new is being added) and convenience. It will be interesting to see the side effects associated with the Januvia/Actos combination. TZDs have a number of side effects including edema and congestive heart failure among others and we will look to see if the TZD dose is low enough to avoid the side effects. We also understand that when patients use TZDs earlier in disease therapy, side effects can be less common — this may bode well for results in patients taking the combination who are early in disease progression.

Notably, Merck also showed an updated pipeline with a number of early stage diabetes drug candidates, including two in phase 2 for diabetes, four in phase 1 for diabetes, and one in phase 1 for obesity. Wow! Few details about these clinical development programs have been released, but given

Merck's track record of introducing first-in-class drugs, we think that it is possible that one or more of these drugs will have novel targets. The phase 1 obesity compound is the sole clinical obesity drug in development at Merck after taranabant was dropped in phase 3 at the end of 2008. By our accounting, Merck continues to optimize the pipeline; it dropped three phase 2 compounds in the last year (two diabetes and one obesity) and three phase 1 compounds. Dr. Kim had scant news on the major (n=14,000) cardiovascular outcomes trial for Januvia, but did disclose its name: TECOS, or Trial to Evaluate the Cardiovascular Outcomes with Treatment with Sitagliptin. As of 3Q08, the stellar global marketing and sales execution was running at full steam as the Januvia franchise annualized \$1.9 billion in its eighth quarter on the market and as Merck management forecast sales of \$2.4 to \$2.7 billion for the drug for 2009. Clearly, Merck is investing enormously in this franchise while relishing its status as the sole DPP-4 inhibitor approved in the US.

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

4. 27th Annual JP Morgan Healthcare Conference

The diabetes and obesity field has expanded enormously over the past few years, and we now report back from over 35 conferences annually around the world. The first one that always starts the New Year is the JP Morgan Healthcare Conference in San Francisco, which took place this year from January 12-15, 2009. There were so many companies at the 27th Annual JP Morgan Healthcare Conference that we made our own JPMCW (JP Morgan Company Watch). We were very pleased to see that the number of diabetes and obesity-related companies presenting had increased, and we reported on 39 companies over the course of the conference. Updates on when key milestones will be expected in 2009 represented most of the “new” news – we always eagerly await more input on timing so this was very useful from our view. This is the 27th annual conference – the bank is an outstanding convener of life science companies – we say thank you to JP Morgan for convening so many leaders in the life sciences.

At the moment, it appears that drug development is moving forward, at least amongst companies that have products in phase 2 or phase 3. The meeting reminded us that we have lots to look forward to in 2009 as many companies let us know of new data releases planned, including Amylin (pramlintide/ metreleptin phase 2b – 3Q09, second generation amylinomimetic phase 2 – 4Q09), Arena (lorcaserin phase 3 (BLOOM) – 1Q09), Bidel (overall submission strategy for VIAject – 1Q09), BMS (Onglyza long term safety efficacy phase 3 data – ADA/EASD 2009), EnteroMedics (top-line EMPOWER data – 2H09), Halozyme (PH20-insulin phase 2 data – ADA and EASD 2009), InteKrin (INT131 phase 2b – 3Q09), ISIS Pharmaceuticals (ISIS 113715 phase 2 data – 1H09), MannKind (Afresa NDA submission – February 2009), NxStage (Home Hemodialysis quality-of-life results – 1Q09), and Takeda (alogliptin PDUFA update – June 2009) to name a few. See below for our review of the companies presenting on the diabetes and obesity fronts.

- **Abbott – Focuses on broad company optimism:** EVP Finance and CEO Thomas Freyman reported strong performance over the past year for the company, raising its guidance twice in 2008. Abbott expects this growth to continue, and has given 2009 guidance representing double-digit growth from 2008. No detailed discussion was included about any aspect of the diabetes business, and in particular Abbott provided no information on a second-gen CGM system, which we are hoping to see in the near future.
- **Alkermes – Looks toward LAR submission:** Although this presentation was focused more on currently-marketed products at the company (Risperdal and Vivitrol), President and CEO David Broecker did give an update on exenatide LAR. Much of the information was similar to the updates given by Amylin CEO Daniel Bradbury during the Amylin presentation. Broecker reiterated that the NDA filing for exenatide LAR would be submitted in 1H09; DURATION data were expected soon; and

the Byetta monotherapy indication was still with the FDA. On the financial front, Alkermes is cash flow positive on an operating basis, and it is expecting >\$320 million in revenue for FY09. The company also retired some of its debt early and is continuing its share buy-back program.

- **Amgen — Expresses confidence in phase 2 pipeline:** Chairman and CEO Kevin Sharer led the Amgen discussion where he spoke generally about the difficulty in biotechnology given the uncertainties in the regulatory and economic environment. He noted, with regret, the recent 15% downsizing at the company. He highlighted the increasing regulatory focus on safety, adding that the new US administration's policies may present some difficulties to healthcare but that industry should be ready to work with this new government. On the new drug pipeline front, he provided no information about AMG 221, Amgen's DPP-4 inhibitor candidate currently in phase 2; the AMG 221 program is likely the most advanced in its diabetes and obesity pipeline. Sharer did express confidence in the promise of Amgen's phase 2 pipeline though he did not elaborate further.
- **Amylin Pharmaceuticals — Exudes clarity in goals for 2009 and shares plans on CVD outcomes study:** CEO Dan Bradbury gave a clear, crisp presentation on five key areas of value creation for 2009: Byetta, exenatide LAR, Symmlin, obesity (pramlintide/metreleptin), and operating costs, with most of the presentation devoted to updates on Byetta and exenatide LAR. For Byetta, the monotherapy indication and updated labeling is anticipated sometime this quarter (1Q09). For exenatide LAR, NDA submission is still expected at the end of 1H09. As expected following the FDA guidance on cardiovascular risk assessment, a meta-analysis of exenatide safety data will need to be carried out and there are plans to undertake a cardiovascular outcomes study – we heard the first details on this and look for interim results in 2012 and final results in 2016. While we believe a long-term outcomes study could support a cardioprotective label, there is no proof at present and we applaud the investment in this randomized controlled trial. The company's belief is that exenatide will reduce cardiovascular events in people with type 2 diabetes. On the safety front, FDA has received safety data for Byetta on pancreatitis, and it sounds like the company continues to have a very high level of comfort with the data and are confident that much of the noise has dissipated. The company sounded confident in the results, which we understand show that there is no more pancreatitis in patients on Byetta than is found in the general diabetic population. Bradbury mentioned Symmlin, which we understand is now being taken by 20% more people versus a year ago; he also briefly mentioned davalintide, the second generation Amylin analog, with phase 2 results expected in 4Q09. On obesity and pram/leptin, the phase 2b dose-ranging study results will be available in 3Q09.
- **Arena Pharmaceuticals — Looks to file lorcaserin by the end of 2009:** Jack Lief, President and CEO, discussed Arena's phase 3 trials of lorcaserin, its leading obesity drug candidate. The first of the three trials, the BLOOM trial, is nearing completion and data are expected in March. Of the other two trials, BLOSSOM is expected to be finished in September, and BLOOM-DM, the trial in diabetes patients, should be completed by mid-to-late 2010. The company expects to submit an NDA for lorcaserin near the end of 2009, and there are plans to enter partnering negotiations some time after the phase 3 trials are complete; however Arena left open the option of continuing solo up to the NDA or even beyond. Arena expects to have sufficient cash to last until the NDA submission without raising any additional funds. While their phase 2 data were promising in some respects, phase 3 results will provide more context for comparison with Vivus' Qnexa and Orexigen's Empatic and Contrave. The company still maintains that lorcaserin is specific for the serotonin 2C receptor, with no off-target activity on other receptors.
- **Bayer — Forecasts market share gains:** CEO Arthur Higgins led the company's fairly bullish update. He expressed confidence in the diabetes care franchise and stated that the business had not been affected by the global recession and went on to say that Bayer should benefit from economic volatility by leveraging their currently strong position to gain market share. He cited Bayer's blood

glucose meter franchise, currently #3 globally, as the fastest growing in diabetes care over the last three years (from a smaller base than leaders J&J and Roche). Notably, he characterized Bayer's diabetes care business as growing two percentage points faster than the market with regards to 2008 sales growth during the first nine months of 2008 – we look forward to hearing 2008 full year results on March 3.

- **Becton Dickinson — Benefiting from strong growth in insulin delivery:** Edward Ludwig, Chairman and CEO, mentioned Becton Dickinson's diabetes sales only briefly in the presentation; BD remains, of course, the global leader in insulin needles. Management said that the company is continuing to experience strong growth in the insulin delivery sector. We imagine this will only be buffeted further by new ADA/EASD guidelines, which advocated earlier use of insulin. The pen needle market is reportedly growing at a double-digit clip, and notably, 2008 was the first year in which sales of pen needles surpassed that of insulin syringes at slightly more than \$350 million in revenue. The company plans continued increases in its R&D spending to spur company growth. The presentation mentioned the BD Ultra-Fine III Mini Pen Needle as an example of innovation in diabetes treatment. We are glad pen needles are selling well; we believe that pens are a great innovation, since they make insulin intake easier for patients. Robust sales are likely a sign that reimbursement is improving in the US. Currently, we believe some patients who have reduced beta cell production are taking orals because they haven't been trained or encouraged to take insulin – or, that they are taking basal insulin only when they have mealtime insulin needs. In our view, far more patients should be on more aggressive therapy, including insulin, than currently are: 44% of patients in the US are not at their glycemic target (A1c 7% or less), but only 23% are taking insulin, according to Diabetes Care. Furthermore, some of those patients that are on basal insulin could likely benefit from prandial insulin as well, particularly if they have significantly reduced beta cell function.
- **Biodel — Looks to market entry of VIAject in 18-36 months:** President and CEO Solomon Steiner began by stating that in the best case, VIAject will be available on the market in one and a half years, and in the worst case, within the next three years. We were pleased to hear that Biodel now has a 100 IU one-part formulation insulin, as injection site pain with the 25 IU two-part formulation insulin would have presented some difficulty.– that said, we didn't think the 25 IU was ever planned as a product for submission. Dr. Steiner also made a point to review a recent study of the effect of VIAject on oxidative stress and postprandial endothelial function that was presented at the Diabetes Technology Conference in November 2008. The study demonstrated that VIAject reduces postprandial oxidative stress and improves vascular function more effectively than regular insulin and insulin lispro (Eli Lilly's Humalog): very compelling (available online at <http://www.biodel.com>). Taken together with previous data, Dr. Steiner felt very confident in VIAject and its positive cardiovascular signals. Lastly, Dr. Steiner provided an update on the status of the phase 3 analysis. Biodel hired a group of independent regulatory experts to help analyze the anomalous findings in the preliminary analysis. Dr. Steiner was encouraged by the results of the investigation, which have been shared with the FDA, and they are planning to discuss the data and related analyses with the FDA at the end of the month. The company anticipates being able to give further details on the overall submission strategy later this quarter. He contrasted two scenarios: Plan A and Plan B. Plan A involves NDA submission with current data and concurrently initiating phase 3b trials. Following the pre-NDA meeting, a strategic decision will be taken which may call for plan B, which is to initiate another trial (in type 1s only) and hold-off on submission. Elsewhere in Biodel's pipeline, we saw that VIAtab, an oral sublingual prandial insulin for early type 2 patients failing on diet and exercise, was still in phase 1.
- **Bristol Myers Squibb — Plans DPP-4 and SGLT-2 phase 3 data announcements at ADA and EASD:** EVP, CSO, and President of R&D Elliot Sigal gave little information about diabetes aside

from the pipeline update on its DPP-4 inhibitor Onglyza (saxagliptin) and dapagliflozin, its SGLT-2 inhibitor. As a reminder, Onglyza was submitted in the US and the EU at the end of July 2008, and the company is still awaiting decisions on both filings. Phase 3 long-term safety and efficacy data will be released at either ADA or EASD. On dapagliflozin, phase 2b and initial phase 3 data will be released later this year. This is highly awaited data as it will be the first phase 3 SGLT-2 data. Aside from saxagliptin and dapagliflozin, the company's website lists two drugs that are currently in pre-clinical or early clinical development for diabetes. In a chart of focus areas — primary, secondary, additional — building the major metabolic capacity was listed under “additional areas considered.” Sigal sounded fairly positive about the FDA raising the safety bar to protect patients and went out of his way to publicly applaud the FDA guidelines. He took the opportunity to hedge a bit, however, on potentially altered timelines due to additional safety studies.

