DIABETESCLOSEUP

The Leading Source of Diabetes Business News

Big Announcements Begin New Year

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The New Year got off to a momentous start, with several organizations and companies announcing groundbreaking partnerships, as well as new investments in promising early-stage technologies, as well as FDA approvals. Of these, we are particularly excited by FDA's approval of Novo Nordisk's liraglutide – in addition to making a new choice available for type 2 patients not in good control (about ten million at last count), this approval also reflected the FDA's stance that more alternatives are needed. We were very glad to hear this. And then, there was lots that happened on the device front! Notably, JDRF announced new collaborations both with Animas/DexCom, to develop a first generation artificial pancreas, and with Becton Dickinson, to improve the convenience and speed of insulin delivery in pumps. Insulet is also working with JDRF on a number of initiatives that we think are very exciting. Indeed, the artificial pancreas has been hastened along by the JDRF for years through investments and partnerships in CGM, pumps, and other technologies; these investments finally seem to have brought the artificial pancreas within reach. While we eagerly await interim updates, these partnerships represent a greater industry-wide commitment toward improving the daily management of diabetes. This is a big deal from our view and the clinical and commercial implications should be significant.

Also on the technology front, we saw new investments in disposable pump technologies, reflecting a growing interest in this segment of the market. Currently, Insulet dominates the disposable pump market with its reach likely to extend into Europe and Asia following an exciting recently signed agreement with Ypsomed. While Insulet is moving forward with its smaller second-generation pump (expected in late 2010 pending regulatory), pump giant Medtronic is planning to launch its patch pump in late FY2011 (this date was moved further out recently). At the same time, an entirely new generation of disposable pumps for type 2 patients is also emerging: in this issue, we cover the CeQur insulin infuser, a new pump for use in type 2 patients, and, as we went to press, Calibra's "insulin patch-pen" for type 2 patients, known as the Finesse, received 510(k) clearance from the FDA, and this should be followed shortly by Valeritas. Overall, we are excited to see that more interest is driving faster innovation – lower costs and simplicity for the patient and healthcare professionals will be key to success in our view. From a macro perspective, there are certainly many positives, especially the fact that given poor control, many more type 2 patients should be on more aggressive therapy than they currently are, and many that are already on basal insulin should advance their insulin management so they are in meeting their goal.

As pump makers continue to innovate and look to expand the pump market, identifying which type 2 patients are most likely to adopt and benefit from pump therapy will be a key consideration. Potential type 2 pump adopters include patients on oral medications moving to insulin therapy, patients on basal therapy moving to a basal/bolus regimen, and patients already on a basal/bolus regimen or insulin mix or regular insulin regimen looking for a new delivery system. In our view, the type 2 pump market may get an indirect bump from the results of the 4-T study presented at this year's IDF World Diabetes Congress. This study demonstrated that patients can safely achieve superior glycemic control by initiating or intensifying insulin therapy after failing oral medications or basal therapy, respectively. Whether this outcome will indeed encourage more type 2 patients to switch to an insulin pump remains unclear, although the trial's findings certainly support the use of advancing insulin options when people

are not in good control – there's certainly a large group of millions of patients that fit that bill, by anyone's math. In this issue, we have included a thorough analysis of the 4-T study and its implications, as well as a glimpse of the most fascinating sessions from the World Diabetes Congress.

Of course, other innovation happening on the type 2 front on the GLP-1 front may also delay some from going on insulin – in addition to Novo Nordisk's liraglutide approval, the FDA should weigh in soon on Amylin/Lilly/Alkermes' exenatide once weekly. This is the most highly awaited news in diabetes today, in our view, and we look most forward to hearing what happens in early March, both because this could be a transformational therapy and also because it should signal more about the FDA's current views on diabetes management and alternatives for patients. The FDA delayed its decision on MannKind's Afrezza last month, and we also look forward to further word on that in the coming months.

Indeed, we expect to learn lots more about cutting-edge technologies at the annual Advanced Technologies and Treatments for Diabetes (ATTD) conference in mid-February – Jessica, John, Coco and I will be in Basel and we'd love you to let us know if you'll be there too, we'd relish the chance to say hello in person. In particular, we will stay closely tuned for any updates on insulin delivery systems, continuous glucose monitoring (both ambulatory and in-patient), closed-loop systems and algorithms, and new insulin analogs – but as the faculty and attendees are always so interesting, we'll be staying very tuned on all news on the diabetes and obesity fronts.

Closer to home, we'll be covering the ADA Postgrad next weekend here in San Francisco – we'd also love to see you here and will be gathering a group together at our home in the lower Haight Ashbury for beer either Friday or Saturday evening (5:30-7:30 pm) when the sessions end, so if you can join us, let us know! In the meantime, we hope you have a most excellent month of February …

Yours truly,

Kelly L. Close

Major Headlines

In This Issue

Videos

Below is our favorite video in diabetes this month:

- Aaron Kowalski, head of the Artificial Pancreas Project, addresses concerns surrounding JDRF's recent investments in Animas, DexCom, and Becton Dickinson. http://promise.jdrf.org/blog/jdrf-leadership/live-video-event-to-answer-your-artificial pancrea.aspx

Coming soon in DCU…

We are in the midst of covering the 4Q09 and full-year financial results for several diabetes and obesity companies. The Close Concerns team is currently attending various conferences, which we plan to review in upcoming issues, including the 39th Critical Care and Congress and Post-Congress meeting, the 1st International Congress on Abdominal Obesity, and a new conference on Diabetes and Diabetic Retinopathy. Lastly, we continue to look forward to updates from the FDA on decisions regarding Amylin/Lilly/Alkermes' exenatide once weekly (EQW) and any partnership discussions among the three companies with late-stage obesity drugs (Arena, Orexigen, and Vivus).

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1. Quotable Quotes in Diabetes

Satisfying the CV risk requirement

"It seems to me that most people are realizing that the better way to skin the cat is to do a dedicated outcomes study that doesn't have as its primary objective to show that the drug is a better glycemic control agent than the placebo or active comparator. Rather, the goal of the outcomes study would be to show, in a population of patients at high risk for events, that addition of the drug candidate to their overall regimen for achieving optimal glycemic control does not somehow increase that risk."

— David Orloff, MD (Medpace, Cincinnati, OH), on designing clinical trials for diabetes drugs to comply with the FDA's updated guidance requiring a CV risk assessment

The soup of complications

"Waist circumference is associated with a minestrone soup of metabolic abnormalities."

— Jean-Pierre Despres, PhD, FAHA (Laval University, Quebec, Canada) discussing the importance of visceral obesity at the 1st International Congress on Abdominal Obesity.

The White House tackles childhood obesity

"Obesity is also one of the biggest threats to the American economy. If we continue on our current path, in ten years, nearly 50 percent of all Americans will be obese. Not just overweight, but obese. So think about the related conditions like heart disease, cancer, and diabetes. Think about all the missed days of work and decreased productivity we may see as a result."

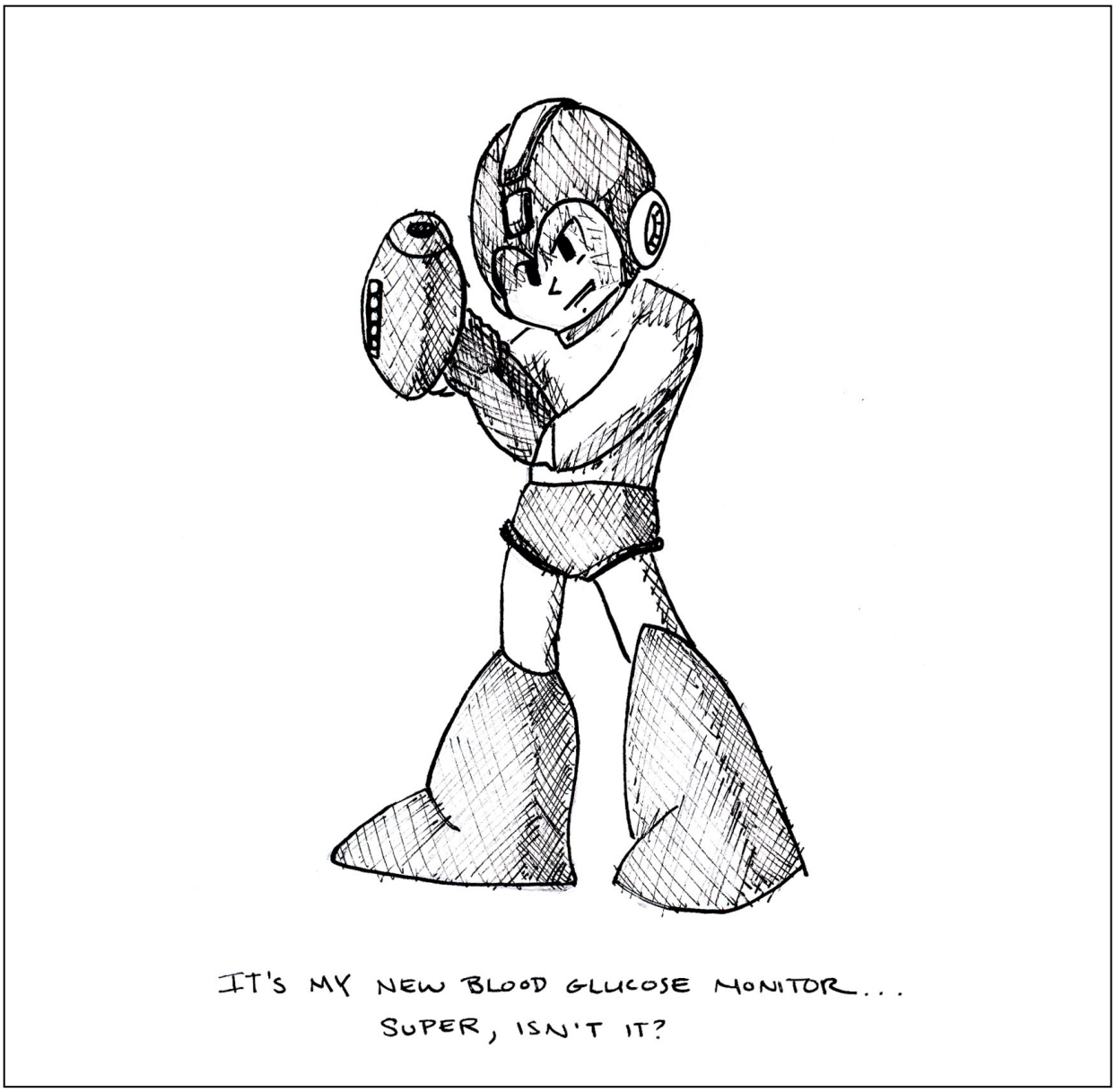
— First Lady Michelle Obama stresses the importance of addressing the burgeoning obesity epidemic in the US.