- **CV Therapeutics — Intrigues with an adipose tissue lipolysis inhibitor (CVT-3619):** Chairman and CEO Louis Lange singled out its diabetes candidate CVT-3619 for special mention in the pipeline update; CVT-3619 is a first-in-class drug for diabetes that inhibits adipose tissue lipolysis, reducing levels of circulating free fatty acids and increasing insulin sensitivity. The compound is currently in phase 1. CV Therapeutics has quite a strong balance sheet, and we are eager to watch it move forward, especially if it garners a cardioprotective label. Lange also spoke about a recently approved label for Ranexa designed to treat chronic angina — chest pain that typically happens with increased activity or stress. While not primarily intended for the treatment of diabetes, this drug has been shown to improve A1c in diabetics with angina, and it may pose an attractive alternative to other medications like beta-blockers that can worsen hypoglycemia.
- **DexCom — Pre-announces very strong 4Q08 revenue:** CEO Terry Gregg gave an update on DexCom's continuous glucose monitoring reimbursement progress, partnerships with J&J's Animas (integrated sensor and insulin pump) and Edwards Lifesciences (in-hospital glucose monitoring), and pre-announced very positive topline 4Q08 results. In 4Q08, DexCom expects \$2.4 million in product revenue, up 27% from \$1.9 million in 3Q08. This beats Wall Street analyst revenue estimates of \$2.1 million. Approximately 1,200 new starter kits were sold in the quarter, up 55% from the third quarter. Sensor revenues increased 25% sequentially from 3Q08 to 4Q08. On the reimbursement front, Gregg noted the positive impact of the JDRF CGM study results on coverage policies, particularly the United Healthcare policy, characterized as the most “liberal” thus far. He discussed recent amendments to the Animas partnership granting Animas exclusive rights to DexCom technology going forward for integration into Animas pumps outside the US. He provided no update on the Insulet partnership, save to note that the Animas partnership is moving faster because Animas has more capital than Insulet and has the added impetus of playing catch up to Medtronic, which has the only integrated sensor/pump on the market.
- **Edwards Lifesciences — Could benefit from NICE SUGAR data to be presented in March:** Chairman and CEO Michael Mussallem briefly discussed the innovation opportunities in critical care, citing glycemic control as a \$200 million market in the hospital. We continue to believe significant opportunities for CGM exist because blood glucose monitoring is generally underused and because CGM in the hospital has the potential to dramatically change patient outcomes. He described the company's 2009 objectives on this front as demonstrating technological and regulatory success and introducing a first generation product in Europe (4Q09 was the most recent estimate we heard). We believe Edwards Lifesciences is pursuing the European path first because of the more straightforward and efficient regulatory process in Europe compared to the FDA. Reiterating comments at their investor conference on December 11, 2008 Mussallem noted the importance and difficulty of monitoring glucose levels in critically ill populations. He characterized current methods of glucose monitoring in critical care environments as burdensome. He then highlighted the mounting

clinical evidence emphasizing the degree to which glycemic control in the ICU improves outcomes. We believe many are watching and waiting for NICE SUGAR data – this data will be presented March 24-26 in Brussels at the International Symposium on Intensive Care. Closing the presentation, he expressed confidence in partner DexCom’s ten plus years of experience in the field of glucose sensing.

- **Eli Lilly – Pipeline looking fuller than it has in years:** Executive VP Science and Technology Dr. Steven Paul emphasized that the therapeutic focus of Lilly would be on diabetes and obesity, Alzheimer’s disease, cancer, and inflammation-autoimmunity. He gave an update on the pipeline, which showed seven compounds for diabetes and two unidentified compounds for obesity. Five diabetes compounds were listed in phase 1, including an anti-IL1 beta antibody, a basal insulin, two unidentified compounds, and PEG-GLP-1 (LY2428757). The latter compound will likely be a long-acting GLP-1, as poly(ethylene glycol) (PEG) is attached to various protein medications in order to prolong dosing intervals. For example, PEG-interferon alpha is injected once-weekly, rather than three times per week for conventional interferon-alpha. GLP-1 Fc (LY2189265) was listed in phase 2, and in phase 3 the pipeline showed teplizumab, an anti-CD3 monoclonal antibody being developed with MacroGenics. Exenatide LAR has, of course, finished phase 3 studies, and the plan continues to be for submission to the FDA by the end of June 2009.
- **EnteroMedics – Moving into diabetes:** President and CEO Mark Knudson provided a thorough overview of the clinical experience with and future steps for the Maestro system and VBLOC therapy. VBLOC therapy is a technique aimed at treating obesity by intermittently blocking signaling from the vagus nerve of the stomach and the brain. The company has also recently decided to focus on diabetes and hypertension as indications. So far, nearly 400 patients have been implanted in multiple studies and clinical sites. The Maestro system has had a clinically favorable safety profile with no deaths or unanticipated adverse device events (UADEs). Knudson reviewed sub-group analyses from VBLOC-RF1 and VBLOC-RF2 – two feasibility studies - that demonstrated improvements in diabetes and hypertension. The sub-group analyses in diabetes patients found that VBLOC therapy resulted in significant improvements of A1c levels in six patients with type 2 diabetes. Similarly, following activation of VBLOC therapy, both systolic and diastolic blood pressure showed improvement in an n=19 sub-group analysis. We look forward to more data in this group. Knudson reviewed the timing of key events for 2009. Enrollment for the diabetes feasibility study is expected in 1H09, with the one-month follow-up data in 2Q09. Top-line results for the EMPOWER trial will be available in 2H09 with PMA submission expected to follow soon thereafter. On the financial front, EnteroMedics has completed a \$20 million debt facility providing cash expected to last into 2010 and the release of phase 3 data.
- **Halozyme – Looking to phase 3 in 2010 for formulation of PH20 and insulin:** The company is working on a formulation of PH20 (recombinant human hyaluronidase enzyme) with insulin for a potential best in class prandial insulin. As we noted last quarter, this has come out of nowhere as far as we are concerned. Hyaluronidase is a tissue permeability modifier that facilitates absorption of other drugs by loosening connective tissue. President and CEO Jonathan Lim believes that it could be a “best in class” compound based on a product profile that includes faster onset, more physiological duration of action, lower insulin dose requirements, less weight gain, a more ideal profile for pump application, and reduction in hypoglycemia. Halozyme has plans to have the formulation as a subcutaneous injection, and the company is developing it in two forms: a pen and a titratable vial. Accomplishments cited for 2008 included presentation of phase 1 data at ADA and initiation of phase 2 in 4Q08. According to Dr. Lim, the study is on track for interim results in mid-2009 with data and results planned for presentation at ADA 2009, and full results planned for presentation at EASD 2009. Phase 3 will follow soon after in 2010, if all goes as planned. The

company plans to carry out insulin pump studies in parallel. It will be a busy year, and we plan to keep a very close watch on this company.

- **Home Diagnostics — Highlights CMS playing chicken:** President and CEO Dick Damron emphasized Home Diagnostic's role as the value player in blood glucose monitoring, while emphasizing its record of product innovation and its efforts to further expand its base in retail and mail-order pharmacies. The company highlighted its new TRUEtest no-coding platform, which it believes results in more accurate glucose readings than the no-coding offerings of its competitors due to very low product differentiation. While we don't believe patients or providers make choices based on accuracy anymore, we found this claim of interest. The company reported a decline in gross margins in 2008, which they attributed to the recent release of the TRUEresult and TRUE2go, which have not been on the market long enough to build considerably higher-margin strip sales. Home Diagnostic's value and co-branding based strategy could serve them well in the current economic downturn among the Medicare and Medicaid population: effectively, the uninsured and underinsured, which is a growing population. Historically, however, one of the challenges with the business has been the relative lack of predictability compared to the larger players. Additionally, one slide in their presentation noted a 9% across-the-board decrease by Centers for Medicare & Medicaid Services (CMS) for mail-order strips – this has had a negative impact on the entire industry. Clearly CMS has much room to bargain – this must have been unwelcome, but what is an industry to do? We think CMS likely has little idea of the long-term detrimental impact to patients of such a move.
- **Human Genome Sciences — Starting phase 3 Syncria trials this year:** President and CEO Thomas Watkins gave an overview of HGS, explaining that the company is targeting five disease areas including diabetes. Watkins briefly discussed the status of Syncria, their long-acting GLP-1 candidate, and the only diabetes drug listed in the company's diabetes pipeline. The company reminded listeners eager to hear about more about Syncria that GlaxoSmithKline (GSK), to whom Syncria is licensed, is responsible for the decisions and disclosures concerning the drug and that most information would come from GSK. This notwithstanding, they did suggest phase 3 trials would begin during 2009. Watkins spoke optimistically about the financial strength of his company and its strong cash position, which the company expects to maintain throughout 2009.
- **Insulet — Smaller pod looking good, patients eager to see it asap:** Insulet CEO Duane DeSisto discussed two major ongoing initiatives to improve the OmniPod disposable insulin pump. The first initiative is the next generation pump, which is expected to deliver all of the same features in a smaller footprint: availability is targeted by late 2010. This pump is over 40% smaller by volume than the current system and when we saw it, we felt patients would be quite impressed by the difference. Notably, this pump is also going to be easier and cheaper to manufacture, with 40 parts going to 30 parts and weight going from 30 grams to 20 grams. The second initiative is the partnerships with Abbott and DexCom to develop an integrated pump/CGM system. We believe Insulet will go to market with Abbott first and then DexCom, both in 2009.

In addition, Insulet is working to expand the OmniPod into type 2, gestational diabetes, and non-US markets. We think gestational and non-US makes a lot of sense since the tubeless feature could be a strong selling point for a device that would only be used in the gestational period. The reimbursement issue would be a bigger hurdle to overcome in the type 2 market. Management said that the OmniPod has been placed on the United formulary, obviously a big reimbursement win for the company. They said that currently 65% of patients who apply for an OmniPod are eventually shipped a device, and they would like to get that number up to 70%-80%. In the international arena, the company hopes to have CE approval by the end of the year to enable commercialization of the OmniPod in the European Union and in countries in Asia and Latin America that recognize the CE Mark. The company will also expand its footprint in 2009 by seeking Canadian regulatory approval. Last, we are optimistic about

Omnipod use in type 2 patients, particularly those using U-500 insulin – we heard great enthusiasm from clinicians involved in these trials. Finally, on the financial front, the company anticipates a positive gross margin in the fourth quarter.

- **InteKrin – Market research on INT131 sounds very promising:** Dennis Lanfear, President and CEO, gave an update on InteKrin's main drug in development, INT131, a next generation insulin sensitizer currently in phase 2. INT131 was developed over ten years with Tularik and Japan Tobacco to maintain the efficacy level of Actos (Takeda's pioglitazone) and Avandia (GSK's rosiglitazone), but to eliminate safety issues (e.g. weight gain, edema, bone fracture risk) by selectively targeting PPAR-gamma. Lanfear believes that INT131 has the potential to be a best in class drug, especially on the safety front. In order to emphasize the safety profile of INT131, Lanfear discussed results from preclinical studies. Studies in two preclinical models – rat and monkey – showed that for INT131 safety multiples declined in a dose/time dependent fashion. Lanfear stated that INT131 safety margins exceeded typical TZDs by greater than 50 to 250 fold, and they were maintained over time. Safety margin data has also been obtained from studies in mice, but it has not yet been analyzed. Lanfear then gave a quick update on the status of the phase 2b study, which is currently ongoing. This study is looking at 360 patients in six treatment groups: placebo, 0.5 mg/day of INT131, 1 mg/day of INT131, 2 mg/day of INT131, 3 mg/day of INT131, or 45 mg of pioglitazone. Completion of recruitment for this study is targeted for the end of 1Q09, with phase 2b data completion in 3Q09. At the end, Lanfear made an interesting note about market research on INT131: a survey of primary care physicians (PCPs) and endocrinologists indicated that 33% would be willing to start patients on INT131. In addition, 43% of PCPs and 48% of endocrinologists would switch to INT 131. Notable advantages of the drug, if efficacy and safety hold, are single tablet once daily dosing, possible co-formulation with metformin, efficacy equivalency to Actos, lack of cardiovascular risk, and a positive safety profile.
- **Ipsen – Highlights patient-friendly elements of taspoglutide:** Stéphane Thiroloix, EVP of Corporate Development used taspoglutide, Ipsen's once-weekly GLP-1 candidate partnered with Roche, to illustrate the company's core expertise inspired by endogenous human hormones. Using a slide from the Investor Day held earlier on January 8, he highlighted the long-acting profile of their candidate as a way to improve therapy adherence. The slide also showed the smaller 29-gauge needle to be used with taspoglutide juxtaposed with the larger 23-gauge needle intended for use with exenatide once weekly.
- **ISIS Pharmaceuticals – Plans to share phase 2 results in coming few months:** President and CEO Stanley Crooke presented the update on ISIS Pharmaceuticals, a drug discovery and development company that focuses exclusively on antisense RNA based drugs in a variety of therapeutic areas, including cardiovascular disease, metabolic disease, cancer, and inflammation. ISIS has four drugs being developed for diabetes, with ISIS 113715 being the furthest along and now in phase 2. ISIS 113715 is an insulin sensitizer that, in preliminary studies, has been shown to reduce glucose levels without hypoglycemia or weight gain: quite a potential product profile. Dr. Crooke pointed out that ISIS 113715 also reduces LDL-cholesterol, which should work in its favor given FDA interest in cardiovascular risk and diabetes medications. Phase 2 results for ISIS 113715 are expected in 1H09. ISIS has three other diabetes drugs in its pipeline: ISIS 325568 (glucagon target), ISIS 377131 (glucocorticoid receptor target), and ISIS 388626 (SGLT-2 target, expected to enter clinical trials in 2009).
- **Keryx Pharmaceuticals – Suffers major layoffs while awaiting word on KRX-0701:** Chairman and CEO Michael Weiss outlined progress on its pipeline compounds for end stage renal disease and cancer, but he did not comment on KRX-0701, its pipeline drug for diabetic neuropathy that is currently in phase 2. Keryx has recently eliminated about 70% of its workforce and closed multiple facilities to reduce costs, and the company is discussing the possibility of partnerships. The

company currently has about \$17 million in net cash, with an estimated burn in 2009 of \$1 million per month. We'll watch to see if this company moves forward with its diabetes pipeline: for now, it's obviously a challenging period.

- **MannKind — More details given on 350,000-page NDA filing:** Dr. Peter Richardson and Al Mann, CSO and President of MannKind respectively, delivered a confident update. Dr. Richardson discussed successful completion of bioequivalency studies comparing the insulin inhaler developed for commercial use to the version used in clinical trials. He also gave an overview of the mammoth 350,000 page FDA filing which has all the necessary components to go forward with NDA submission in February 2009, a few weeks shy of the previously forecasted submission date at the end of December 2008/January 2009. He addressed the lack of A1c superiority of Afresa compared to rapid acting analogs and also theorized on possible explanations for the unexpected finding that fasting plasma glucose was higher in patients taking Afresa. Specifically, he said lack of hypoglycemia for Afresa results in an average glucose level that is slightly higher than that found with the analogs. We would like to better understand this since it was our impression that Afresa shouldn't actually affect fasting blood glucose at all. We believe CGM data will explain the discrepancy better, and we wonder whether post-prandial data reflects average post-prandial scores (they weren't taken every day as we understand it). Of note, a new study using pumps to deliver basal insulin in which investigators will compare Humalog and Afresa is on the horizon. This study, which will use CGM, should get to the bottom of the A1c inferiority question.
- **Medco Health Solutions — Highlights Therapeutic Resource Centers and forecasts generic insulin:** Chairman and CEO David Snow noted that at Medco, growth seems to be moving forward as usual despite the recession. The company said that it was on track to deliver 29-31% EPS growth in 2008, certainly higher than the S&P Healthcare Index. The company reported that it has \$440 million in cash as of September 2008, and management expects that to double by year-end 2009. The company seems to be putting increased emphasis on its Therapeutic Resource Centers, citing statistics showing that the centers have higher adherence rates and compliance with ADA guidelines than retail pharmacies. We certainly aren't surprised to hear this, as we believe patients need far more diabetes education than they are receiving; this represents a novel alternative, and we're glad they don't seem overly focused on the ROI short-term. Medco management expects the Obama administration to facilitate regulatory approval for follow-on biologics, and expects that several analog insulins will go 'generic' in the next ten years. How easy they will be to manufacture then becomes a primary question.
- **Medtronic — Touches on new pump FDA submissions:** Chairman and CEO Bill Hawkins delivered the Medtronic presentation during which he praised Medtronic's market leading position in diabetes medical technology and characterized the diabetes business as one of the company's areas with the most opportunity for growth in the near-term. He emphasized the company's focus on leveraging sensor-integrated insulin pumps (Paradigm and new X23/X54). As we understand it, these products have been submitted for approval. He characterized CGM as the most exciting part of the diabetes business. We were also happy, from a patient perspective as well as an analyst perspective, to hear Medtronic's clear commitment to the closed loop. On a broader note, Hawkins discussed the difficulty associated with predicting how healthcare reform will play out with the new administration.
- **Merck — Delivers news on various indications for Januvia in the works:** President and CEO Richard Clark gave the Merck presentation to a standing-room only audience where he discussed various indications for Januvia – clearly that is a product that has been extremely successful and much of the talk was focused on indications. Notably, Merck will be filing for an indication in 2009 for Januvia as an add-on to insulin. Now they're working on indications for insulin, pioglitazone (Takeda's Actos), and simvastatin – all important steps in the diabetes therapeutic progression and

products that could be critical in forming novel combination therapy. As part of the strategic plan, Clark also mentioned new fixed dose combinations (Januvia and either pioglitazone or simvastatin), new formulations (extended release Janumet), and outcomes based trials (Januvia cardiovascular outcomes trial - TECOS). Filing for the Januvia/simvastatin combination is expected in 2010. The Januvia/pioglitazone combination and extended release Janumet formulation have an anticipated filing date in 2011. On the geographic front, we learned that Januvia has become a key focus in Japan. Though details of the timing are not yet available, Januvia is expected to be the first DPP-4 inhibitor within this market: this is obviously unfortunate for Takeda, which filed alogliptin in Japan in September 2008 and is currently held up at the FDA due to FDA resource constraints, according to Takeda.

- **Nektar — Points to GLP-1 as development target potential:** President and CEO Howard Robin led the presentation on Nektar. The company had little to say about diabetes and only mentioned that they had retained the intellectual property rights to inhaled insulin (formerly Exubera) when they sold the majority of their pulmonary delivery assets to Novartis. During much of the presentation, they emphasized their strong patent portfolio in polymer conjugation chemistry of small molecules, large molecules, and nucleic acids. In particular, they pointed to GLP-1 and GLP-2 as potential conjugation targets for development. In a sign of the times, in the Q&A we heard that Nektar “got out of the [diabetes] business a long time ago” – in fact, it was actually only a little over a year ago.
- **NxStage — Home Hemodialysis system reaches 3,000 patients:** President and CEO Jeff Burbank focused on how NxStage is working towards the implementation of a Home Hemodialysis system, for which it has executed a number of clinical trials. Burbank began his talk by discussing the success thus far of these trials in terms of decreased mortality rate and improved quality of life. Burbank was upbeat about the company’s present and future, noting that it has increased the number of patients using its product to 3,000. (This number is challenging to increase because death rates are so high in this very sick population. Other reasons for a decline in the number include when caregivers get too exhausted using the service.) Look for a publication of the results of a one year quality-of-life study in March 2009. CFO Robert Brown also spoke briefly, underscoring the fact that the company is the first and only provider of small, portable, home hemodialysis systems, a promising therapy for people with diabetes and others with renal disease.
- **Orexigen — Discusses controversial phase 3 Contrave data:** Graham Cooper, the CFO of Orexigen, reviewed the phase 3 Contrave results released in early January 2009 and the results of the phase 2 dose-ranging study of Empatic. We think that the phase 3 Contrave data, while demonstrating that the drug is fairly effective compared to current treatments (Roche’s Xenical and Abbott’s Meridia), would not ultimately compete well against Vivus’s Qnexa if it is approved. As a reminder, the 56-week randomized double-blind trial (n= 793 obese patients), delivered decent results in our view, with 20 pound weight losses for the treated group (baseline 221 pounds) and 65%, 42%, and 29% of patients on Contrave losing over 5%, 10%, and 15% of their weight, respectively, compared to 43%, 20%, and 11% of placebo patients (placebo patients did well due to an intensive lifestyle management program). Although the company says it has met the primary endpoint in the study, from our view, some confusion persists over whether the results of the first study, strictly speaking, met FDA guidelines for obesity drugs because the requirement of the 5% difference between the treated group and the placebo group wasn’t met (it was 4.3%). We could see FDA approving it and we could also see reason for a delay– this is impossible to forecast from our viewpoint, although on balance, we think FDA does feel pressure to approve an obesity compound. Slides showed an overall plan to market Contrave as a drug for ‘mild-to-moderate’ obesity while the more effective Empatic (still in phase 2) is intended for ‘severe’ obesity. At least on the surface this seems like a solid strategy,

and it may end up being marketed similar to Vivus' strategy with different doses of Qnexa. We are interested to see how Orexigen and Vivus compete on the market, assuming that they both receive approval by the FDA.

- **OSI Pharmaceuticals — Briefly discusses early-stage diabetes pipeline:** CEO Colin Goddard discussed how diabetes continues to play an important role in OSI's strategy, both in terms of DPP-4 royalties and pipeline development. The company said that a substantial portion of its \$150 million in cash flow stemmed from DPP-4 royalties, but did not go into detail. We imagine that they had not forecasted such success with Januvia though early plans probably would have had Novartis' Galvus approved by now. Management mentioned two pipeline drugs in diabetes, the GPR119 agonist PSN821 and the serotonin/norepinephrine reuptake inhibitor PSN602, both of which are in phase 1. They said that a key element of the company's strategy in the future would be to develop a 'personalized medicine/neuroendocrine platform' for the treatment of diabetes and obesity. At the current time, however, the majority of the company's focus and investor interest was in Tarceva, OSI's drug for lung and pancreatic cancer. We're interested to see where OSI's early-stage diabetes pipeline is headed.
- **Pfizer — Discusses commitment to diabetes:** Martin Mackay, President of Pfizer, discussed Pfizer's choice to focus on a few select areas, including oncology, pain, Alzheimer's, inflammation/immunology, and notably, diabetes; though of these areas, diabetes currently has the fewest late-stage developments. During the breakout session, he noted that compounds in the diabetes pipeline were generally earlier stage than the rest of the compounds in their investment areas. He noted their DPP-4 inhibitor program (in phase 2) as their most advanced, though he acknowledged the strong competition in the field. Underscoring the company's continued interest in diabetes, he pointed to even earlier stage programs including their GLP-1 agonist. He mentioned the company's exit from the obesity business—the exit from obesity and other disease areas do not affect Pfizer's portfolio of marketed products, development of compounds in phase 3 or any launches planned in the next three years. McKay spoke generally about prioritizing Pfizer's development portfolio to deliver the most value and increasing the percentage of compound that progress beyond phase 2. We look forward to the next pipeline update in March 2009.
- **ResMed — Partnership with LifeScan a win/win:** In this presentation, President and CEO Kieran Gallahue emphasized that sleep disturbances like sleep apnea are not just a symptom of other conditions (such as type 2 diabetes and heart disease) but primary conditions that may cause symptoms of their own. He claimed that treating sleep disturbances in people with type 2 diabetes or heart disease could alleviate other symptoms that were thought to be associated with the primary diagnosis. In the \$2 billion sleep disturbance product market, ResMed holds a 15% market share within the US and 10-15% abroad. In the past seven months, ResMed has brought a large number of products to market, and management predicts that this trend will continue in the next 18 months. ResMed and LifeScan put together a partnership last year that seems focused largely on increasing awareness of both diabetes and sleep apnea – a major win/win from our perspective since both conditions have so many patients who are undiagnosed.
- **Roche — Diabetes businesses not discussed:** CFO Erich Hunziker situated Roche's strategy for 2009 in the context of a worsening global recession. Hunziker focused on the company's innovation and young product portfolio as ways for the company to weather the downturn. The company emphasized that it does not plan to reduce R&D efforts as a cost-cutting strategy. Roche Diabetes Care was not addressed separately from the rest of the business, nor was its pharmaceutical pipeline in the primary presentation.

- **Sirtris — Delivers presentation focused on SRT501:** CEO Christoph Westphal gave an overview of the SIRT1 activators and their benefits, specifically in reference to diabetes, but also noted how Sirtris will be looking into applying SIRT1 activators to a range of other therapeutic areas. The key benefits noted with SRT501 (a proprietary formulation of the compound resveratrol) treatment include insulin sensitization, improved glycemic control, increased mitochondrial function in skeletal muscles, mimicking calorie restriction, and inhibiting inflammatory cytokines (IL-10, IL-11, IL-1 alpha, MCP-1, MCP-3, MIP-2, and TNF-alpha). As a reminder, SRT501 is in phase 1b. Sirtris is continuing to investigate new chemical entities (NCEs) and will also look into targeting the other classes of sirtuins; there are seven known classes of sirtuins (SIRT 1-7). Unsurprisingly, the subject of outcomes studies arose in the Q&A, and Westphal stated his belief that fewer heart attacks and increased lifespan would be seen.
- **Takeda — No new news beyond resource constrained FDA:** President Yasuchika Hasegawa gave an update on alogliptin (SYR-322) and indicated that the PDUFA updated date would be available by June 26, 2009. As a reminder, on the PDUFA date, the company will be told whether or not the FDA will accept an NDA or BLA submission for priority review. Alogliptin was also submitted to regulatory authorities in Japan in September 2008, and it is currently in phase 3 in the EU. A review of the pipeline showed that development of SYR-472, a DPP-4 inhibitor, was continuing, and it is currently in phase 2 in both the US and the EU.
- **Tolerx — Update on DEFEND:** Although Tolerx did not present at the JP Morgan conference this week, we were fortunate enough to be able to meet with President and CEO Doug Ringler to discuss otelixizumab, the company's anti-CD3 monoclonal antibody now in phase 3 development. Dr. Ringler provided us with updates on the regulatory pathway, the competitive landscape, and gave us more detail on product attributes. First, Dr. Ringler described DEFEND, its phase 3 clinical trial. Enrollment began recently and should be complete by the end of 2009. Dr. Ringler didn't give an estimated time of Biologics License Application (BLA) submission for otelixizumab, but we believe that it could be submitted as early as late 2011 or 2012. Tolerx also has an ongoing phase 2 study, TTEDD, that is further optimizing the dosing of otelixizumab. Notably, Dr. Ringler emphasized that the side effect profile for otelixizumab appears to confer best-in-class status; as he explained, utilizing their phase 3 dosing regimen (discovered from their dose optimization work in TTEDD), little-to-no release of TNF-alpha or IL-1 occurred. As a reminder, these are pro-inflammatory cytokines that are cytotoxic to beta cells. This result is particularly notable in our eyes as an inflammatory response against beta cells is a key problem in individuals with type 1 diabetes.

We also discussed the promise of potentially using otelixizumab as a preventative measure, although that will be a later-stage focus: as Dr. Ringler had mentioned when we interviewed him last summer, there are plans for a prevention trial, but details are not yet available. We continue to hear much about combination therapy and this area is no exception; Dr. Ringler cited potential combinations with other molecules, particularly INGAP (islet neogenesis-associated protein) and CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4, BMS's Orencia) as possibilities. We were glad to hear that data on otelixizumab is now published in the form of a review in *Advances in Immunology*, Volume 100, Chapter 2. While we heard a great deal of positive points during the conversation, we were most struck to hear that the company has simplicity and ease of use in mind as important attributes. GSK, Tolerx's partner, is working on developing a subcutaneous injection of otelixizumab, which could be quite beneficial from a patient perspective. Notably, Dr. Ringler also shared that Tolerx has reduced the time needed for the intravenous injection from two hours to 15 minutes – very exciting.

- **Vivus — Qnexa data looks spiffy:** President and CEO Leland Wilson discussed the recently released phase 3 results from the OB-301 study examining the effectiveness of Qnexa in obese patients. In that trial, subjects treated with full-dose (15 mg phentermine/92 mg topiramate CR) and

mid-dose (7.5 mg phentermine/46 mg topiramate CR) Qnexa had weight loss of 9.2% and 8.5% respectively (19.8 lbs and 18.2 lbs), while the placebo group saw 1.7% (3.3 lbs) weight loss. Qnexa was reportedly well-tolerated, and no serious drug-related AEs were seen in the study. The company believes that the results of this trial will set them up for a very favorable review by the FDA. In addition, the phase 2 DM-230 study demonstrated that Qnexa was effective in improving the A1c of patients with diabetes. At 56 weeks, Qnexa reduced A1c by 1.6% from a baseline of 8.8% compared to a 1.1% A1c reduction from a baseline of 8.5% for placebo (ITT LOCF p=0.0381). We are becoming increasingly positive about Qnexa as additional trial results are released, and we believe that it has proven itself to be markedly effective in reducing weight and improving the glycemic control of obese people with diabetes. Good tolerability and ease of use are big positives if safety and efficacy hold. We also believe that because of its secondary effects on triglycerides, cholesterol, and other CV risk factors, it could well be used for metabolic disease as well as obesity. A sub-study released by Vivus early in the conference noted a 0.1% A1c drop in pre-diabetic patients from a very low mid-5% baseline. In our view, it is very smart from a health economics perspective as the drug may be able to revert those with pre-diabetes to normoglycemia and potentially even those with early-stage type 2 diabetes to pre-diabetes.