Not so nice about NICE-SUGAR

"NICE-SUGAR basically says cake doesn't taste good just because you can't cook."

— James Krinsley, MD (Stamford hospital, Stamford, CT) arguing that just because hospitals may not be effective at safely controlling glycemia in the hospital (to a target of 80-120 mg/dl), it does not imply that such control is unsafe.

2. diaTribe FingerSticks



— by Daniel A. Belkin

3. DCU Company Watch

- **Becton Dickinson – Partners with JDRF to enhance insulin delivery:** On January 19, the JDRF and Becton Dickinson announced a novel partnership to improve insulin delivery by upgrading current infusion sets/pumps and by developing microneedles to reduce pain and improve the speed at which insulin works. BD is also striving for less kinking, fewer infections and overall "greater convenience." In our experience, these kinds of problems have presented major deterrents for patients and lower overall satisfaction with pump therapy. The JDRF will contribute over $4 million through milestone payments to BD.

  In our view, BD's decision to enter this field is a major statement. As with the Animas/JDRF partnership announced days before this one (see below), BD's undisclosed investment is several times larger than JDRF's and, as we understand it, is likely on the order of $20 million. BD is the leader in traditional insulin delivery, dominating the syringe (75-80% market share) and insulin pen needle (leading share) markets. BD's decision to move into pumps signals its confidence in the size and growth potential of this market. BD also believes both traditional and patch pumps are major opportunities, as its announcement clearly stated the company will be researching and developing new products that will deliver insulin through both infusion sets and patch-pump configurations. We are excited to see what BD develops, particularly related to manufacturing and technology.

- **Medtronic – Invests $15 million in GI Dynamics:** Medtronic announced a $15 million strategic investment in GI Dynamics, makers of the EndoBarrier Gastrointestinal Liner. This investment follows the EndoBarrier receiving a CE mark in December 2009 for six months of therapy to treat obesity and type 2 diabetes (for more information, see page 13). Funds from Medtronic's investment will be used to promote the device in the EU as well as further develop the EndoBarrier. As a reminder, the EndoBarrier is a 60 cm fluoropolymer gastrointestinal liner that is endoscopically inserted into the small intestine. We expect the highly awaited results from these trials to be reported throughout 2010 and 2011. GI Dynamics also raised $15 million in Series C financing in February 2009 from several investors, including Johnson & Johnson Development Corp (the private equity arm of J&J), an entity that seems increasingly savvy about the obesity space. GI Dynamics plans to launch the device in the EU in 1H10.

- **Animas – Partners with the JDRF to bring first-generation artificial pancreas to market:** The JDRF and Johnson and Johnson's Animas have announced that they will partner to develop a commercial-grade first-generation artificial pancreas. The objectives of the partnership are to develop the automated sensor-algorithm-insulin pump system, conduct clinical safety and efficacy trials, and to submit a market-ready product to the FDA for approval. Notably, and as a reminder, the FDA has designated the artificial pancreas as one of its "critical path" initiatives, signaling the eager anticipation of this technology and, we hope, greater time and resources put on this path. In addition to the years of JDRF research that make this endeavor feasible, the JDRF is contributing $8 million in funding to the project, which is designed to culminate in the creation of a partially automated system composed of an insulin pump (to be designed by Animas) that wirelessly communicates with a CGM sensor (supplied by DexCom), and a computer system (within the pump) designed to regulate basic insulin dosing based on CGM output and control algorithms in development. We suspect Animas' investment is several times larger than JDRF's, although official terms were not disclosed.

- **MicroCHIPS – Brings in $16.5 million in venture capital to advance implantable glucose sensor:** Massachusetts-based MicroCHIPS announced $16.5 million in its third significant financing to advance the development of its implantable sensor technology. The

newest investor for the company was InterWest Partners of California (a very strong name given its previous TheraSense investment), supplemented by existing investors Novartis Venture Fund, Medtronic, Polaris Venture Partners, Saints Capital, Intersouth Partners, Care Capital, CSK Venture Capital, and Flybridge Capital Partners. This round bring MicroCHIPS's total financing to roughly $70 million. MicroCHIPS is a private company founded by Drs. John Santini, Michael Cima, and Robert Langer of Massachusetts Institute of Technology, and Terry McGuire of Polaris Venture Partners. The company is currently developing long-term implantable sensing and drug delivery technology; the implantable glucose sensor is said to last for about a year and is designed for discreet wear under the skin reporting data wirelessly to a handheld monitor. The company plans to initiate clinical trials with its implantable glucose sensor in 2010.

We believe an implantable CGM would be a very welcome addition to the currently available devices, all of which are worn on top of the skin. The major advantage of an implantable sensor would be its discreetness and presumably assured adherence (we see no reason why patients would turn off the device except if alarms were not properly set). Another advantage would be ease of use, assuming that the user interface and technology are straightforward. Several questions remain relating to reimbursement (we assume it would be an additional expense for the surgery and doctors' time), business model (COGS, etc.), duration of use (six months? one year?), type of receiver, etc. If the technology is proven, we could see this company as a valuable partner for pump companies without CGM partners.

From a competitive perspective, we believe DexCom has an implantable CGM in development. As we understand it, the development of the DexCom implantable CGM is on hold but management remains enthusiastic about the opportunity; the project, called "Sleeping Beauty," was placed on the back burner around 2006/2007, as we recall, and we assume more resources will be directed toward it over time. VeriChip is also developing an implantable glucose-sensing microchip and General Electric recently invested in similar wearable technology, though details remain scant. We would imagine that significant technical barriers exist as well as regulatory and reimbursement challenges associated with developing such a device – we assume the device is a good three to four years away from the market, but very exciting nonetheless.

- **Vivus – Announces positive topline results from phase 2 study of Qnexa in patients with obstructive sleep apnea:** Vivus announced impressive topline results from a small (n=45), single-center, randomized, double-blind, placebo-controlled study evaluating Qnexa's safety and efficacy in treating obstructive sleep apnea (OSA) in adults. Qnexa significantly reduced the number of sleep apnea events by 69% from 46 (categorized as severe OSA) to 14 (categorized as mild OSA), compared to a reduction of 39% (still quite sizable, in our view) from 44 to 27 in the placebo group. Notably, patients also experienced an average weight loss of 10.2%, or 23.8 lbs, after 28 weeks of Qnexa treatment, compared to 4.3% in the placebo arm. The extent to which weight loss was responsible for the reduction in sleep apnea events remains unclear. Although we presume further multi-center studies will be required before Vivus seeks an additional indication for OSA, these data are encouraging for the drug's overall potential as a treatment for obesity-related comorbidities, especially considering the increased incidence of OSA in obese patients, reported to be between 71% and 91% (the vast majority of cases are undiagnosed). We assume the company will be able to leverage the safety data generated from the phase 3 program that evaluated Qnexa for obesity.

  During Q&A, management noted that it has lobbied on Capitol Hill to amend a law that currently states that obesity products will not be reimbursed through Medicare or Medicaid. Although they highlighted early success and positive discussions, it remains an open question whether changes will be made in time for a Qnexa launch. Nevertheless, management believes it is "highly likely"

Qnexa will receive reimbursement for obesity within a "reasonable time after [they] launch the product." We are also interested in the company's overall plans to launch the drug in the event they do not announce a Big Pharma partnership prior to FDA approval. Nevertheless, we suspect significant weight loss, A1c reductions, and, now, apnea-hypopnea index (AHI) reductions will only add value to Qnexa as a potential partnership opportunity; regulatory and safety questions are likely paramount.