- **WebMD – Shares general trends of note:** Although WebMD’s seminar did not include any direct discussion of diabetes, President and CEO Wayne Gattinella shared some interesting trends in healthcare. He first talked about the continuing increase in patient self-education on the Internet. According to survey information, doctors frequently referred patients to look up their conditions on the web rather than explaining the details themselves. The two most common websites that doctors recommended to patients were WebMD and CDC.gov. He believes that this indicates an increasing legitimacy to the online medium as a source of medical information. This phenomenon has been accompanied by a shift towards patient-targeted advertising by healthcare product providers. He did not address the ethical considerations of this change, rather focusing on this growing target market’s effects on advertising revenue. We see this trend as largely related to economics – doctors, regardless of preference, undoubtedly save significant time in sending patients to trusted online sources. In addition to their patient-oriented website, WebMD also owns MedScape, an online medical reference source for physicians. Their site usage data estimates that 1.5 million physicians access MedScape each month.
- **Wyeth – Characterizes diabetes as a small but important player in Wyeth’s developmental focus.** Metabolic disease was listed as one of Wyeth’s six areas of developmental focus going forward, areas that they said they would pursue through a program of targeted licensing and acquisition. The biggest update on products for diabetes involved Tygacil, Wyeth’s broad-spectrum antibiotic for the treatment of skin infections and complicated intra-abdominal infections. The company plans to file for a new Tygacil indication to address diabetic foot infections in late 2009. We’re assume this doesn’t differ from its current use to treat skin infections but that the goal is to garner a first line therapy indication.

— by Kaku Armah, Kelly Close, Alexandra Gladstone, Brendan Milliner, Melissa Tjota, and Nick Wilkie

5. DCU Interview with Dr. Viswanathan Mohan, Diabetes Specialties Center

During our visit to Chennai, India for the Diabetes Summit for Southeast Asia (see Letter from the Editor), we were lucky to be able to talk at length with Dr. Viswanathan Mohan, CEO of Dr. Mohan’s Diabetes Specialities Centre (www.drmoahnsdiabetes.com). The goals of this incredible enterprise are two-fold: to provide comprehensive care of diabetes including associated complications and to make

modern and efficient diabetes services available to a wider population. It is one of the few centers in the world to offer a one-stop comprehensive facility treating at the primary (screening level), secondary (preventing complications for all patients with diabetes), and tertiary (treating diabetes complications) level. There are currently six locations that serve around 175,000 patients, making this the largest diabetes practice in the world. While it is notable that 13,000 new patients are added each year, it also speaks to the rapid growth of diabetes in India, which is currently at about 12% of the Indian population – and closer to 20% in urban centers.

One of the most encouraging elements of our time in India was being in the field and seeing how change is happening, ranging from prevention to screening to treatment programs. There has been major success seen with education, as shown by Dr. Mohan. His clinic has had a very positive result of reducing average A1c in treated patients from 9.8% to 8.0% over a year stemming from community-oriented local work and a major focus on lifestyle and other diabetes education. Some significant success has also come from more macrofactors, such as when care was pushed down to the paramedic level rather than the doctor level – certainly a positive given that India has seen incredible capacity constraints in terms of endocrinologists and family care doctors. Successes with screening programs both for diabetes and complications has also been notable, many driven by Dr. Mohan. We applaud his work and look forward as he and his center continue “Towards excellence in diabetes care” (motto for Dr. Mohan’s Diabetes Specialities Centre).

Kelly Close: Thank you so much for joining us, Dr. Mohan. Hearing about the history of your diabetes specialty centers during my time in India was so inspiring!

Dr. V. Mohan: Thank you! I’m glad to have the opportunity to speak with you.

Background on Dr. Mohan’s Diabetes Specialities Centers

Kelly: Broadly speaking, can you tell us a little about the public perception of diabetes in India and why you chose to focus on diabetes?

Dr. Mohan: Until the late 1940’s, there were virtually no diabetes specialists in India. My late father, Prof. M. Viswanathan, was one of the pioneers in diabetes in India. In 1971 when he left the Government Medical College, I joined him as an undergraduate student to assist him in his work on diabetes. That was the start of my interest in the field, and I worked with him till 1991 and helped him build a diabetes hospital and research center. In 1991, my wife, Dr. Rema, who is an ophthalmologist and currently the Managing Director of Dr. Mohan’s Diabetes Specialities Centre, and I decided to start our own center in a small way. It has now grown tremendously, and we now run a total of six diabetes centers across south India in addition to two Research Centers under the banner of the Madras Diabetes Research Foundation.

Kelly: Dr. Mohan, could you please share with our readers a little more about your practice – probably the largest diabetes practice in the world! Do you really have 175,000 patients? and 50 doctors?

Dr. Mohan: Yes, we do have a total of 175,000 registered patients with diabetes across our six centers although only a third of these probably receive regular follow-ups. Our team is comprised of diabetologists, ophthalmologists, surgeons, radiology & imaging specialists, dentists, foot specialists, biochemists, other lab specialists, nutritionists, dietitians, and various researchers.

Diabetes Treatment in India

Kelly: Please tell us about diabetes treatment in India. As I understand it, it is estimated that only half of all patients estimated to have diabetes are diagnosed. Is this improving? How many of your patients are treated with some oral anti-diabetic medication or insulin?

Dr. Mohan: Currently, as you say, only 50% of the 40 million people with diabetes in India are diagnosed, and of the latter only 50% are on any kind of treatment. Roughly, 80% of patients are on oral drugs, 15% on insulin, and 5% are controlled through diet and exercise. 50% to 60% would be only on oral drugs while another 20%-30% would be on a combination of oral drugs and insulin. Of those on insulin, about one-third have type 1 diabetes and two-thirds have type 2 diabetes. Overall in India, 95% have type 2 diabetes, about 2-3% have type 1 diabetes, and the rest have rarer forms of diabetes.

Kelly: For the 80% on orals, how does it divide between a TZD, metformin, Januvia, or other drugs?

Dr. Mohan: We normally start with metformin or a sulfonylurea. The current recommendation is to start on metformin first but that applies to the obese Western population. Since many of our patients are lean, we start with either metformin or a sulfonylurea or sometimes both in about 80% of the individuals. Of the remaining 20%, 5%-10% would be on Januvia, and approximately 10-15% would be on a TZD.

Kelly: Is there anything that you can say about GLP-1 analogs?

Dr. Mohan: Byetta (Amylin/Eli Lilly's exenatide) has not been received well because of the negative association with shots in India, which we hope changes over time. Also, the fear of pancreatitis is putting physicians and patients off Byetta. However, the DPP-4 inhibitors like sitagliptin (Merck's Januvia) and vildagliptin (Novartis' Galvus) are more popular.

Kelly: What are the perceptions of TZDs in India?

Dr. Mohan: Pioglitazone (Takeda's Actos) use is now increasing because opinion has been more against rosiglitazone (GSK's Avandia). At the moment, I can't see rosiglitazone coming back in a big way. Januvia is replacing pioglitazone in a lot of patients because of its safer side effect profile even though it is more expensive. However, it does not have weight gain, edema, heart failure, or hypoglycemia.

Insulin in India

Kelly: What kind of insulin is most commonly prescribed to your patients?

Dr. Mohan: Premixed is the most common followed by regular insulin and an intermediate acting insulin like NPH. Individuals who can afford it can also choose Lantus or Levemir. For individuals with severe diabetes, we put them on short-acting insulin and long-acting insulin. When we first add insulin to an oral drug regimen in patients with secondary failure to oral drugs, we normally start with a bedtime NPH insulin or Lantus.

Kelly: Can you talk about the need for insulin therapy in India?

Dr. Mohan: No one argues about the need for insulin, but it is all about affordability and acceptability. Affordability is an important issue for everyone, and acceptability is an additional issue people have to deal with, especially among more affluent people. Many

people try to put it off as long as possible because they have to inject themselves.

Kelly: Is generic insulin available?

Dr. Mohan: Not generic insulin but Indian-made companies such as Wockhardt and Biocon produce insulin that is exported to many countries. Wockhardt once had a problem in quality, but they are now back on track. Biocon is also growing a lot and exporting to some 20 or 30 countries. Many of the low and middle-income countries get their insulin from Indian companies.

Kelly: What do you think is the most interesting research that has been going on globally?

Dr. Mohan: What would be exciting for me would be easier ways to deliver insulin. We are waiting to see if the buccal/oral delivery will work. Insulin or oral insulin comes. Insulin is time-tested, and if you can give it while eliminating the pain of injections, that would be great.

Paying for Treatment

Kelly: What percent of your patients can afford to buy diabetes treatment?

Dr. Mohan: As ours is a Private Center, most of our patients buy their diabetes medications. Luckily, since we have generic tablets in India, they are not very expensive. Of course insulin is much more expensive.

Kelly: What would be the right approach for very low-income patients if they can't afford any drugs?

Dr. Mohan: In India, we have very inexpensive generics produced by Indian companies with Indian drug names, but I think companies should further mass-produce the same drug but without names — a generic within a generic. They could also be packed differently to make them much cheaper. If one really wants to help poor people, you would agree that lowering costs would help us distribute it to more people.

Kelly: How would you break down the types of treatment you give to your patients? As we understand it, in your practice, some patients pay more, effectively subsidizing those who pay less or nothing?

Dr. Mohan: Yes, my wealthy patients subsidize my poor patients. Those who cannot afford any treatment at all are offered completely free treatment through a Charitable Trust, which my wife and I set up for this purpose.

Clinical Research in India

Kelly: Could you please tell us a little bit about clinical research in diabetes in India? What role does it play? How much do you expect it to expand in the upcoming years?

Dr. Mohan: India is a great place to do clinical research because we have well-qualified doctors. Widespread use of the English language is an advantage, and we have large numbers of patients in India. I see the clinical trials expanding rapidly in India, but we should maintain strict ethical principles.

Kelly: Can you talk about the DREAM study? What did you think about your experience with DREAM?

Dr. Mohan: The focus of DREAM was to try two independent drugs in a two-by-two factorial design. The basis of the DREAM study was the TRIPOD study that was done using troglitazone (Pfizer's Rezulin that was taken off the market). In fact, they had a much greater effect of 62% seen with troglitazone, which was almost double the efficacy seen with metformin. So we thought rosiglitazone should be tested, and the other drug used was ramipril. There was some circumstantial evidence from the HOPE study that ramipril would help in the prevention of diabetes, but the HOPE study was not planned for that or designed for that.

From that result, we took the lead and asked can you prevent diabetes if you give rosiglitazone? Even if ramipril didn't prevent diabetes, it might have prevented cardiovascular disease that was already known. As you know, the result of the DREAM study showed that rosiglitazone prevented diabetes while ramipril did not. However, there was a lowering of the blood glucose with ramipril. In DREAM, rosiglitazone achieved a 72% reversal rate of IGT to normal, which even beat troglitazone, and 62% of patients treated with rosiglitazone did not progress to diabetes.

Concluding thoughts

Kelly: Dr. Mohan, I think we can learn a great deal from you about diabetes in India. I was particularly struck by how you are able to galvanize local communities. Can you share a little more about your work in local communities and how you have motivated leaders in remote villages to talk about diabetes with their peers?

Dr. Mohan: Based on our experience in urban areas, we started a major project on prevention of diabetes in the rural area of Tamil Nadu with the support of World Diabetes Foundation. This project has already reached out to 50,000 people in 42 villages in and around Chunampet about 80 miles south of Chennai. This success was achieved with the help of the local leaders and employing people from the local villages. These health workers have been trained as Diabetes Educators and help us spread accurate diabetes messages to rural people. This project helped us to bring down the glycated haemoglobin of the whole community from 9.8% to 8.0% within a period of one year using low-cost medications.

Kelly: You have a new center being built in Chunampet. What have been the major hopes for this center and when will it be finished?

Dr. Mohan: We hope to complete this new Rural Diabetes Center in the next 3-4 months. This will be one of the first rural diabetes centers in India and will be a model not only for India but for the rest of the world.

Kelly: Dr. Mohan, all our thanks to you for sharing so much with us. We salute you and your wife and your whole team for the pioneering work and your life calling!

— by Kelly Close and Melissa Tjota

6. DCU Interview with Lars Sørensen, CEO of Novo Nordisk

During our same trip to India in late November, we were lucky to have the opportunity to sit down with one of the most forward-looking CEOs we know in diabetes, Lars Sørensen. He has been CEO and President of Novo Nordisk since 2000, and he helped found the World Diabetes Foundation (WDF) in 2002. The mission of the WDF is to educate people about diabetes and provide care for impoverished individuals with diabetes in developing countries. The four focus areas are awareness and prevention of

diabetes, education and training of patients and healthcare professionals, improvement of access to essential medicines in diabetes, and enhancement of detection, treatment, and monitoring of diabetes. To date, the WDF has supported 183 projects in over 83 countries. According to the WDF, these projects will have the potential to impact over 66.5 million people in developing countries. Novo Nordisk gave \$100 million to WDF in 2002 and recently pledged another \$100 million over the next ten years. That's walking the talk ...

Insulin

Kelly Close: Mr. Sørensen, it is terrific to see you again and to be able to share some time with you here in Chennai, India. I'd like to start by talking about insulin. The arrival of insulin analogs in the late 1990s was groundbreaking, of course. I am getting a sense that we are on the cusp of seeing even more innovation in insulin – smarter insulins, ultra-rapid acting insulins, as an example. Is that right?

Lars Sørensen: Absolutely! There are still ways that we can improve insulin, and we have just seen the first phase 2 results from a new basal insulin which we are going to develop over the next few years that has a truly long-acting profile. In fact, it's so long-acting that you might even consider using it three times a week. It could be very useful, for example, for type 2 patients who still have some insulin production capacity. For type 1 patients, this product may enable a very flat basal insulin profile once they reach an equilibrium state.

Kelly: It's very interesting to watch the research because it seems to dovetail with all the comments made at scientific meetings in 2008 that diabetes therapy should be more personalized.

Mr. Sørensen: The concept that we are contemplating is whether or not it is possible to find insulins that are more tissue-specific and that have a tendency to be more active on the insulin receptors on the liver as opposed to the insulin receptors that are in the periphery. That would mean that we could achieve the same control with a lower dose of insulin, and therefore would induce less weight gain, which would be very beneficial. Today as you know, you can keep yourself in good control, but the tradeoff is that if you overeat, you gain weight, because the insulin will ensure that the sugar gets transported into adipose tissue.

Kelly: I think this is particularly important for patients who experience hypoglycemia and overeat. For example, it is virtually impossible for me not to eat too many carbs when I am hypoglycemic, and I know many other patients struggle with this issue.

Mr. Sørensen: Yes, it is related to overdosing of the meal related insulin component that then induces you to eat, and also, in some cases, the unreliable profile of the basal insulin, which can lower the blood sugar too much if you overdose. We are nowhere near the end of researching insulins. We can still improve basal, mixed, and the bolus insulins and we are very encouraged by what we see.

Kelly: What are your thoughts on getting insulin to developing countries?

Mr. Sørensen: This has been very challenging due to all the structural barriers. I recruited board members for the WDF that have worked in developing countries for years. We came to realize that the main issues in developing countries were the capacity to make diagnoses and the capacity to deliver care. We also realized that we have to make the resources that are being consumed as cheap as possible. Therefore, Novo Nordisk

decided to offer insulin in a preferential pricing scheme where we are offering our insulin at cost to the poorest countries in the world. The 50 poorest countries in the world can buy our insulin at cost.

This way, I build on a system where we have a mechanism by which we fund these problems in developing countries with the hope that it will lead to an increase in healthcare capacity allowing patients to be treated. Someday in the future this should develop into a market for the company, so long-term there is also a self-interest component.

Regulatory and Funding Situation

Kelly: What percentage of people in India with diabetes do you think could be in good control? I was very naïve before visiting and hadn't realized every patient paid for 100% of their medications. Of course, this issue is closely tied into the economy. What are the implications of the striking economic weakness that has hit the first world in the last four months?

Mr. Sørensen: This is a poverty problem. I was trying to make the point in my talk at WDF that this is a government responsibility, but we can't wait until the governments assume that responsibility. It's not without problems that private corporations are the donors and that profit-based companies are developing businesses based on a general population poverty situation. The government is not doing it, so we have to assume the responsibility or at least take some action.

Kelly: This is what you are doing with WDF, isn't it?

Mr. Sørensen: Exactly. I don't really like it from a theoretical perspective because we don't have a democratic mandate. We may be distorting priorities in developing countries because this draws people to one specific area. It has been very difficult for us to consistently ensure that personnel are being retained in the diabetes clinics. For example, in Africa, there are HIV programs with many more resources, and they're absorbing the professional working force.

That is why we have the condition for projects supported by the World Diabetes Foundation that we will only build and support programs where we have reasonable assurances that the necessary resources will be provided by the government, and that these resources will continue to be available after the completion of the WDF involvement – this improves the chances for sustainability. Otherwise, they will move on to the next donor project and the next philanthropist hobby and so on. My fundamental hesitation on philanthropy and private-oriented structures is that they may distort overall priorities in developing countries. Say, for instance, we come to a developing country and suggest that the country should be developing a project for improving diabetes care. I could be criticized for distorting local priorities by making diabetes a higher priority than it might have been otherwise, because we are coming with resources and people who are interested in doing something about diabetes in particular.

We need to ensure that the programs that we are supporting have governmental support, and the government will prioritize diabetes and put policies in place such that we are not being accused of distorting local priorities. I had to think about this, because I knew I could be accused of not doing anything, and I could be accused of

doing too much.

Kelly: How optimistic are you about the governments stepping in?

Mr. Sørensen: I think we have to be optimistic. Five or six years ago when I started this foundation, there was a complete lack of awareness and understanding that chronic disease was a problem in developing countries. Now, it is on the agenda. Even WHO is talking about it and focusing on having resources committed to creating policies and papers. We recently saw the Indian Minister of Health acknowledging the fact that diabetes and non-communicable diseases are significant problems. They have come a long way, but does that mean that the governments in Africa and in India are going to rush out and build capacity? No, I don't think so, but in time they will.

Kelly: It's a major difference. What would it take for really big philanthropists out there like the Gates Foundation to address diabetes?

Mr. Sørensen: I have been trying. It would be a major win for WDF to work with the Gates Foundation, but we have not been successful in trying to contact them. As you will hear, none of us can afford to build parallel structures where we compete for resources with the individuals working to tackle AIDS, TB, and malaria. I think we could do a lot of things by working together.

Kelly: Yes, I agree. Type 2 patients used to die earlier deaths in the US and from an economic perspective, staying alive longer has brought with it many more expenses, particularly related to complications. As such, an "unwell elderly" sub-population has begun to emerge. If they could get earlier, more aggressive treatments leading to a healthier elderly population, that would be so much better in our view.

Mr. Sørensen: You are absolutely right. What has happened in the past was type 2 diabetes was not being treated aggressively enough, and many patients lived poorly for a great number of years. They are at a significantly greater risk for developing complications, so their quality of life in their final years is way below what society should provide. The interesting thing now is that we see people getting type 2 diabetes at a younger and younger age. It used to be that our sixty or seventy year old grandparents got diabetes, and people were less interested in investing in them because they were no longer part of the active workforce. Of course, there are big problems with this as well because pensioners and old people are contributing to society in many ways. They are the support network for a lot of activities in the community. The interesting thing here is that now it's an obesity mediated disease in our society. Due to the obesity epidemic, type 2 diabetes presents earlier, and it becomes a real productivity issue because patients are in the active workforce.

As you have been hearing in India, a lot of economic growth in the future will depend on the economic growth in developing countries. Increasingly, we are dependent on the global economy participating in economic growth in places like India and China. Globally, and particularly in developing countries, people are getting type 2 diabetes much earlier in their productive years. So, the extent to which we allow diabetes to influence the economic growth and productivity in this area also affects the economic future of Western societies. It's all connected.

The Beginnings of the WDF

Kelly: Moving back a few years, could you talk a little bit about how you had the idea to create the WDF?

Mr. Sørensen: Yeah, that is an interesting story. We've long had the philosophy in the company of trying to identify areas that could evolve into challenges or opportunities. One of the controversial issues for the pharmaceutical industry that we had identified was access to essential medicines in developing countries. Starting from this point we were working in the company on how to formulate a strategy and a policy for the company in regards to the availability of our products. Now as you know, we don't have the same problem of access to insulin as the HIV/AIDS manufacturers because insulin is generically available. There are local manufacturers of insulin all over the world.

Kelly: You mean like Biocon?

Mr. Sørensen: Yes, they have local manufacturers here, and there are several international companies producing non-patent protected insulins, so we don't have the same problem of patents and technology being in the way of access. Insulin for an Indian with diabetes costs as much each day as a cup of coffee. Even though it may not be much for individuals in the US or Europe, it is still too much for many of them. We are aware that cost is still an issue that needs to be addressed.

When I got my job as CEO of Novo Nordisk, I ran right into the big public debate about access to HIV/AIDS medications because we as a company were part of the industry's lawsuit against the State of South Africa. It takes a little time to explain, but the pharmaceutical industry took issue with the State of South Africa's wish to abolish patent rights for administrative reasons, because South Africa is a member of the WTO. As a member of the WTO, you cannot just enjoy the benefits of being part of the trade system and then put aside patent restrictions. As an industry in general we were criticized for not offering our drugs to the poorest countries of the world. The reason why I was involved in the lawsuit was for another drug, which is inconsequential in the big scheme of things. This incident accelerated my personal understanding of the issue because I found out that the mortality of people with diabetes in developing countries was very high. I could see that there was an emerging epidemic of chronic disease in developing countries.

Kelly: That is notable that you were already able to foresee diabetes becoming such a vast problem in these countries.

Mr. Sørensen: This experience led me to emphasize that companies in developed countries are obliged to identify underprivileged groups where they can take some social initiatives to ensure that these groups are being treated and diagnosed. In a way, along with the patient associations, we are acting as advocates in developed countries. So, I said that I needed to create a foundation in developing countries that would be funded by taking a few cents for every insulin vial sold, and we started off by making a commitment of \$100 million for 10 years.

After five years, I realized that this foundation was quite successful, and I wanted to expand further, so I committed another \$100 million. In total right now, we have a commitment for \$200 million over 15 years. The premise for the foundation is that it should be involved in identifying, highlighting, and piloting sustainable long-term

solutions for dealing with diabetes. This translates into policymaking, guideline development, awareness building, and education for doctors, nurses, patients, and everybody involved. However, it does not mean dissemination of products because I did not want this foundation to be confused with being a marketing tool for the company.

Now, as a principle we want to benefit the poorest. We want to facilitate collaborations so people from India that have developed projects help people in Africa. We're also obliging the projects that we are supporting to be operating within existing structures. Ideally, we need commitments from the ministries of health saying that they will support the programs with the personnel and the necessary infrastructure because otherwise it's not sustainable.

We are also requesting co-funding. We are never funding, or very rarely funding 100% of the project, because if the interest is not there and there is no local contribution, then it's not sustainable.

Obesity and Diabetes in Asia

Kelly: One thing we have heard quite often is that fat distribution in India is very different, so obesity is present even if people do not have elevated BMIs using US definitions. We understand that in affluent schools, 30% of the students are obese.

Mr. Sørensen: This statistic is very scary for them because they have this predisposition to have a higher prevalence rate for diabetes than Caucasians. If the kids start to get obese in childhood, India will have an explosion of diabetes. We see a similar thing in Asians of Chinese or Japanese origin: they develop type 2 diabetes at a much lower BMI than we are used to in the US.

Kelly: Diabetes is already a big problem here, so the prospect of obesity worsening is quite worrisome, isn't it? I hadn't realized the extent to which things could worsen further here due to obesity.

Mr. Sørensen: Yes, if they have this genetic predisposition and fetal programming combines with a rapidly escalating epidemic of obesity, this would lead to a significantly worse problem than we are currently seeing here. There is also a positive angle to this issue. If we focus on maternal health, we can curb the particular part of the type 2 diabetes prevalence that stems from "babies being programmed with a higher risk." Combining it with community health programs aimed at healthy living may lead to long term benefits!

Liraglutide and GLP-1s

Kelly: On liraglutide, I like how the company is working to treat type 2 diabetes everywhere along the continuum. Is liraglutide going to be for monotherapy?

Mr. Sørensen: We hope so, but I think in all fairness it is most likely going to be used together with metformin. The data with liraglutide in combination with metformin are very strong. The data on pre-diabetes are also quite compelling.

Kelly: It is exciting to hear that because there is a big need to not only treat patients throughout the diabetes continuum but also those with pre-diabetes.

- Mr. Sørensen:* Absolutely! Another thing about liraglutide that we are trying to improve is that it is still an injectable drug that is competing with oral medication in the type 2 diabetes space. Even in the pre-diabetes space, where there is no medicine really available, introducing an injectable could be seen as a hurdle, so we are also working on developing an oral GLP-1.
- Kelly:* How possible will it be to develop an oral GLP-1?
- Mr. Sørensen:* We think that we can do this. That would be exciting for the early type 2 individuals where we are up against other oral medications. There is also potential for a pre-diabetes application.
- Kelly:* When liraglutide comes out, by how much do you think it could delay putting patients on insulin? If it were used right away, would it be possible to delay beta-cell death?
- Mr. Sørensen:* That is still being evaluated. We have shown that a single dose of liraglutide improves beta-cell function. Whether this translates into longer term beta-cell survival – is still uncertain. I would have to say from the data that we have seen on Byetta, it does not seem to be the case.

The WDF and Insulin for Children

- Kelly:* We were excited to read in December 2008 about your donation of free insulin to 10,000 children in Africa, Asia, and Central America over the next five years.
- Mr. Sørensen:* Yes, it is a sad fact that the life expectancy for a child with type 1 diabetes in the poorest countries is only a few years!
- Kelly:* That is clearly an incredibly sobering statistic for a patient like me for whom diabetes is a chronic disease.
- Mr. Sørensen:* Indeed, it is totally unacceptable, and we need to do something, thus, moving forward with the funding for the 10,000 children. We need to focus on increasing capacity, awareness, and the diagnosis rate. Even though individuals are diagnosed with diabetes, they live a very short life because they do not have access to medicine, which is why we will aim to secure free insulin for all the children.
- Kelly:* How will you distribute the insulin?
- Mr. Sørensen:* We will start by expressing our goal of supporting 10,000 children in the poorest countries with insulin by 2015. And that's exactly the right question, how will we make this possible? This will require that we start by developing a distribution system and figure out how we can do this in a way that is sustainable under these circumstances. We need to take into account the logistics as well as educating healthcare professionals, patients, and patient families. Projects like these are generating tremendous engagement within Novo Nordisk. That is the main short term benefit for the company.
- Kelly:* We are so moved by all the steps you are taking to improve the situation in these underdeveloped areas, particularly for children. Thank you so much for leading Novo Nordisk and on behalf of your company, for the work you are doing to improve life for people with diabetes.

by Kelly Close and Melissa Tjota

7. In the News: ADA-ACC-AHA Joint Statement

The American Diabetes Association, American College of Cardiology, and the American Heart Association issued a joint statement on December 17, 2008, discussing the results, questions, and clinical implications of the ACCORD, ADVANCE, and VADT studies. The statement, which was signed by a powerhouse team of authors (including Drs. Jay Skyler, Richard Bergenstal, John Buse, Edwin Gale, and Robert Sherwin, among others), concludes that the data from these three trials do not call for “major changes in glycemic targets” but do suggest that an A1c target for most patients below 7.0% is appropriate because it has been shown to reduce microvascular risk (i.e. retinopathy, neuropathy, and nephropathy). The authors further state that an A1c goal below 6.0% is inappropriate for patients with advanced diabetes.