- **MannKind – FDA delays decision on Afrezza:** On January 8, MannKind announced that the FDA has delayed its decision on Afrezza (formerly known as Afresa) due to the inspection of N.V. Organon, a third-party insulin manufacturing facility and supplier to MannKind. The company has not received any notice of when the FDA will make a final decision on Afrezza. The original PDUFA date was set for January 16, 2010. MannKind CEO Alfred Mann believes the FDA has completed all other inspections of third-party suppliers and clinical trial sites, however, we don't believe the FDA has officially disclosed this information to the company. The FDA has also completed a pre-approval inspection for a manufacturing facility in Danbury, Connecticut. Lastly, after discussions with the FDA, MannKind has agreed to plan a phase 4 study evaluating Afrezza in 500 pediatric patients (≥4 years of age); we assume the company sees significant potential for Afrezza in the pediatric population. It is unclear whether the delay is more related to FDA backlog and ongoing resource issues or to questions surrounding this drug itself. As noted through 2009, we would very much like to see more resources directed towards the FDA and we would not be surprised if insufficient resources increase the frequency and duration of these delays. If Afrezza is truly found to have first-phase insulin response, we would assume this would set it quite apart from other inhaled insulins and other therapies overall; we believe more alternatives are needed for patients and healthcare providers and look forward to seeing how this is assessed on the simplicity and ease of use fronts. MannKind has some significant clinical supporters and we look forward to seeing more from the company.
- **CeQur – Raises $10 million in late 2009, completing $30 million in total Series A financing:** Swiss-based CeQur, an early stage company developing a disposable insulin pump just announced that it had raised 10.3 million CHF ($10 million) in Series A funding in late 2009. CeQur was founded in early 2008 as a spin-off company from Danfoss A/S, an industrial products company that began developing initial prototypes for CeQur's insulin delivery technology. The company's product, the CeQur Insulin Infuser, is a sleek-looking disposable pump intended for type 2 diabetes patients. The pump has an on-demand mechanical bolus feature that allows bolus delivery by pushing a button. There is a disposable component of the device, which stores insulin, as well as a reusable electronic component.

  Although we believe those on/initiating MDI are the primary initial targets, this device should encourage those failing orals to start insulin earlier. The major message of the recent 4-T trial, in our view, was not just that inadequately controlled patients on early-stage oral agents benefit from advancing to insulin therapy, but that subsequent insulin intensification to a basal/bolus regimen can further help control glucose levels safely. We believe this pump could be very helpful for patients moving from basal insulin only (sanofi-aventis's Lantus or Novo Nordisk's Levemir) to the next level of basal/bolus therapy.

  This investment brings the total Series A funding for CeQur to 31.7 million CHF ($29.6 million). CeQur noted that the financing will go towards obtaining CE Mark approval for the CeQur Insulin Infuser, launching the product in the EU, and proceeding with the regulatory process in the US. CEO Jim Peterson said that the Series A funding provides the company with the resources to achieve critical regulatory and launch projects related to the pump in 2010. While CeQur has not reported any further details on the regulatory status of its pump, Peterson's statements suggest

the company is preparing for a 2010 launch in the EU. Notably, Eric Milledge, former group operating chairman at J&J and former head of LifeScan/Animas, is chairman of CeQur; no doubt, confidence in his leadership was a major factor in the funding for this company. We continue to believe reimbursement is the biggest challenge in the market for type 2 patients on pumps, an issue driven by both cost and efficacy. Clear data showing benefits in health outcomes would be a major positive for the field, as would a low cost of goods sold (COGS). From a patient perspective, size of the device seems very significant. Additionally, simplicity of the device is extremely important, both from a patient and provider perspective; we believe sanofi-aventis's Lantus and Merck's Januvia in the insulin and oral drug segments have been so commercially successful largely because they are not only clinically useful but are also easy for providers to teach and prescribe, particularly, but not limited to, doctors on the primary care front.

- **Living Cell Technologies – Partners with J&J subsidiary Centocor to develop human cell encapsulation technology:** A subsidiary of Johnson & Johnson, Pennsylvania-based Centocor Ortho Biotech, has entered into an agreement to support Living Cell Technologies' research and development of human cell encapsulation technology. As a reminder, Living Cell Technologies is currently conducting phase 1/2 trials of its proprietary type 1 diabetes treatment called DIABECELL in Russia and New Zealand. DIABECELL consists of a seaweed-derived encapsulation technology used to protect porcine insulin producing cells, which are injected into the abdominal cavity of type 1 diabetes patients. The encapsulation technology allows the cells to be protected from the body's immune system thereby circumventing the need for immunosuppressant drugs, while allowing the cells to function much as they would inside a normal pancreas (however, they secrete porcine insulin, not human insulin). Preclinical and phase 1 results from trials involving DIABECELL suggest the technology is safe and efficacious, and the company is currently pursuing dose optimization studies.

  J&J has entered into an agreement to pursue development of the seaweed-derived encapsulation technology with human cells, instead of porcine cells, which are currently not approved for use in humans in the United States. The agreement is accompanied by an exclusive two-year option to exercise a global license for the technology for use with human cells. J&J and Living Cell Technologies are keeping silent about what type of cells will be used with the technology, although they did disclose that a specific field will be targeted. While it is too early, and dare we say too tantalizing, to speculate that the technology could be used for human islet cells, it is at least a possibility amongst other options. Centocor is currently focused on three fields: immunology, oncology, and nephrology. The cell-encapsulation technology could potentially be developed for the treatment of various diseases—Living Cell Technologies is in various stages of exploration in using human cells for treating hemophilia, Huntington's Disease, Parkinson's Disease, and stroke.

- **Insulet – Partners with Ypsomed to distribute OmniPod in ex-US markets:** Insulet signed a very exciting five-year agreement with Swiss-based Ypsomed to commercialize and sell the OmniPod insulin pump in Europe, China, and Australia. Ypsomed will be granted exclusive rights to market the OmniPod in nine countries throughout Europe as well as China and Australia. The OmniPod will be co-branded with Ypsomed's mylife Diabetes care brand and commercialized by roughly 200 Ypsomed employees. We view this as a clear positive for Insulet for a number of reasons: 1) A minimum purchase requirement of $100 million over the next five years must be met for Ypsomed to maintain exclusivity; 2) Ypsomed's deep knowledge of the field and key segments (pumpers and MDI); 3) Ypsomed's very strong reputation throughout Europe, its very well-known brand, and its clear passion for helping the field; and 4) Ypsomed's vast experience with a range of diabetes products, namely pumps and blood glucose monitors. Based on OmniPod's performance in the US, we believe there is significant opportunity for Insulet in the

EU; roughly 70% of patients on the OmniPod in the US were on MDI prior to switching to the pod and we would imagine this would be higher in the EU given lower overall pump penetration. Initially, Ypsomed will market the OmniPod in France, Germany, and the UK beginning in June 2010 and will continue to launch in Australia, Belgium, Finland, Norway, Sweden, Switzerland, and the Netherlands in the second half of 2010. A launch in the Chinese market is expected in the first half of 2011. Ypsomed will play a major role in securing reimbursement in these 11 countries, leveraging its expertise with Disetronic and Roche previously (as a result of this deal, Ypsomed will no longer market Roche pumps, which represented a declining business in 2009 in most geographies).

While we do not expect increased volumes to immediately impact COGS in 2010, if Ypsomed succeeds at gaining reimbursement and driving adoption of the OmniPod, it could contribute to lower aggregate gross margin per pod beginning in 2011. This will likely be offset by reduced SG&A spending in the EU, as those costs will be borne by Ypsomed. As a reminder, Insulet has been improving gross margins at an impressive clip, with a gross margin of 31% in 3Q09 and we believe we will see a 5-7% improvement per quarter over the next several quarters. Overall, this is an exciting deal and a major win for Insulet, in our view. Indeed, whose strips will be used in the Insulet pump handheld is a major question: presumably either Abbott's strips or Bionime's test strips, as Ypsomed has a partnership in place with Bionime for the Pura blood glucose monitoring system. As we understand it, Bionime is angling heavily for the business and Ypsomed has noted that they would like to leverage their Bionime relationship, if possible. Things get more complicated when CGM is considered; little is known about the prospects for an integrated pump/CGM outside the US and we'll be watching this space closely. Overall, we believe this deal could signal that Insulet will be an independent company for a longer period of time than might have previously been assumed. Kudos to Carsten Boess for forging this notable deal.

- **Dr. Reddy's Laboratories – Announces positive-but-vague topline results from first phase 3 study of partial PPAR gamma agonist balaglitazone:** Hyderabad, India-based Dr. Reddy's Laboratories announced positive topline results from the first phase 3 study of its selective partial PPAR gamma agonist, balaglitazone. As a reminder, Dr. Reddy's is developing balaglitazone, in collaboration with Rheoscience, a subsidiary of Nordic Biosciences, a privately owned biotech company with operations in Denmark and China. Dr. Reddy had initially licensed balaglitazone to Novo Nordisk in 1997, but development was suspended and rights to the drug were eventually returned to Dr. Reddy's in 2004. The reported study was a 26-week randomized, double blind trial (n=409) investigating the safety and efficacy of balaglitazone 10 mg and 20 mg compared to pioglitazone 45 mg (Takeda's Actos) and placebo in type 2 diabetes patients on stable insulin therapy. Patients taking balaglitazone experienced dose-dependent reductions in fasting plasma glucose (FPG) and A1c compared to placebo. Balaglitazone was slightly more effective at reducing A1c than pioglitazone, lowering FPG by a slightly greater margin, although statistical significance was not provided for any measurements. This was surprising and hard to reconcile, particularly since baseline A1c levels were not given, making interpretation of the data challenging. The announcement of this phase 3 trial described balaglitazone's safety and tolerability as better than Actos; however, the data provided make any independent assessment impossible. Complete data was not given on side effects – particularly edema, weight gain, congestive heart failure, and bone fractures.