Specifically, the statement notes that the ADA’s A1c goal of <7.0% for non-pregnant type 1 or type 2 patients should be maintained to reduce microvascular complications (AHA/ACC Level of Evidence A¹). Furthermore, it states that until further evidence is obtained, the goal of ≤7.0% A1c in the context of macrovascular disease is reasonable (Level of Evidence A). The lack of significant reduction in CVD outcomes from randomized controlled trials reduces the strength of this recommendation although the long-term follow-up of both the DCCT and the UKPDS are “suggestive of long-term risk reduction of macrovascular disease” following treatment to A1c targets of below or around 7.0%.

The document goes on to state that on a patient-by-patient basis, a lower A1c goal (less than 7.0%) may be reasonable if achievable without significant hypoglycemia or other adverse effects (Level of Evidence C²). In the same vein, a similar patient-by-patient analysis may make a less stringent target more appropriate for certain patients (e.g. those with history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbidities, or long duration of diabetes). Blood pressure treatment including lipid-lowering with statins, aspirin prophylaxis, smoking cessation, and behavior modification as outlined in the ADA Standards of Medical Care in Diabetes and the AHA/ADA guidelines for primary CVD prevention should be maintained.

We believe this statement is a positive message overall for the diabetes industry. The authors clearly emphasize the importance of diabetes self-management education, appropriate use of blood glucose monitoring, and effective use of glucose lowering agents.

— by Kaku Armah and Kelly Close

8. In the News: DPS Health’s Virtual Lifestyle Management Software

Dr. Kathleen McTigue, University of Pittsburgh researcher, internist and co-developer of the Virtual Lifestyle Management (VLM) service, presented a live demonstration of the VLM at the recent Diabetes Technology Society meeting. The VLM is an online program that helps people at risk for or with type 2 diabetes set weight-loss goals, design a specific lifestyle plan, and then achieve results. The University of Pittsburgh worked with DPS Health to create the program based on the lifestyle regimen used in the Diabetes Prevention Program (published in 2002) that was created by the University under a grant from the NIH. Studies of the VLM software have demonstrated remarkable weight-loss efficacy—38% of users lost more than 7% of their weight after 9 months. The program is designed to be hosted and managed by a healthcare provider or company as a service for its patients or employees to help them lose weight and improve metabolic outcomes. From what we’ve seen, this program looks very positive, both in terms of improving participants’ health and potentially helping to control the costs of overseeing lifestyle support programs. We think the system may appeal to a broad range of organizations as it

¹ **Level of Evidence A:** Data derived from multiple randomized clinical trials or meta-analyses.

² **Level of Evidence C:** Only consensus opinion of experts, case studies, or standard of care.

provides an opportunity for substantial health improvements (and reduced costs!) with a minimum of additional training or manpower.

- **The program is a one-year intensive weight loss tool composed of a number of different online components that users engage in parallel.** First, there are a series of lessons to help users learn about ways to lose weight. The program includes 16 weekly lessons and eight monthly lessons to engage users in learning about healthy habits throughout the entire course of the program. The second aspect is a behavior tracking and planning tool that helps users to design and follow a regimen of regular physical activity and healthy eating habits. Users can schedule an activity plan using a drag-and-drop graphical interface and view graphs of trends in their weight, food consumption, and 'step count' from exercise that users measure using an accelerometer. Users can also set diet and physical activity goals, and the program automatically adjusts those goals based on their activities. Finally, the communications aspect of the program lets users send and receive secure messages with a coach (always a healthcare professional) at the institution hosting the program and attend moderated group chat sessions with other users.
- **From the healthcare professional or coach side, the VLM service includes tools to monitor users' progress.** Coaches can send secure personalized updates to each user based on the patient's specific performance. The coach can view individual progress or generate group reports about a specific population of users taken together, and can send users individualized tips or answers to specific questions.
- **Studies of the VLM have demonstrated remarkable weight-loss efficacy.** An abstract published by McTigue et al. in the March 2008 supplement to the Journal of General Internal Medicine reported 9-month data from 50 patients showing average weight loss of 5.53 kg from a mean BMI of 36.8. By the end of the study, 34 users who had weight data in the 9-month window had weight loss of 7.13 kg, and 38% of those users had achieved >7% weight loss. Fat consumption had decreased by 8.4 grams/day and step count had increased by 1538 steps/day after 6 months of use. Twelve month data will be available in the near future.
- **The VLM program is intended as a service hosted by a healthcare provider, group of providers, or other entity and made available online to its patients or employees.** DPS Health (www.dpshealth.com/vlm) has been granted a license to bring the Virtual Lifestyle Management service to healthcare provider organizations. Many different organizations have begun to take advantage of the VLM, including the Air Force, the Motion Picture and Television Fund (a healthcare provider), the USC General Internal Medicine practice, Mental Health America, the Government Employees Hospital Association of Kansas City (a health plan), and Monarch Healthcare (a physician group in Southern California).

— by Brendan Milliner

9. Conference Pearls: Diabetes Technology Conference

November 5-7, 2008 • Bethesda, MD • www.diabetestechology.org

The Diabetes Technology meeting covered a wide range of topics, and we reported on talks covering continuous glucose monitoring, closed-loop studies, insulin delivery, self-monitoring of blood glucose, regulatory/approval process, as well as telehealth. Notably, we saw positive results from a secondary JDRF CGM study looking at a cohort with A1c levels below 7.0%. Also of note were closed-loop data from the labs of Drs. Claudio Cobelli, Boris Kovatchev, César Palerm, and Ed Damiano. We include highlights from the conference below.

Continuous Glucose Sensing and Monitoring

- **Bill Tamborlane, MD (Yale University, New Haven, CT)** presented results from a 26-week study which was performed simultaneously with the primary JDRF CGM study and was similar in design to the primary study except that it examined type 1 subjects who had A1c below 7%. The study randomized 129 subjects to CGM and control groups following a run-in period in which all patients wore blinded CGM for at least six out of seven days. In the CGM group, the change in frequency of daily sensor readings ≤ 70 mg/dL decreased over 40% (very statistically significant) from 91 minutes to 54 minutes after 26 weeks whereas in the control group, there was a non-significant decrease from 96 minutes to 91 minutes (5%) after the 26-week study period. The difference between the groups was not significant from the primary statistical analysis. In secondary analysis with truncated outliers and combination of 13 and 26 week data, the between group differences were significant. Notably, there was maintenance of A1c in the CGM group at 6.4% while A1c in the control group rose from 6.5% to 6.8% by the end of the study. Importantly and unlike in the primary JDRF CGM study, the results obtained in subjects ≥ 25 years was similar to those obtained for subjects under 25 years (data not shown). There was no significant difference in severe hypoglycemia between groups. The study is currently being reviewed and we look forward to publication of these powerful data.
- **Geoff McGarraugh, MS (Abbott Diabetes Care, Alameda, CA)** noted that current CGM was a poor diagnostic device but an effective monitoring device. He presented a study that looked at CGM detection of hypoglycemia or within 30 minutes of the event. Results from the hypoglycemia study suggest that low alarms should be set around 90mg/dL to get good hypoglycemia detection where hypoglycemia was defined as <70 mg/dL (mild) or < 60 (moderate). The corresponding hyperglycemia experiment showed that setting the hyperglycemia alarm 10% below the desired threshold for hyperglycemia would result in 57% detection of blood glucose equal to or above 140 mg/dL. In order get to the point where we have alarms good enough to remove the need for blood glucose testing, CGM must be able to display 95% of results be within ± 15 mg/dl of the actual value at <75 mg/dL, or $\pm 20\%$ at ≥ 75 mg/dl according to specifications of ISO 15197 for blood glucose meters. McGarraugh emphasized that CGM were not diagnostic tools and did not advocate off-label use.

Closed-Loop Studies

- **Cesar Palerm, PhD (Medtronic Diabetes, Northridge, CA)** discussed his attempts to integrate insulin-dependent feedback into his group's closed-loop control algorithm. He used a pharmacokinetic model to predict insulin levels and use them to affect future insulin delivery to attempt to achieve earlier insulin delivery before meals (without a bolus). His results in clinical trials with type 1 patients show that the incorporation of predictive insulin feedback significantly improves the glycemic control that is possible with a closed-loop system. However, while postprandial glycemic spikes were markedly decreased, there were episodes of hypoglycemia following meals in five out of eight subjects.
- **Ed Damiano, PhD (Boston University, Boston, MA)** discussed preliminary data in an ongoing clinical study in type 1 subjects 18 and older using closed-loop and open-loop delivery of insulin and glucagon. Six closed-loop, two open-loop, and two control experiments have thus far been completed. Subjects were fed three large meals daily and glucose values were quite well controlled in closed-loop studies, except for mealtime excursions which, Dr. Damiano explained, resulted from the reduction of aggressiveness in the algorithm parameters due to the fact that these were among the first set of human experiments. Some challenges with individual patients with slow insulin pharmacokinetics (both peaking and clearance) have been found.

Insulin Delivery

- **Thomas Forst, MD (Biodel, Danbury, CT)** investigated the effects of VIAject, an ultra-rapid-acting insulin, on postprandial endothelial function and oxidative stress. The study, done in 14 insulin-naïve type 2 patients, showed that VIAject increased blood flow and O₂ saturation at 30 and 60 minutes after a meal and decreased markers of oxidative stress compared to both NPH and insulin lispro (Humalog). The effects of the insulins on overall postprandial glycemic control were not different. This study points to an importance of rapid insulin kinetics on endothelial function, independent of glycemic control. With all the focus on CV health with new diabetes treatments, this bodes well for patients in our view.
- **Blair Geho, MD (Diasome Pharmaceuticals, Conshohocken, PA)** discussed a novel approach to the delivery of insulin, which can be either injected or taken orally and is compatible with all current insulins and analogs. The technology (termed nanotechnology) involves a spherical assembly of vitamin-like subunits attached to insulin molecules and tagged with a factor that “targets” the delivery of the insulin to a specific cell type. In animal studies and phase 2 human studies, the use of this technology with human insulin targeted to the liver seems to improve post-prandial glycemic control to a degree comparable to that achieved with Humulin analog insulin. The drug has completed phase 2 studies.
- **Sarah Mehdi, BSc (Imperial College, London, UK)** discussed an intriguing study comparing glycemic variability in subjects on continuous subcutaneous insulin infusion (CSII) to subjects on multiple daily injections (MDI). Given the lack of standard glycemic variability measures, investigators used a combination of five measures, namely standard deviation, mean amplitude of glycemic excursion (MAGE), M value, J index (not validated for CGM), and mean of daily differences (MODD). Mehdi found significantly lower A1c in the CSII group (7.75% vs. 8.68%) and significantly higher glycemic variability in the MDI group. There was a positive correlation with A1c in the MDI group and in the overall population but not in the CSII group, and we wonder if this could be suggestive of a positive impact of CSII on glycemic variability. Glycemic variability was positively correlated to urine albumin to creatinine ratios, and negatively correlated with estimated glomerular filtration rate. Mehdi inferred that this finding might suggest a role of glycemic variability in the development of microvascular complications. Glycemic variability was also found to be positively correlated with age, which is pretty depressing for anyone with diabetes who wants to live a long time – just another reason to lobby harder for CGM.

Regulatory Environment

- **Arleen Pinkos, MD (Food and Drug Administration, Rockville, MD)** discussed some of the barriers facing the development and approval of an artificial pancreas. Most importantly, she focused on “thinking like Murphy” (of Murphy’s law) and addressing all of the possible problems and concerns with a product during submission to the FDA. She also briefly addressed the importance of addressing the problem of patients who try to circumvent safety devices for their own ends.
- **Charles Zimlik, PhD (FDA, Rockville, MD)** did a thorough analysis of the FDA’s view on regulation of decision-support software such as an insulin-dosing calculator. The four primary review areas for decision-support software are: intended use, algorithm, clinical evidence, and documentation. He advised developers to take advantage of free pre investigational device exemption (IDE) submissions as well as *other* FDA resources such as the 513(g) service that allows you to call in and figure out if your software qualifies as a device. There is also a call in number for which the FDA will give you a risk assessment on your device. For free pre-IDE submissions, call 240-276-4034. For 513 (g) call 240-276-4027. For a risk assessment, call 240-276-4023.

Telehealth and Adherence Studies

- **Cheryl Pegus, MD, MPH (SymCare Personalized Health Solutions, Westchester, PA)** presented the new SymCare internet diabetes health software, designed to help patients and doctors keep in better control of diabetes. One of the most interesting things about this product in our view is the rewards system, through which patients can obtain discounts on products from Amazon.com by completing diabetes management goals.
- **Jim Mingle, BS (MyCare Team, Acton MA)** discussed MyCare Team (MCT), an FDA 501 (k) cleared device that stores and transmits diabetes management information in a HIPAA compliant fashion. Mingle reported that the software has been used successfully in multiple studies with type 2s to significantly reduce A1c by an average of two points. MCT supports 31 meters and provides healthcare providers with a dashboard to allow data analysis across all platforms.
- **Gérard Reach, MD (Hospital Avicenne, Paris, France)** defined therapeutic non-adherence as the lack of equivalence between the behavior of the patients and their prescribed medical treatment. He discussed an eye opening study, which found that subjects not adherent to beta-blocker therapy had twice the mortality risk compared to adherent subjects. Interestingly, they found a similar trend in the placebo group. What's more surprising, the adherent group in the placebo arm had a lower mortality risk than the nonadherent group in the treatment arm! (Simpson et al, *BMJ*, 2006, 333). He pointed out that the reward of adherence is abstract and delayed e.g. "You can avoid complications in 10 years." People often prefer smaller rewards sooner to larger results later. Technology to improve adherence being developed should take this into account.