  Therefore, we cannot yet assess whether the data is positive enough to attract a Big Pharma partner who could take on the responsibility of further phase 3 development and FDA submission. We await complete data on primary and secondary outcomes, which the company expects to present at an upcoming international scientific meeting (presumably ADA in June or EASD in September). Earlier in the year, GSK partnered with Dr. Reddy's to sell its branded drugs

in emerging markets; at that time some discussion was made of a potential launch of balaglitazone by 2011, pending positive phase 3 results and regulatory approval. We would assume this timeline would be extremely ambitious; in the US, we would assume the compound would be multiple years away from market since no more phase 3 trials are ongoing and FDA approval requires proof that balaglitazone doesn't cause cardiovascular disease. As a reminder, Actos will likely go generic in 2011, before balaglitazone approval would be expected. Overall, we believe that improving the TZD side effect profile (water retention, weight gain, potential bone loss, CHF) significantly without sacrificing the efficacy will be extremely challenging with a partial agonist like balaglitazone; data suggest this may be more likely with a "selective" PPAR-gamma modulator (SPPARM).

- **Biodel – Submits NDA for VIAject to the FDA:** In the end of December, Biodel filed an NDA for VIAject with the FDA, delivering on its promise to submit before the end of 2009. VIAject is Biodel's proprietary formulation of ultra-rapid acting insulin. The company is seeking to market the pH 7 (neutral) 100 IU/cc injectable liquid formulation in the US in the form of 10 ml vials and 3 ml insulin pen cartridges. In a statement released by the company, Biodel CEO Dr. Sol Steiner reiterated VIAject's strong safety profile, noting that this quickly-absorbed insulin has a reduced risk of hyper- and hypoglycemia and less weight gain when compared to recombinant human insulin. In a time when clinicians are paying more attention to hypoglycemia and weight gain, we are curious to see how the FDA approaches this new insulin. If the drug is approved by the FDA, we expect the next hurdle to be partner selection, as future marketing will likely require significant resources to be devoted to health care provider education on the product as well as clear differentiation from analogs. A study was published in the January 2010 issue of *Diabetes Care* suggesting that VIAject may offer more benefits above and beyond glycemic control. When compared to regular human insulin and insulin lispro (Eli Lilly's Humalog), VIAject-treated patients experienced less postprandial oxidative stress (suggesting reduced cell damage) and enhanced postprandial vascular function. We still believe a trial examining glycemic variability would be very helpful to the company, potential partners, and patients.
- **Vivus – Submits NDA for Qnexa to the FDA:** Vivus announced the filing of a New Drug Application (NDA) to the FDA for obesity drug candidate Qnexa (combination phentermine/topiramate) on December 29, 2009. This was on target with the company's guidance of end of year 2009. Vivus is second of the three companies with late-stage obesity compounds to file with the FDA recently: Orexigen plans to submit its candidate Contrave in the first half of 2010. We look forward to more phase 3 data for Qnexa in the second half of 2010, with nuances of phase 3 results to be presented at meetings throughout the year (ADA, ACC, TOS, and EASD) and published in major journals. We believe the company is on track to file within the EU in the second half in 2010. Ongoing trials with Qnexa include a one-year extension study of patients from the CONQUER trial (ClinicalTrials.gov Identifier: NCT00796367; estimated completion in November 2010).
- **Merck/Arena – Part ways on dyslipidemia drug MK-1903:** On the heels of Arena's NDA submission for lorcaserin, it was reported that Merck would be dropping its collaborative agreement with Arena for the development of MK-1903, a niacin receptor agonist for the treatment of dyslipidemia. The announcement follows negative results from a phase 2a trial investigating the safety and efficacy of MK-1903, in which treated patients did not meet the primary endpoint for efficacy. The four-week randomized controlled trial aimed to show decreases in LDL and increases in HDL relative to placebo; results suggested the drug failed to significantly increase HDL. While this drug was still in early-stage development, this is nonetheless a major setback for Arena; had the development gone in a better direction, Merck may well have been positioned as the logical partner for Arena.

As a reminder, Arena also holds APD597 in its development pipeline. APD597 targets the GDIR receptor for the treatment of type 2 diabetes, and is in phase 1 trials initiated by J&J/Ortho-McNeil-Janssen. Merck has a number of compounds in its R&D pipeline for the treatment of diabetes, including MK-0431C (combination Januvia/ pioglitazone; phase 3; expected to file by 2011), extended release Janumet (phase 3; expected to file by 2011), MK-0431D (combination Januvia/simvastatin; phase 3; submission expected in 2010), MK-0893 (compound reduces glucose production; phase 2), MK-0941 (compound increases insulin secretion, decreases glucose production; phase 2), MK-4074 (compound increases insulin sensitivity; phase 1), as well as MK-0524A, MK-0524B, and anacetrapib for the treatment of atherosclerosis (all phase 3).

- **OSI Pharmaceuticals – Cuts 2010 revenue guidance; DPP-4 royalties should see further robust growth:** OSI Pharmaceuticals provided updated revenue guidance for 2010, trimming forecasts for the overall revenue percentage growth rate to the mid-teens. This is reduced from the estimate of high-teens given at the company's December 3rd R&D Analyst Day. The reduction stems from the recent announcements of an FDA advisory panel that recommended against a label expansion for OSI's lung cancer drug Tarceva, which contributes the majority of the company's revenue. However, management reaffirmed that adjusted earnings per share would grow in 2010 at 10% or more. OSI expects 2009 revenue of $425 million.

  We suspect losses could be supplanted by DPP-4 inhibitor royalties, which continue to grow at an impressive rate – royalties were $17.3 million in 3Q09, up 35% from $12.8 million in 3Q08 and 30% from $13.3 million in 2Q09. Growth in royalties reflects growth in DPP-4 inhibitor sales, which we expect will annualize over $2.7 billion in 2009, up from $1.8 billion in 2008. To reach $2.5 billion (mid-range of the $2.4 to $2.7 billion estimate given in 2008), Merck's 4Q09 revenues for its Januvia franchise must reach $680 million (this would be a record quarter, but we believe it is achievable given the pace of growth since approval in late 2006). We believe Novartis revenue for Galvus will come close to $200 million and BMS/AZ revenue for Onglyza should pull the category over $2.7 billion in global revenues. Royalties for OSI should also rise in the next several years as additional companies enter the space; as a reminder, companies with DPP-4 inhibitors in their late-stage pipelines in addition to the three companies with approved compounds include Takeda (alogliptin; was submitted, now undergoing CVD trial), Boehringer Ingelheim (linagliptin/Ondero; completed phase 3), Pfizer (PF-00734200; completed phase 2), Amgen (AMG-222; phase 2), Glenmark Pharmaceuticals (melogliptin; phase 3), and Phenomix (phase 3).

- **GI Dynamics – Announces CE Mark approval for EndoBarrier and plans to launch in Europe in first half of 2010:** On December 22, GI Dynamics announced the EndoBarrier Gastrointestinal Liner received CE Mark approval for six months of therapy to treat obesity and type 2 diabetes. The company received CE mark for a three-month indication for Diabetes and Obesity in January 2009, and now has received approval for a six-month indication for diabetes and obesity. CEO Stuart Randle indicated at this year's Cleveland Clinic Obesity Summit that GI Dynamics plans to launch the product in Europe in the first half of 2010. Randle also noted that the EndoBarrier is already an endoscopic solution in Europe for the broad insulin-naïve type 2 population with a BMI between 30-45 kg/m^2. We suspect this device could reach a significant portion of patients eager to lose weight but unwilling or hesitant about undergoing a surgical procedure. Although we are unaware of how the EndoBarrier will be priced, we expect the endoscopic insertion and explant procedure to be considerably less expensive than surgical alternatives such as the Roux-en-Y gastric bypass or gastric banding. However, these financial and procedural incentives are balanced by EndoBarrier's moderate efficacy relative to gastric banding or gastric bypass. We remain curious whether physicians in the obesity space will readily

use this device and expect adoption to be driven by ease of administration and minimal required physician/staff training time and device-related complications.

- **CPEX Pharmaceuticals – Completes enrollment of phase 2a clinical trial of Nasulin intranasal insulin:** CPEX Pharmaceuticals announced that it has completed enrollment in phase 2a clinical trials of their intranasal insulin candidate, Nasulin. CPEX has developed a delivery platform called CPE-215 that facilitates the transport of large molecules such as insulin across skin, mucosal barriers, and even the epithelium of the eye. The technology has been used by Auxilium Pharmaceuticals to deliver its skin-absorbed testosterone gel Testim. The clinical trial of Nasulin will be a double-blind, placebo-controlled study of 94 people with type 2 diabetes. All participants are currently taking basal insulin and oral hypoglycemic medications. Results from the trial are expected in the first quarter or the beginning of the second quarter of 2010. The company has said that the drug has been taken by roughly 300 subjects and that no serious drug-related adverse events occurred.