Non-Invasive Continuous Glucose Sensing and Monitoring

- **H. Michael Heise, PhD (Dortmund University of Technology, Dortmund, Germany)** discussed the use of near-infrared spectroscopy to measure glucose levels. Near-infrared spectroscopy is a technique to identify particular chemical compounds based on their absorption of radiation across the spectrum, and can be used to determine glucose concentrations in the blood of capillaries of the skin. Similar to other non-invasive techniques, however, there are many challenges to this approach – the biggest of which is likely background noise.
- **Lior Ma'ayan, MS, MBA (OrSense, Nes Ziona, Israel)** discussed OrSense technology, which is based on occlusion spectroscopy. Research done thus far has included *in silico* modeling (Monte Carlo simulations and analytical modeling), *in vitro* (finger phantoms), and *in vivo* (animal studies and hypo/hyper human clamp studies). Human data in the controlled setting of an ICU using over 24 hours of continuous monitoring of multiple blood parameters – glucose, hemoglobin, oxygen saturation – had 75% of paired values in zone A of the Clarke Error Grid (CEG) while 21% of the values were in zone B.
- **Avner Gal (Integrity Applications, Ashkelon, Israel)** discussed his company's combination of three different technologies to measure glucose noninvasively. The GlucoTrack measurement concept uses ultrasonic, electromagnetic and thermal technologies each of which is based on different physical property of the tissue, in turn correlated with blood glucose changes. The measurement site is the earlobe since it has a large blood supply (well correlated with finger capillary) and is a fairly homogenous site. With the most recent system improvements, the percentage of readings in the A zone of the CEG went up to 58% from 42% initially, and with the addition of an on-line validity filter (for ambient and body temperature), up to 66%.

– by Kaku Armah and Brendan Milliner

10. Conference Pearls: Diabetes Summit for Southeast Asia

November 27-30, 2008 • Chennai, India • www.worlddiabetesfoundation.org

The Diabetes Summit for Southeast Asia, organized by the World Diabetes Foundation (WDF) in collaboration with the World Health Organization (WHO), the South East Asia Regional Office (SEARO), the International Diabetes Federation (IDF), and the World Bank, took place November 27-30, 2008 in Chennai, India. The rise in diabetes and obesity in India has been striking – over 40 million people in India have diabetes. The minimal attention given to diabetes and obesity because of the country's lack of resources is truly astonishing, especially when compared to the resources addressing communicable diseases in many developing countries. Rapid urbanization has created an obesogenic environment, and the poor health of individuals is exacerbated by the fact that Asians have a lower risk threshold for obesity. Thankfully, we see evidence of some real steps to address this disparity, as well as a trend toward greater focus on diabetes prevention and treatment.

- **Unfortunately, the price of progress in Southeast Asia is an increasing prevalence of obesity due to unhealthy lifestyle habits.** It was noted that along with rapid urbanization and a higher standard of general living came the regrettable downside of an increasingly sedentary lifestyle (especially among those with higher incomes) as well as an increase in stress levels and consumption of junk food. Exacerbating the situation is the fact that Asians have a lower risk threshold for obesity, creating a region heavily prone to obesity and diabetes. According to Viswanathan Mohan, MD (Dr. Mohan's Specialities Centre, Chennai, India), 30% of children in affluent schools in India are obese compared to 10% of children in low-income and middle-income schools. Overall, the rate of obesity among children in India is 20%.
- **In India, type 2 diabetes prevalence is estimated at 12% and prevalence for impaired glucose tolerance is estimated at 14%; both figures are nearly double the estimates in the US.** According to Meer Mustafa Hussain, MD (Tamilnadu Medical University, Chennai, India), out of 1.1 billion people in India, 31 million have type 2 diabetes (Diabetes Atlas 2006 quotes 41 million), a number that is increasing alongside the rate of obesity. Frighteningly, when we visited a hospital and asked about diabetes prevalence, one nurse noted that most women simply assume that they will one day be afflicted with the disease. This assumption is disconcertingly justifiable when taking into account that the prevalence of type 2 diabetes in women over 50 in urban areas exceeds 50%.
- **Michael Engलगau, MD, MS (The World Bank, Washington, DC) discussed broad differences in healthcare systems between developed and developing countries.** In developing, lower-income countries, most citizens pay privately for health expenses. For example in India, the percentage of private health expenditures is around 85%, and 85% of that percentage is out of pocket. This point is significant when considering that 34% of India lives in poverty (according to 2004 estimates). In contrast, in high-income countries, there is a nearly equal distribution of financing between patients' out of pocket expenses, National Health Service, national health insurance, or private health insurance models.
- **In developing countries, there is a tug-of-war between focusing on infectious diseases and focusing on chronic diseases.** Progress has been made by programs dedicated to malaria and tuberculosis because many major non-profits focus on communicable diseases; however, there has been surprisingly little attention paid to chronic diseases. The IDF estimates that \$8-\$9 billion is currently being channeled to fight healthcare problems in developing countries, and the underwhelming percentage of this money that is devoted to non-communicable disease rounds down to 0.0%! Aside from the obvious health impacts, there are also detrimental economic effects; WHO statistics indicate that India and Pakistan will lose 0.5%–1% of their gross national product over the

next ten years due to deaths from chronic disease. On the upside, there was a very moving resolution made at the meeting to promote more focus on chronic diseases by the UN, with major requests to government agencies to follow.

- **A presentation given by A. Ramachandran (India Diabetes Research Foundation, Chennai, India) pointed out that the Indian Diabetes Primary Prevention Trial (IDPP) demonstrated that primary prevention of type 2 diabetes was possible.** The IDPP took place from 2001 to 2005 and was published by Ramachandran *et al.* Diabetologia 2006. 11,000 subjects were screened for impaired glucose tolerance and 531 subjects were randomized into four groups: control, lifestyle modification, metformin 500 mg, or lifestyle modification plus metformin. Lifestyle modification consisted of dietary changes and increased physical activity. Compared to a cumulative incidence of diabetes in the control group of 55%, the lifestyle group had 39.3%, the metformin group had 40.5% and the combination lifestyle/metformin group had 39.5% (all significant differences).
- **We were also pleased to hear about the Chunampet Project being run by Viswanathan Mohan, MD (Dr. Mohan's Diabetes Specialities Centre, Chennai, India).** The project is aimed at benefiting rural communities with little or no access to diabetes care by providing screening for diabetes and its complications. As a side note, 75% of qualified medical consultants practice in urban areas. The Tele-Diabetology van is one such screening program; it uses live teleconsultation with Dr. Mohan's Diabetes Specialties Center in Chennai via V-Sat to diagnose complications such as retinopathy. Dr. Mohan projects that with \$0.57 million investment from the World Diabetes Federation over four years, the potential economic gain/saving due to early detection and prevention is ~\$8.5 million over five years.

— by Kaku Armah, Kelly Close, Alexandra Gladstone, and Melissa Tjota

11. Conference Pearls: Metabolic Disease Summit

November 6-7, 2008 • Boston, MA • www.gtcbio.com/conferenceDetails.aspx?id=138

This past winter we spent two days in Boston attending the Metabolic Disease Summit. This meeting was very basic-science oriented, and most of the data presented was from preclinical studies with cell cultures or animal models. There were speakers from nearly all the major players in the pharmaceutical industry including Amgen, AstraZeneca, Eli Lilly, Elixir Pharmaceuticals, Merck, Novo Nordisk, Novartis, Pfizer, and Sanofi-Aventis. Increasingly, researchers appear to be trying to approach diabetes and obesity from various avenues, which makes sense because they are such multifactorial diseases. While it will still take quite a bit of time to get any of the targets discussed to market, it was interesting to hear where diabetes and obesity research is going, and we present the highlights below.

Highlights

- **Olga Taraschenko, MD, PhD (Albany Medical College, Albany, NY)** discussed 18-Methoxycoronaridine (18-MC), which was originally studied to treat drug addiction as it helped to reduce self-administration of morphine, cocaine, methamphetamine, nicotine, and alcohol in rats. Dr. Taraschenko has been studying this drug in rats and saw that 18-MC prevented sucrose-induced weight gain while having no effect on weight gain of animals consuming normal chow. They also saw a reduction in sucrose reward, a decrease in the intake of highly palatable substances, a reduction in fat deposition, and no effects on the consumption of water. Dr. Taraschenko believes that 18-MC could potentially be used in the clinic to treat obesity, but it still needs to be shown that the effect of 18-MC on satiety and fat deposition can be replicated in humans.

- **Yang Li, PhD (Amgen, Thousand Oaks, CA)** reviewed his research on the fibroblast growth factor 21 (FGF21), a protein that stimulates glucose uptake in adipocytes. In addition, FGF21 transgenic mice are resistant to aging-related obesity and type 2 diabetes and do not have an increased incidence of tumor growth. Xu *et al.*, in press, *Diabetes*, showed that FGF21 (0.1 mg/kg or 10 mg/kg) reduced body weight and adiposity in diet-induced obesity (DIO) mice. There was also an improvement in the metabolic and cardiovascular profile: decrease in blood glucose, decrease in lipid levels, and improvement of GTT (glucose tolerance tests). Overall, Dr. Li felt FGF21 is emerging as an important metabolic regulator. It has been shown to be quite efficacious in the mouse, but studies have not yet shown it has the same effect in humans. FGF21 could have an advantage in the playing field of drug development as it appears to improve cardiovascular factors (e.g. lipids and cholesterol). According to Eli Lilly's analyst meeting on December 10, 2008, the company is developing an FGF21 with Amgen.
- **W. Todd Penberthy, PhD (University of Cincinnati, Cincinnati, OH)** works with zebrafish as a new screening method to test obesity drugs in an animal model system that is inexpensive and addresses whole body concerns. Using this animal model, he studied adipogenic and lipolytic pathways and presented data on treating zebrafish with resveratrol (Sirtris). Resveratrol consistently reduced the fat content in all of the zebrafish, and another molecule, Vat B, appeared to be even more potent than resveratrol in reducing lipid content. Dr. Penberthy highlighted how this drug could be a safe and efficacious anti-obesity medication. He also pointed out that another future direction could include studying CD38 deficient mice that are resistant to high fat induced obesity due to an increase of NAD-SIRT1-PGC1 alpha mitochondrial biogenesis. Thus, Dr. Penberthy believes targeting of CD38 may provide a possible new medication for obesity or metabolic syndrome. However, he pointed out that the possibility of infections would need to be closely examined as CD38 deficient mice have a compromised immune system.
- **Ruojing Yang, PhD (Merck, Rahway, NJ)** discussed his research, which focuses on the role of c-Jun N-terminal kinase 1 (JNK1) in the liver. JNK plays a role in regulating cell differentiation, inflammatory conditions, cytokine production, cell proliferation, and other cellular functions. Liver-specific knockdown of JNK1 showed enhanced hepatic glycolysis and triglyceride synthesis (Yang *et al.*, *Journal of Biological Chemistry*, 2007). Cho *et al.*, *American Journal of Physiology*, 2008 is the only study at the moment to show that a JNK inhibitor improves insulin sensitivity in DIO mice. At the moment, work on JNK has only been carried out in cell cultures and animal models, and it needs to be verified in humans.

— by Melissa Tjota

12. Literature Review: Standards of Medical Care in Diabetes

The American Diabetes Association (2009) “Standards of Medical Care in Diabetes.” *Diabetes Care*, 32: S13-S61.

To start off 2009, the American Diabetes Association (ADA) released revisions to the clinical practice recommendations. These revisions reflect the relatively new data from the Juvenile Diabetes Research Foundation (JDRF) continuous glucose monitoring trial, the long term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) study, and the A1c-Derived Average Glucose (ADAG) trial.

In summary, continuous glucose monitoring (CGM) has been upgraded from a potential “supplemental tool” to a potentially “useful tool” in adults over 25 years, and the recommendations do acknowledge that some younger patients may also benefit. The relationship between mean plasma glucose values and

A1c percentages has been updated to reflect ADAG trial data. The revised recommendations distinguish between proven microvascular benefit from near normal A1c and the potential cardiovascular risks associated with lowering A1c below 7.0% in certain high-risk patients. A section on bariatric surgery has been added that suggests consideration of bariatric procedures in patients with type 2 diabetes and a BMI ≥ 35 kg/m². In critical care populations, the revised recommendation introduces a differentiation between surgical and non-surgical patients. They still recommend maintaining glycemia as close to 110 mg/dL as possible, in surgical patients; however, the recommendation for nonsurgical patients has increased to < 140 mg/dL.

Self-Monitoring of Blood Glucose (SMBG)

- **The function of SMBG in non-intensively treated patients was redefined.** For these patients, the 2009 Standards of Care document states that SMBG may be used as an assessment tool to monitor the success of other therapies whereas the 2008 document positioned SMBG as a useful tool in achieving glycemic goals – both level E recommendations. In our view this will be useful if it leads to patients looking at blood glucose test strips less like an added expense and more like a useful tool for diabetes management. From our view, patients need SMBG to reach targets whether or not they are intensively managed.

Continuous Glucose Monitoring (CGM)

- **The level of evidence for CGM recommendations has been upgraded from a single level E recommendation to three recommendations of levels A, C, and E respectively.** Presumably, this change comes in large part from the JDRF continuous glucose monitoring trial data. The new recommendations describe CGM use as valuable in patients who are on intensive insulin regimens, and over 25 years of age - level A recommendation. Other groups may be helped by the technology though the evidence is “less strong” and success correlates strongly with adherence. Overall, we would say this is a major step up for CGM.
- **Unlike the 2008 Standards of Medical Care in Diabetes document, the updated 2009 document does not explicitly limit the CGM recommendation to type 1s.** The 2009 document states that CGM may be a “supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.” While we acknowledge that these are more typically phenomena observed in patients with type 1, we believe this is positive for the CGM industry since the previous iteration only said CGM “may be a supplemental tool to SMBG for selected patients with type 1 diabetes, especially those with hypoglycemia unawareness.”