- **Senzime – Looking to partner for final development and commercialization of in-hospital continuous monitoring sensor:** In a recent announcement, Senzime, a Swedish biosensor company, relayed its intention to seek a corporate partner to support continuing development and commercialization of the company's proprietary in-hospital continuous glucose monitoring sensor. The company claims that its biosensor technology has been efficacious in continuously monitoring blood glucose levels in four patients in the intensive care unit. The company says that the sensor has demonstrated longevity, stability, and precision for whole blood measurement of glucose in the clinical setting, although the data has not been made available. Senzime is looking for a corporate partner to support the development of the sensor and provide the marketing channel once the product is at the stage of commercialization.

  As we understand it, with Senzime's technology, enzymes that interact with the target (measured) compound are anchored to a solid substrate. Every three to five minutes, the device exposes the enzyme to the surrounding fluid, and the enzyme-catalyzed reaction generates heat proportional to the concentration of the target compound. An attached thermal sensor then measures the amount of heat flow and returns the signal to be processed by a computer. Although the sensor is disposable, the heat-sensing and digitizing device is a permanent and reusable component.

- **Phosphagenics – Transdermal insulin patch re-entering clinical trials:** Melbourne-based company Phosphagenics has announced re-commencement of clinical trials for its proprietary transdermal basal insulin patch following formulation optimization. In January 2009, the company reported positive human clinical results, which demonstrated the efficacy and safety/tolerability of the insulin patch in patients with type 1 diabetes. While specific statistics were not disclosed and the trial was not placebo-controlled, the company released a statement suggesting that the patch reduced glucose in the majority of type 1 patients in the trial. Since those trial results, the company has been at work exploring dose optimization and testing the improved patches in animal models of diabetes. The technology used in the patch is an internally generated TPM (targeted penetration matrix), for which the company holds several granted or pending patents for use in drug delivery in various diseases. TPM technology uses vitamin E phosphates to enhance transdermal absorption of large molecules such as insulin. The new patch, slated to begin human trials in the first half of 2010, is said to be more patient-friendly and to require minimal handling. Phosphagenics has been shy with details, but we look forward to learning more after these next clinical trials have completed in 2010.

  In addition to Phosphagenic, ISIS Biopolymer, Altea Therapeutics, TransPharma Medical, and Dermisonics are exploring transdermal insulin delivery; however, information has also been scarce. We believe significant wariness still exists about alternate forms of insulin delivery but we

suspect patients and healthcare providers would become much keener if FDA approved a product that ultimately gained patient visibility through strong reviews that reflected comfort, safety and ease of use.

- **Biocompatibles/AstraZeneca – Agree to initiate phase 2 clinical trials for the GLP-1 analog CM3:** Biocompatibles and AstraZeneca announced that they have agreed on terms to develop the GLP-1 analog CM3 through phase 2 trials. Phase 1 trials are expected to begin in January 2010, with phase 2 scheduled to begin later that year. CM3 is a GLP-1 analog, though we haven't heard many details about it yet. Biocompatibles has a European patent, granted in 2007, for a GLP-1 fusion protein, although we are not sure if this formula is used in CM3.

  CM3 was developed by a subsidiary of Biocompatibles called CellMed, with AstraZeneca agreeing to pay €8.8 million ($12.9 million), €4.3 million ($6.3 million) of which will be paid this January. AstraZeneca is permitted to license patents involved with this product at any time during the development phase (scheduled for completion in 2012) for a payment of €25 million ($36.8 million). A milestone payment of €37.5 million ($55.1 million) would be paid by AstraZeneca prior to marketing of the product. Crispin Simon, CEO of Biocompatibles, has said that their formulation offers "options for dosing and alternative routes of delivery" which implies a potential non-injectable form in the future. This could be in the form of drug-eluting beads; CellMed has already developed a GLP-1 eluting bead that is used to prevent cell death (apoptosis) after a severe form of stroke. This product, called "CellBead Neuro," is expected to enter clinical trials in 2010.

— by Sanjay Trehan, Eric Chang, Jessica Swienckowski, Nick Wilkie, and Kelly Close

4. Conference Pearls: International Diabetes Federation 20th World Congress

October 18 – October 22, 2009 • Montreal, Canada • http://www.worlddiabetescongress.org/

Here we present our highlights from the International Diabetes Federation's 20th World Diabetes Congress, held at the Palais des Congrès de Montréal in Montreal, Canada. Per usual, this year's meeting proved to be a worldly affair, with over 12,000 physicians, nurses, political officials, and industry professionals coming together from 150 countries around the globe. With over 300 speakers and six thematic tracks, there was a lot to be learned at IDF, both in the formal presentations and in the informal conversations taking place throughout the conference hall – truly, diabetes affects individuals regardless of class and country lines, and we appreciated hearing varying global perspectives on the growing epidemic.

PIVOTAL TRIALS RESULTS

- **Rury Holman, MB, ChB, FRCP (Diabetes Trials Unit, Oxford University, Oxford, UK) discussed the 4-T (Treating To Target in Type 2 Diabetes) study that has reached its final conclusion after three years.** Insulin naïve patients were randomized to either basal, prandial (mealtime) or biphasic (mix) insulin and after the first year, the basal group had the poorest control, but the least weight gain and hypoglycemia. A1c in all groups went from around 8.5% to around 7.5%. After the end of the first year, patients not reaching 6.5% A1c added another type of insulin, so that those originally on basal added prandial, those originally on prandial added basal and those on biphasic added a lunchtime prandial injection. At the end of the trial, 75% of all patients had added a second insulin. The groups were titrated to a target of

6.5% A1c and at the end of the third year, A1c was in the range 6.8%-7.1%. In fact, 43% of the (originally) basal group reached an A1c <6.5%, which is very impressive.

Accordingly, the first headline of the trial is that the entire group was successfully able to reach a tough target and sustain it over a three-year period. Wouldn't it be fantastic if the patients globally could achieve the same results as the 4-T trial? Actually, we think it would be truly wonderful if patients could reach normal A1cs – but this is a start. Of course it wasn't without costs (more on hypoglycemia and weight gain to follow) but still this was good progress from the end of year 1, where basically patients on what we think of as "insulin monotherapy" (either basal or bolus or mix) really didn't do particularly well (See *Diabetes Close Up* October 2007 for an overview of 4-T after the first year).

The second headline is that the patients starting originally on basal had the best glucose control, the best rate of hypoglycemia and the lowest weight gain. Therefore, the 4-T study group concluded that the best way to give insulin is basal first and then prandial. The patients from the (original) prandial group ended up on the same regimen as the basal group and had the same total daily dose. So the question is why do we see this result? The basal group had a higher mix of basal insulin, and the prandial group had a higher mix of prandial insulin (as a reminder, after the first year, patients not achieving target on basal therapy added prandial insulin and patients not achieving target on prandial therapy added basal insulin to their regimen). Therefore, it appears that tackling fasting glucose first is a better way of minimizing weight gain and hypoglycemia. We view this as a positive for sanofi-aventis as well as Novo Nordisk. Although some may see it as a negative for prandial insulin, since this doesn't suggest that patients start on mealtime insulin, we don't think that was being advocated anyway so there should not be too many changes in actual practice.

- **Thomas Danne, MD (KinderKrankenhaus Auf Der Bult, Hannover, Germany) presented results from the ONSET trial, which investigated the use of CGM on top of pump therapy for about 160 newly diagnosed type 1 children for 12 months.** The entire group showed very good glucose control (7.5% A1c), and a non-significant 0.2% lowering of A1c for the sensor group. Hypoglycemia was lower in the CGM group. The frequency of sensor use declined quite quickly over time. However, as with the JDRF trial, the people who used sensors regularly (more than 50% of the time) did better, lowering their A1c by 0.5% more than the other patients. From our view, this makes very clear the message to industry – if you can make the sensors more reliable and accurate with less hassle, more patients will use them. In turn, the improved data will increase reimbursement and there will be higher usage – we need to be into a virtuous cycle. Notably, more frequent use led to both higher c-peptide levels and lower glycemic variability – Dr. Danne speculated that perhaps these two facts are causally related. Dr. Danne also believes that starting patients from diagnosis on CGM gives them an entirely different way of thinking about glucose cause and effect, which will lead to better future outcomes - even if CGM use is reduced. Although it is still early for CGM use in pediatrics, this trial vividly shows the strong potential of the technology.
- **Matthew Riddle, MD (Oregon Health Sciences University, Portland, OR) provided an in-depth review of the relationships between the risk for mortality and CV events and A1c levels in the ACCORD study and also presented recently identified predictors of mortality.** Notably, the risk for all cause mortality and CV death was higher compared to standard therapy when A1c was >7% whereas the risk for MI was lower compared to standard therapy when below A1c is <7%. As we have heard before, this suggests that we should not turn our back on good control – especially early on – but be cautious with patients that don't respond to intensive therapy quickly. Regarding non-fatal MI, there was a steady increase in risk

(less steep than CV and all cause mortality) as A1c increased from 6% to 9%. However, interestingly, there was a flat relationship between non-fatal MI risk in the standard treatment group with increasing A1c levels. Overall, there was a significantly lower overall risk for non-fatal MI with the intensive strategy. Dr. Riddle cautioned that they were unable to identify the causes of the excess risk associated with an intensive treatment strategy. However, three baseline characteristics were significantly associated with downstream mortality: those with baseline A1c ≥8.5%, a history of neuropathy (self-reported), and a history of aspirin use. The last two are probably proxies for pre-existing micro- and macrovascular disease. So all this evidence can be taken together to suggest that higher A1c is a risk factor – not lower A1c, as some concluded. During Q&A, Dr. Riddle hypothesized that another important factor of risk could be related to behavioral problems and other lifestyle issues not assessed in this study and generally more difficult to accurately and quantitatively measure.

- **John Chalmers, MD (University of Sydney, Sydney, Australia) discussed the trends between A1c and various complications in the ADVANCE trial as well as the association between anthropometric markers and the risk for cardiovascular disease.** The risk for both microvascular and macrovascular complications increased steadily with increasing A1c (from 6% to 10%). In addition, every 1% reduction in A1c was associated with a 22% reduction in risk for a macrovascular event and a 26% reduction for a microvascular event; there were also 22% and 25% reductions in all cause mortality and CV mortality events, respectively. For microvascular complications, the risk increase with A1c is linear. For macrovascular risk, however, there is a linear trend, which was flat for A1c levels below 7%, suggesting that an A1c below 7% in this population did not confer any added benefit regarding macrovascular complications - we imagine over time that it may and we feel we can assess this only with great caution given how long it takes for macrovascular complications to develop in many patients. Switching gears to markers of cardiovascular disease risk, the investigators only found that the waist circumference (WC) and the waist to hip ratio (WHR) were significantly correlated with an increased risk for coronary events (elevated WC and WHR conferred a 13% and 17% increased risk for coronary events, respectively). Only the WHR was associated with CV death, reducing the risk for CV mortality by 19%. These data, along with results from other recent data, suggest a greater role for the waist circumference and the waist-to-hip ratio as superior markers for cardiovascular risk compared to BMI; we believe this is likely because these markers more directly reflect visceral adiposity than BMI (for example, muscle mass can contribute to a high BMI and a short muscular individual will have a high BMI). Lastly, Dr. Chalmers cited a recent meta-analysis (Diabetologia, August 2009, Turnbull) that showed a significant 9% reduction in major CV events (MACE) and a 15% reduction in myocardial infarction following intensive glucose lowering therapy, combining data from the ACCORD, ADVANCE, VADT, and UKPDS studies. From what we understand, although there have now been multiple meta-analyses examining risk, this paper users patient level data (combined, reanalyzed patient level data) whereas other analyses are averages of averages of published papers – not as sound or robust as this review, in which the study groups of ACCORD, VADT, ADVANCE, and UKPDS all worked together.

TREATMENT GUIDELINES AND CLINICAL RECOMMENDATIONS

- **David Owens, MD (University Hospital Llandough, Penarth, UK) highlighted new SMBG guidelines for type 2 patients not on insulin – very welcome, indeed.** The guidelines have some valuable elements in our view that stress team care, the absolute importance of using SMBG data to help guide therapy, and the importance of documenting glucose reading evaluation and action plan. Of late, of course, there has been controversy and concern about the value of SMBG for insulin naïve type 2 patients both from a clinical and a

healthcare cost management perspective. Recently we have seen some well-publicized negative trials, but they have all had significant design weaknesses – notably that therapy changes were most often based only on A1c. A meta-analysis of all the SMBG studies shows a decline of 0.4% in A1c with more frequent testing, but even better results can be obtained. Fortunately, the IDF has come down clearly in favor of SMBG, with the important proviso, again, that both patient and physician have to have the intention to improve therapy as a result of the information provided by testing. We were very impressed by Roche symposia at both EASD and IDF that showed new 360◦ view data that facilitating patient engagement and interaction between patient and provider to analyze, understand, and take action on SMBG data is very important. As for the guidelines themselves, we were disappointed in the degree to which they stopped short of any real suggestions on intensity and frequency of SBMG and instead suggested individualization of therapy – this in our view gives an "out" that isn't ultimately helpful. While it is very important for patients not to fall into the "one size fits all" trap, the danger of having no specific recommendations is that patients will not receive recommendations from their doctors. As such, although we know it is difficult to generalize, we would have liked to have seen more guidelines around how SMBG could and should be used day to day for patients at target and not at target. We thought it was important that the guidelines reinforced that SBMG should be used on an ongoing basis to guide therapy and should be used when therapy is changing, in particular; however, therapy changes may not arise if regular SMBG is not taking place! The guidelines can be found at http://www.idf.org/clinical-practice-guidelines.

- **Guillermo E. Umpierrez, MD, FACP, FACE (Emory University School of Medicine, Atlanta, GA) discussed his own opinions about glycemic management of diabetes in the hospital and revealed motivating factors in the ADA's revised recommendations.** He began by highlighting contradictory data regarding optimal glycemic targets while in the hospital, discussing NICE-SUGAR (NEJM 2009) and Van den Berghe et al., (NEJM 2001), among others. While Van den Berghe's work suggested that there could be benefits to keeping hospital patients within a glycemic range of 80-110 mg/dl, the NICE-SUGAR study suggested that three-month mortality increased 14% with this tight control. According to Dr. Umpierrez, the risk of hypoglycemia is key. Hypoglycemia has been clearly associated with an increased mortality (most studies say between a two to three fold increase) in various studies. Dr. Umpierrez discussed interesting data suggesting patients at the most risk are those who experience hypoglycemia and are not treated with insulin. This would mean that patients spontaneously developing hypoglycemia have a higher risk. After citing a laundry list of potential negative cardiovascular effects of hypoglycemia, Dr. Umpierrez also criticized the use of 40 mg/dl as the cutoff for hypoglycemia in the majority of studies in the subject area—a level he believes is absurdly low (he recommends 70 mg/dl). After reviewing this body of data, Dr. Umpierrez suggests that blood glucose below 110 mg/dl and above 180 mg/dl is not recommended, but a range between 140-180 mg/dl is recommended for most patients, while it may be acceptable to target 110-140 mg/dl in surgical ICU patients. Dr. Umpierrez expressed regret in the way the contradictory data has disorientated the medical community. He believes there is substantial variability across hospitals' treatments and he emphasized the necessity for organizations to think critically and develop consensus guidelines. He concluded by giving practical advice about how these standards of care could be executed, mainly focusing on the importance of turning off insulin drips when glucose nears lower levels. He also advocated the use of a basal/bolus in-hospital insulin regimen over sliding scales of regular insulin. We agree strongly with a criticism brought up in the Q&A session—a significant issue in all of these in-hospital target studies is that they assess mortality in the 30-90 days following hospitalization; however, they have no way of controlling glycemic levels after the patient has left the hospital. In future trials, it will be critical to control for this factor. We are happy to hear Dr. Umpierrez is already pursuing this research.

- **George Alberti, MA, DPhil, BM, BCh (Imperial College of London, London, UK) presented the findings of the WHO expert committee on the diagnostic criteria for diabetes.** Dr. Alberti was not able to reveal full details as the report still awaits final approval by the organization, yet he gave the audience a clear view of the thought process followed by the committee in selecting the new targets. He began by discussing the historic diagnostic criteria set by the organization and subsequent changes that have taken place since its formal designation in 1980 by the WHO and the NDDG (National Diabetes Data Group). In his review, he noted that many of the original decisions were made on the basis of compromise (a standard 75 g glucose load for glucose challenge tests), soft data (two hour cut-off), and "guesstimations" (fasting plasma glucose). Despite revisions to FPG criteria in 1997 and a decision to maintain diagnostic criteria in 2006, problems with the criteria persist. According to Dr. Alberti, the main problems include that there is no threshold for macroangiopathy taken into account, there is substantial variability in dietary variation for the oral glucose tolerance test, the two-hour gold standard had been tarnished, fasting plasma glucose misses potentially 30% of the affected population, and values are based on cross-sectional research.

  In 2008, an international expert committee was convened by the ADA to consider the use of A1c for the diagnosis of diabetes and soon after the WHO expert committee was formed to come to a resolution on the recommendations of the WHO and IDF. Dr. Alberti cited several pros and cons for the use of A1c, highlighting positive aspects such as its stability, reproducibility, and ease (no fasting required), but also noting drawbacks such as its expense and limited availability in some parts of the world and lack of solid data upon which to substantiate cutoff points. He went on, fairly, to list the pros and cons of plasma glucose. Citing findings from the massive DETECT-2 study, Dr. Alberti conceded that A1c is a theoretically good measure with both sensitivity and specificity in predicting retinopathy, but emphasized difficulty in choosing appropriate cutoff values for diagnostic use. He also noted that the prevalence of diabetes could easily double over night if particular criteria are chosen. Ultimately, Dr. Alberti concluded that we still do not know the best predictor of long-term outcomes and until we have the longitudinal data to show us which measure is better, we cannot draw any firm conclusions. In his final remarks he cautioned the audience to be cognizant of the needs and resources of all health systems worldwide.