A1c and Average Glucose

- **The correlation of A1c with average glucose has been updated to reflect the data from the A1c-Derived Average Glucose (ADAG) study.** The correlation between A1c and estimated average glucose (eAG) was found to be strong (and generalizable) enough to justify reporting both values when an A1c test is ordered. Previous correlates were based on DCCT data that were less comprehensive, and less generalizable than the ADAG sample. Inclusion of both A1c and eAG is a positive change for healthcare providers who will not have to spend consulting time translating the A1c result into a form with which patients are more familiar. The correlation table has been reproduced in Appendix B. The formula derived was $28.7 \times A1C - 46.7 = eAG$.

Impact of Recent Epidemiological Studies on A1c Goals

- **The A1c goal pertaining to minimizing the risk of microvascular complications in non-pregnant adults remains at less than 7% (level A).** Notably, lower goals for selected patients (short diabetes duration, long life expectancy, no significant CVD) are recommended if achievable

without significant hypoglycemia (level B). Likewise, less stringent goals may be more appropriate for those with a history of severe hypoglycemia and extensive comorbidities (level C).

- **The goal of A1c less than 7% for macrovascular risk reduction is reasonable (level B).** This recommendation was based on long term follow-up of the DCCT and the UKPDS cohorts particularly for newly diagnosed patients. The results of the intensive ACCORD arm prevented the general recommendation of more stringent goals for reduction of macrovascular risk. We think, in light of the available evidence, that this is a very balanced and well thought out recommendation. The guidelines that make the most sense to us are the ADA/AHA guidelines, which essentially say that a lower than 6% A1c goal for those with CVD disease should not be made.

Bariatric Surgery

- **This new section mirrored the conclusions from recent obesity meetings we've attended;** bariatric surgery was recommended (level B) along with accompanying lifestyle support (level E) in patients with type 2 diabetes and a BMI ≥ 35 kg/m². As we expected, the committee felt that insufficient evidence was available to support a general recommendation of bariatric surgery in patient with BMI < 35 kg/m². The authors called for well-designed randomized controlled trials (using optimal medical and lifestyle therapy as a control) to examine the long-term benefits, cost effectiveness and risks of bariatric surgery.
- **The fact that bariatric surgery is finally “on the map” brings a positive addition to the diabetes arsenal.** We feel that surgery is unlikely ever to be a general therapy but we believe that the value of this set of therapies will enable a better understanding of the mechanisms of weight loss, weight loss maintenance, and diabetes remission. This understanding will then inform lifestyle, pharmacotherapeutic, and mechanical interventions in obesity.

In-hospital Diabetes Management

- **The 2009 recommendations differentiate between glycemic control in critically ill surgical vs. non-surgical patient populations.** This is an important change over the 2008 document, which considered all critically ill patients as a single population.
- **The updated glycemic ranges recommend maintaining glucose as close to 110 mg/dL (6.1 mmol/L) as possible in surgical patients (level E).** Intravenous insulin infusion protocols were recommended.
- **Given the lack of conclusive evidence in nonsurgical patients, the recommendation for this group is simply to maintain glycemia under 140 mg/dL (level C).** This recommendation leaves the extent of glycemic control largely up to the individual healthcare provider. Intravenous insulin infusion protocols were recommended. We view this as a positive because both groups might have been “downgraded,” which would have been very negative for patients, in our view. Still, presumably more data needs to be shown before tight glycemic control of less than 110 mg/dL average glucose will be targeted.

Diabetes and Employment

- **Formerly the “Hypoglycemia and employment licensure” section, this section calls for a professional medical assessment if a question arises about the medical suitability of a person with diabetes for a particular job (level E).** The recommendation calls for inclusion of glucose data, hypoglycemia (unawareness) history, diabetes-related complications in safety assessment for employment. It specifies that neither urine glucose nor A1c/eAG should be used to assess the level of diabetes control.

- **We view this added detail in the recommendation as a positive step, though the recommendation falls short given likely real-world biases against people with diabetes.** This recommendation does not really address discrimination resulting from an employer's desire to maintain low health insurance premiums. Although this point will be difficult to address, we feel that it is nonetheless important to consider.

Appendix A - Description of levels of evidence

Level A: Data derived from multiple randomized clinical trials or meta-analyses.

Level B: Data derived from a single randomized trial or nonrandomized studies.

Level C: Only consensus opinion of experts, case studies, or standard of care.

Level E: Expert consensus or clinical experience.

– by Kaku Armah

13. Conference Preview: International Congress on Pre-diabetes and the Metabolic Syndrome

April 1-4, 2009 • Nice, France • www2.kenes.com/Prediabetes/pages/home.aspx

While we often say we are excited about attending the diabetes and obesity conferences, it is particularly true for the upcoming International Congress on Pre-diabetes and the Metabolic Syndrome. This conference has probably one of the best line-up of speakers that we have seen at a conference besides the ADA Scientific Sessions and EASD. Just a sampling of the individuals who will be giving presentations at the conference include Drs. Paul Zimmet, Hertzell Gerstein, Rury Holman, Jaako Tuomilehto, George Alberti, Ralph DeFronzo, Louis Monnier, Antonio Ceriello, Steven Kahn, and others. Not only are the speakers impressive but the topics that they will be covering are of major interest of late. Over the past few years, as the public health implications of diabetes and obesity have received more attention, so have pre-diabetes and the metabolic syndrome begun to receive more attention. In face of the ever-increasing prevalence of obesity and diabetes, we think it is particularly important to focus on these two areas. By increasing the awareness of pre-diabetes and the metabolic syndrome, we hope it will encourage people to institute preventative measures, particularly lifestyle modification, and to develop therapies that could prevent progression to full blown diabetes. Below we give you a list of the talks that we feel are the cream of the crop – but we urge you to spend time with the schedule yourself so you can follow talks that might be especially important to you.

Highlights

Day 1: Wednesday, April 1

- **Hall A: (6:30 pm) Insulin action in trouble in the metabolic syndrome.** Emmanuel van Obberghen, MD (INSERM, Nice, France).

Day 2: Thursday, April 2

- **Hall A: (8:30-10:30 am) The Metabolic Syndrome: macro and micro facets.** Jesse Roth, MD, FACP (John Hopkins University, Baltimore, MD); Scott Grundy, MD, PhD (University of Texas Southwestern, Dallas, TX); Sir George Alberti (NHS, London, UK); C. Ronald Kahn, MD (Joslin Diabetes Center, Boston, MA); Andrew Hattersley, MD (Peninsula Medical School, Exeter, UK); Peter Gluckman, MD (The Liggins Institute, Auckland, New Zealand).
- **Hall D: (2:00-3:30 pm) Newly completed and ongoing diabetes prevention trials data.** Paul Zimmet, MD, PhD (International Diabetes Institute, Melbourne, Australia); Ralph DeFronzo,

MD, PhD (University of Texas, San Antonio, TX); Rury Holman, MD (University of Oxford, Oxford, UK); Hertz Gerstein, MD (McMaster University, Hamilton, Ontario); Bernard Zinman, MD (University of Toronto, Toronto, Ontario).

- **Hall A: (4:00-6:00 pm) Should we redefine measurements of blood glucose control and categories on dysglycemia?** Bernard Zinman, MD (University of Toronto, Toronto, Ontario); David Nathan, MD (Massachusetts General Hospital, Boston, MA); Louis Monnier, MD (University of Montpellier, Montpellier, France); Ed Horton, MD (Joslin Diabetes Center, Boston, MA); Stephen Colagiuri, MD (University of Sydney, Sydney, Australia); Paul Zimmet, MD, PhD (International Diabetes Institute, Melbourne, Australia).

Day 3: Friday, April 3

- **Hall B: (8:30-10:30 pm) New treatment targets.** Harold Lebovitz, MD (SUNY Brooklyn, New York City, NY); Alain Baron, MD (Amylin Pharmaceuticals, San Diego, CA); Joseph Grimsby, MD (Hoffman-La Roche, Nutley, NJ); Bo Ahrén, MD (Lund University, Malmö, Sweden); Alexei Kharitonov, PhD (Eli Lilly, Indianapolis, IN); Davie Moller, MD (Eli Lilly, Indianapolis, IN).
- **Hall B: (2:00-3:30 pm) The PPAR family: very much alive!** Markku Laakso, MD (University of Kuopio, Kuopio, Finland); Bart Staels, PhD (University of Lille, Lille, France); Marja-Riita Taskinen, MD (Biomedicum, Helsinki, Finland); Henry Ginsberg, MD (Columbia University, New York City, NY).
- **Hall C: (2:00-3:30 pm) GLP-1 in prediabetes and diabetes.** Daniel Drucker, MD (Mount Sinai Hospital, Toronto, Ontario); Michael Nauck, MD (Diabeteszentrum, Bad Lauterberg, Germany); Avraham Karasik, MD (Sackler School of Medicine, Tel-Aviv, Israel); Jens Holst, MD (University of Copenhagen, Copenhagen, Denmark).

Day 4: Saturday, April 4

- **Hall A: (11:00 am-1:00 pm) New data on glucose/body weight lowering interventions and CV outcomes.** Scott Grundy, MD, PhD (University of Texas Southwestern, Dallas, TX); Lars Ryden, MD (Karolinska University Hospital, Stockholm, Sweden); Robert Ratner, MD (MedStar Research Institute, Washington, DC); Hertz Gerstein, MD (McMaster University, Toronto, Ontario); Rury Holman, MD (University of Oxford, Oxford, UK); Luc can Gaal, MD (University of Antwerp, Antwerp, Belgium).

— by Melissa Tjota

14. Diabetes Comings and Goings

- **Fred Kurland** was appointed in early January 2009 to VP of Finance and CFO at XOMA. Prior to this appointment, he served as CFO at Bayhill Therapeutics, Corcept Therapeutics, and Genitope Corporation.
- **Pierre Legault** was named Executive VP, CFO, and Treasurer of OSI Pharmaceuticals at the end of December 2008 after serving as Senior Executive VP and CAO at Rite Aid.
- **Takashi Shoda**, President and CEO of Daiichi Sankyo, joined the Board of Directors at Ranbaxy.
- **Malvinder Mohan Singh, MD** assumed the role of Chairman of the Board of Directors at Ranbaxy in addition to serving as CEO for the company.
- **John Varian**, currently COO and CFO of Aryx Therapeutics, joined the Board of Directors at XOMA in early December 2008.

15. DCU Stock Chart and Final Thoughts

	22-Jan-09	22-Dec-08		21-Jul-08		22-Jan-08		IPO		Market Cap
AGIXQ	0.055	0.12	-54%	0.64	-91%	0.41	-87%	8	-99%	3.16M
ALKS	10.47	10.09	4%	14.91	-30%	14.03	-25%	5	109%	1.03B
AMLN	10.92	10.75	2%	26.6	-59%	32.47	-66%	14	-22%	1.52B
ARNA	3.38	4.18	-19%	6.52	-48%	8.09	-58%	18	-81%	261.38M
BIOD	3.68	3.71	-1%	15.62	-76%	18.53	-80%	15	-75%	93.66M
CJB	0.09	0.06	42%	0.07	21%	0.09	-6%	5.33	-98%	21.29M
CVTX	11.54	8.91	30%	8.93	29%	8.53	35%	8	44%	718.13M
DXCM	3.28	2.5	31%	6.95	-53%	9.05	-64%	12	-73%	95.92M
ETRM	1.69	1.22	39%	3.98	-58%	9.65	-82%	8	-79%	25.66M
GENR	0.40	0.3	32%	1.55	-75%	1.66	-76%	9	-96%	6.46M
GSK	34.56	35.97	-4%	48.39	-29%	48.84	-29%	-	-	90.85B
HALO	5.50	5.2	6%	7.92	-31%	5.94	-7%	16.03	-66%	465.04M
HDIX	5.93	5.25	13%	7.93	-25%	8.17	-27%	12	-51%	103.67M
HGSI	2.09	1.64	27%	6.3	-67%	10.02	-79%	21.5	-90%	302.2M
ISIS	13.23	13.32	-1%	16.24	-19%	15.57	-15%	10	32%	1.32B
MBRX	0.37	0.41	-10%	1.21	-69%	1.68	-78%	7	-95%	12.97M
MIIS	0.03	0.035	-14%	0.28	-89%	0.5	-94%	0.31	-90%	3.03M
MNKD	3.37	3.53	-5%	2.92	15%	7.22	-53%	14	-76%	363.12M
NVO	51.37	53.32	-4%	62.65	-18%	57.97	-11%	29.2	76%	37.9B
OREX	4.05	5.12	-21%	8.31	-51%	12.13	-67%	12	-66%	148.02M
OSIP	36.59	37.58	-3%	48.26	-24%	40.65	-10%	170	-78%	2.12B
PODD	7.78	7.51	4%	15.03	-48%	20.55	-62%	15	-48%	235.43M
SYI	0.80	1.19	-33%	1.77	-55%	2.56	-69%	26	-97%	2.07M
TTHI	4.18	4.03	4%	11.7	-64%	9.95	-58%	1.25	234%	99.83M
VVUS	4.18	5.34	-22%	7.71	-46%	6.18	-32%	14.25	-71%	307.97M
XOMA	0.66	0.66	0%	2.06	-68%	2.76	-76%	8	-92%	91.38M

It was quite a month— about 33% of companies fell last month in stock price while about 66% increased. There are some big percentage gains though most were generally from very low bases. Virtually all companies are down versus a year ago (actually, all companies are down versus a year ago except CV Therapeutics). We await a return to times when stocks trade on something resembling fundamentals.

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