- **Paul Zimmet, MD, PhD, FRACP, FRCP, FACE, FAFPHM, AO (Baker IDI Heart and Diabetes Institute, Victoria, Australia) presented the findings of the WHO expert committee on the classification of diabetes mellitus.** Once again, the WHO report is currently under review, and committee members are not at liberty to discuss its formal recommendations. Following the format of his colleague Dr. Alberti, Dr. Zimmet reviewed the history of diabetes classification, revealing the direction the new recommendations will likely take. Originally, the classification of diabetes fell into two categories: those with plasma insulin available (type 2) and those with no plasma insulin available (type 1). The classification was almost entirely based upon age and clinical characteristics, with gestational diabetes recognized separately, but prediabetes was thought of as only a retrospective diagnosis. In 1985, malnutrition related diabetes (MRDM) was added to the classification and the terminology "type 1" and "type 2" was dropped. Only a few years later in 1999, the terms type 1 and type 2 were reintroduced and the classification of metabolic syndrome was included for the first time. Dr. Zimmet went on to discuss the increasing complexity of diabetes—we now see slight variations of the disease that slightly overlap such as latent autoimmune diabetes in adults (LADA). We gather from Dr. Zimmet's commentary that the new guidelines will likely maintain the current classifications of type 1, type 2, and gestational diabetes, but there will probably be the addition of a genetic-defect related diabetes classification and a classification of "undefined or unclassified diabetes." Dr. Zimmet reminded the audience that the term prediabetes became popular when the then US

Secretary of Health Tommy Thompson sought to warn (and sensationalize) the American public of the impending diabetes epidemic. Dr. Zimmet ended his talk by noting the WHO will 'likely' recommend the use of the term intermittent hyperglycemia instead of prediabetes.

NOVEL THERAPIES

- **Ele Ferrannini, MD (University of Pisa School of Medicine, Pisa, Italy) gave a review of up to date data on dapagliflozin, AstraZeneca/Bristol-Myers Squibb's SGLT2 inhibitor currently in phase 3 trials.** The main cohort of this placebo controlled study included type 2 drug-naïve patients with an average A1c of 8%. There was also a non-placebo controlled exploratory high A1c cohort (average 11%). There were approximately 60-70 patients in each arm of the study. Patients were given 2.5 mg, 5 mg, or 10 mg doses of dapagliflozin. After 24 weeks of treatment, A1c decreased 0.89% in the 10 mg treatment group and 0.77% in the 5 mg treatment group, while placebo decreased only 0.23%. The exploratory high A1c cohort experienced a drop of 2.88% in A1c at the 5 mg dose and 2.66% at the 10 mg dose. Weight loss ranged from 2-3 kg in the dapagliflozin treated patients. Urinary tract infections and genital infections were higher in the dapagliflozin treated patients, with 4% in the placebo group compared to 12% in the 5 mg dose of dapagliflozin for urinary tract infections and 1% in placebo compared to 12% in 10 mg dose of dapagliflozin for genital infections). Reductions in blood pressure ranging from 2.5-7 mmHg were seen in dapagliflozin treated patients with no hint of dose response. As the increase in urinary and genital infections is the major concern with this new therapy in the HCP community, the increased incidence of this adverse event in the dapagliflozin treated patients is concerning; however, we note that this study is still small and we would like to see phase 3 results with more power before making a judgment on this topic. Dr. Ferrannini noted that this side effect could easily be managed if health care providers are educated about its increased occurrence and taught how to actively screen and treat patients experiencing this side effect.
- **David Moller, MD (Eli Lilly, Indianapolis, IN) talked about how glucagon receptor antagonists can be used in diabetes, and how they can serve as a paradigm for other drug development.** He noted that glucagon is not necessary for survival in humans or in rats; genetic mutations in both species show a minimal phenotype, with only slight hypoglycemia. Thus, it is unlikely that blocking the glucagon receptor will cause a deleterious level of hypoglycemia. He reviewed the ways in which the glucagon receptor can be antagonized: small molecule antagonism, peptide antagonism, binding with monoclonal antibodies, and antisense oligonucleotides inhibition of glucagon receptor expression. There are products of all four types in clinical trials. He noted that exenatide and sitagliptin both reduce glucagon to an extent, but that this is unlikely to completely explain their glycemic effects. There is some convincing animal data showing that glucagon receptor antagonists can almost completely normalize hyperglycemia in animal models, but so far there have been few studies in humans. He showed an unpublished study by J Moyers indicating that glucagon suppression led to both short-term and long-term reduction in hyperglycemia in an animal model. He concluded by noting that there have been no studies demonstrating the net effect of glucagon receptor antagonists, and thus the clinical viability of the class remains unproven.

IDF ATLAS RESULTS

- **The 4th edition of the IDF Diabetes Atlas was launched, offering the latest diabetes prevalence figures and projections and economic cost estimates of diabetes.** According to the Atlas, a daunting 285 million people today are estimated to have diabetes – this is up from an estimated 30 million people in 1985 (clearly a major underestimation), 150 million people estimated in 2000, and 246 million people estimated in 2006. More than half of the 285

people are estimated to be between 20 and 60 years old. It is estimated that worldwide prevalence of diabetes will reach 6.6% in the year 2010, and is projected to rise to 7.8% by 2030 – which equates to 435 million people, significantly higher than previous estimates. The top (used paradoxically in this case, of course) three countries in terms of number of people suffering from diabetes will be India, China, and the US with 51, 43, and 27 million people afflicted, respectively, by the year 2010; these numbers are expected to rise to 87, 63, and 36 million by the year 2030. The countries hardest hit by the disease are very clearly weighted in the Middle East and North Africa (MENA) with Nauru (30.9%), United Arab Emirates (18.7), Saudi Arabia (16.8%), Mauritius (16.2%), Bahrain (15.4%), and Reunion (15.3%) showing the highest prevalence in 2010 (figures listed) and into 2030. This translates into a 93.9% increase in MENA and a 98.1% increase in Africa between 2010 and 2030. In comparison, the rate will increase by 42.4% in North America between 2010 and 2030. The mean health expenditure in 2010 across the world per person with diabetes is expected to be the highest in the United States and Finland (over $6,500), with Australia and most of Western Europe and Japan with the second highest costs (between $3,000-$6,500). In terms of type 1 diabetes, the highest prevalence is expected to occur in Southeast Asia, Europe, and North America/Canada in the year 2010, with incidence most rapidly increasing in Scandinavia, the US, Canada, and Australia. These figures continue to be surprising and quite sobering.

— by Eric Chang, Jessica Swienckowski, Sanjay Trehan, and Nick Wilkie

5. Literature Review: Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes

Treating to Target in Type 2 Diabetes (4-T) Study Group. *NEJM*, Oct 2009, 361: 1736-1747.
http://content.nejm.org/cgi/content/short/361/18/1736.

In the 4-T (Treating To Target in Type 2 Diabetes) study, insulin naïve patients (n=708) on metformin and sulfonylurea were randomized to either basal, prandial (mealtime) or biphasic (mix) insulin. After the first year, the basal group had the poorest control, but the least weight gain and hypoglycemia; patients not reaching a target A1c of 6.5% then received add on insulin therapy, with the basal group adding prandial insulin, the prandial group adding basal, the biphasic group starting a lunchtime prandial injection. At the end of the trial, 75% of all patients were using combination insulin therapy. The groups used a 6.5% A1c target and at the end of the third year, A1c was in the range of 6.8%-7.1%. In addition, nearly 43% of the basal group (patients that were initially randomized to receive basal insulin) reached an A1c <6.5%, which we find very impressive.

The first headline of the trial is that the entire patient group was successfully able to reach an aggressive target and sustain it over a three-year period. The second headline is that a significantly higher number of patients starting on basal insulin therapy achieved optimal glucose control in the end, along with the lowest rates of hypoglycemia and weight gain. The 4-T study group concluded that basal insulin should be initiated first, with prandial insulin as an add-on therapy. In the end, patients from the prandial group ended up on the same regimen as the basal group and had the same total daily dose of insulin. Interestingly, after three years, the basal group had a higher ratio of basal insulin to total insulin, and the prandial group had a higher ratio of prandial insulin to total insulin; which may have contributed to greater reductions in postprandial glucose and higher rates of hypoglycemia. Overall, we view these study results as a positive event for the basal insulin manufacturers sanofi-aventis and Novo Nordisk. Although some may see it as a negative for prandial insulin, since these data do not suggest that patients initiate insulin therapy with mealtime insulin, we don't believe many physicians currently

advocate initiating insulin therapy with a prandial regimen, so actual practice is unlikely to change much. According to the CDC only 27% of patients with type 2 diabetes in the US take insulin, even though nearly half are not at their glycemic target of 7%. Although we realize a portion of these patients could use more effective oral agents to achieve an A1c <7%, we also believe a significant proportion of patients require insulin to achieve tight glycemic control.

- **Insulin-naïve type 2 diabetes patients were recruited in 58 clinical centers across the UK and Ireland.** Inclusion criteria for this study required participants to be at least 18 years of age with at least a 12-month duration of diabetes and an A1c between 7.0% and 10.0% on maximally tolerated doses of sulfonylurea and metformin for at least four months. Participants were required to have a BMI of ≤40 kg/m^2. Patients were excluded if they were on a thiazolidinedione or three oral anti-hyperglycemic agents.
- **Initially, 708 patients were randomized to receive biphasic (n=235), basal (n=234), or prandial insulin (n=239).** Although the overall number of individuals that did not complete the study was not significantly different between groups, the number of participants that withdrew from the study was significantly different between groups. Roughly 5%, 12%, and 9% of patients in the biphasic, prandial, and basal groups (p=0.04), respectively, withdrew from the study. Of the biphasic group, 86% completed the three-year study along with 79% and 81% of the prandial and basal insulin groups, respectively. We highlight that the percentage of patients moving to a second insulin was significantly greater in the basal group compared to the prandial (p=0.04) and biphasic (p <0.001) groups – this may suggest that more patients or physicians were willing to consider add-on in the basal group because of the combined lower rates of hypoglycemia and weight gain.

Group	Biphasic	Prandial	Basal
Number of patients completing	201	188	189
% patients reaching 3 years	86%	79%	81%
% eligible for second insulin	88%	82%	89%
% moving to second insulin	68%	74%	82%
Average total daily dose (units/kg/day)	0.78	0.94	1.03
Average total daily dose (units/day)	70	86	88
Ratio of prandial insulin	40%	70%	48%

- **During the first year of the study (Holman et al., *NEJM* 2007), uncontrolled patients (A1c between 7% and 10%) on maximally tolerated doses of metformin and sulfonylurea were randomly assigned to one of three groups: once or twice daily basal insulin detemir (Novo Nordisk's Levemir), twice daily biphasic insulin aspart (Novo Nordisk's NovoMix 30), or thrice daily prandial insulin aspart (NovoRapid).** Patients used Novo Nordisk's FlexPen to administer all three insulins and continued taking oral agents. During the first year of the study, if patients had an A1c >10% or two consecutive readings of ≥8% after 24 weeks, the sulfonylurea therapy was replaced with a second type of insulin therapy.
- **After one year, all patients with an A1c >6.5% also received a second type of insulin to replace sulfonylurea therapy.** For the biphasic group, midday prandial insulin was added (10% of total daily dose of biphasic insulin; minimum of four units and maximum of six units). For the prandial group, 10 units of basal insulin were added at bedtime. For the basal group,

mealtime prandial insulin was added at breakfast, lunch, and dinner (10% of total daily dose of basal insulin; minimum of four units and maximum of six units).

- **The primary outcome of the three-year study was A1c.** Secondary outcomes of the study were the percentage of patients with an A1c ≤6.5%, and the percentage of patients with an A1c ≤6.5% with no hypoglycemia of grade two or higher; in addition, weight gain, self-measured capillary glucose profiles, the percentage of patients requiring a second type of insulin, the ratio of albumin to creatinine, and quality of life served as secondary outcomes. Hypoglycemia was defined as grade one if patients had symptoms of hypoglycemia with a self-measured capillary glucose of >56 mg/dl (3.1 mmol/l), grade two if patients had symptoms with a capillary glucose of <56 mg/dl (3.1 mmol/l), and grade three if patients required third party assistance.
- **The trial advocated titration to strict targets of 72-99 mg/dl (4-5.5 mmol/l) fasting plasma glucose and 90-126 mg/dl two hours post-meal glucose.** An online trial management system suggested insulin dose adjustments using a common algorithm. Recommendations could be modified by the physician. Patients were also trained and advised to modify their doses between physician visits.
- **Over years two and three, total daily dose (TDD) increased steadily, after a big jump at the end of year one.** TDD was about 1 unit/kg and was roughly the same for the prandial and basal groups. However, the ratios of basal:prandial insulin were different – the basal group had about 48% prandial insulin, while the prandial group had about 70% prandial insulin.
- **By the end of the study, 75% of patients had added a second insulin,** which was not the maximum number of patients eligible, but nearly so. (Note that in year one, it was also possible to add another insulin, if A1c was high, but only a small portion did). At the end of the study, dropout rate was only 18.5%. **No significant difference in median A1c between the three groups was noted after three years, but a significantly higher proportion of patients were able to reach target on prandial and basal insulin therapies compared to biphasic insulin.** The average A1c at baseline was roughly 8.5% and after the first three **months, it was reduced to approximately 7.5%. This decline in A1c was maintained throughout the first year of the study. The basal group had the smallest reduction in A1c (0.8%) at this point. At the end of three years, the biphasic group** had an A1c of 7.1%, the prandial group 6.8% and the basal group 6.9%. We were not surprised that so many patients achieved target levels of A1c; however, we are curious how many patients, in reality, would move to prandial insulin and stay on the therapy.

The following table describes several outcomes of the study:

Group	**Biphasic**	**Prandial**	**Basal**
A1c after three years	7.1%	6.8%	6.9%
% reaching <6.5% A1c (IDF)	32%	45%	43%
% reaching <7% A1c (ADA)	49%	67%	63%
Weight gain (kg)	5.7 (12.6 lbs)	6.4 (14.1 lbs)	3.6 (7.9 lbs)
Increase in waist circumference (cm)	6.**0**	6.6	4.2
# of severe hypo events per patient year	3.0	5.7	1.7
Quality of Life Score	0.76	0.77	0.8
Any serious adverse event	44%	33%	33%
All-cause death	7	9	4
Cardiovascular deaths	4	9	1

- **Weight continued to increase slowly but consistently in years two and three.** The basal group experienced significantly less weight gain than the biphasic and prandial groups. Waist circumference data mirrored the weight gain results. From our view, the weight gain is the most negative aspect of the three-year data. The prandial group gained 14 pounds after three years, while the biphasic group gained 13 pounds, and the basal group 8 pounds.
- **Although the proportion of patients with hypoglycemia in all three groups gradually converged by year three, the basal group clearly had the lowest rates overall.** Patients receiving only basal insulin experienced significantly less grade 1 and grade 2 hypoglycemic events per patient year compared to biphasic and prandial groups. The biphasic group had a significantly lower rate of grade 1 and 2 hypoglycemic events per patient year compared to the prandial group. For patients with an A1c ≤6.5%, those on prandial insulin had significant more grade 1 and 2 hypoglycemic events per patient year compared to those on basal or biphasic insulin; however, no significant difference was noted between the basal or biphasic groups.

  The following table summarizes the incidence of hypoglycemia throughout the trial:

Incidence of hypoglycemia	**Biphasic**	**Prandial**	**Basal**
Grade 1, 2 or 3 (%)	116 (49.4%)	122 (51.0%)	103 (44.0%)
Grade 2 or 3 (%)	86 (36.6%)	105 (43.9%)	79 (33.8%)
Grade 3 only (%)	6 (2.6%)	5 (2.1%)	2 (0.9%)
Hypoglycemic events/patient/year (All patients)			
Grade 1 (median)	3.8	5.7	2.7
Grade 2 (median)	3.0	5.5	1.7
Grade 3 (median)	0	0	0
Grade 2 or 3 (median)	3.0	5.7	1.7
Hypoglycemic events/patient/year (Patients with A1c ≤6.5%)			
Grade 1 (median)	3.0	5.7	3.0
Grade 2 (median)	2.7	5.3	2.0
Grade 3 (median)	0	0	0
Grade 2 or 3 (median)	3.0	5.5	2.0

- **In conclusion, the basal group appeared to have the best mix of results, with minimal weight gain, hypoglycemia and adverse events**. All achieved healthy proportions of patients at target, with prandial and basal having better control compared to biphasic insulin. Patients starting with basal insulin had less hypoglycemia and less weight gain. These findings provide evidence to support starting insulin therapy in type 2 diabetes with a once daily basal insulin. We see this as a major positive for sanofi-aventis, which manufacturers the best-selling basal insulin, as well as for Novo Nordisk, whose basal insulin sales are about 20% of sanofi-aventis'.

— by Sanjay Trehan and Michael Dougan

6. Conference Preview: 3rd International Conference on Advanced Technologies and Treatments for Diabetes (ATTD)

February 10-13 & 10-13, 2010 • Basel, Switzerland • http://www2.kenes.com/attd/pages/home.aspx

In February, the third international conference on Advanced Technologies and Treatments for Diabetes will be held in Basel, Switzerland. Last year, over 770 doctors and educators from 69 countries attended and we hope the meeting in Basel will draw a crowd of the same proportions or even larger. The meeting promises to hold updates on the latest cutting-edge technologies for treating and preventing diabetes and its complications. Several key technologies including continuous glucose monitoring, insulin pumps and alternative delivery systems, closed-loop systems and algorithms, new insulin analogs, and the artificial pancreas, will be discussed. We are especially looking forward to hearing more about the future direction of continuous glucose monitoring (both ambulatory and in-patient), which is likely to garner deep interest considering the overwhelming concern over hypoglycemia spurred on by the results of several landmark trials in the past year.

Highlights

Wednesday (February 10)

- **Benefits of Continuous Peritoneal Insulin Infusion Delivery as Part of an Open and Closed Loop System.** This Roche-sponsored session will feature several esteemed speakers including Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA) and Andreas Lieblv, MD (Bad Heilbrunn, Germany). New improvements in the DiaPort system (an insulin delivery system) will be the focus of the session.

Thursday (February 11)

- **Fighting Glucose Control in Patients with Type 2 Diabetes.** This session will be chaired by Lois Jovanovic, MD (Sansum Diabetes Research Institute, Santa Barbara, CA) and Irl Hirsch, MD (University of Washington, Seattle, WA) and will feature talks on a variety of topics including hypoglycemia in type 2 patients, SGLT2 therapy, new long-acting insulin analogs, Novo Nordisk's once-daily GLP-1 liraglutide, and multi-hormonal treatment of obesity. We look forward to hearing from speakers Bruce Bode, MD, FACE (Piedmont Hospital, Atlanta, GA) and Jay Skyler, MD (Diabetes Research Institute, Miami, FL) among many others.
- **Individualized Decision Support for Improvement of Diabetes Outcome.** The discussions, led by chairperson Satish Garg, MD (University of Colorado Denver, Denver, CO), will be sponsored by Roche Diabetes Care and will cover topics ranging from the current state of decision support for personalized diabetes management to managing post-prandial glucose using a novel-meter based bolus advisor.
- **Hyperglycemia in the Hospital.** In this highly anticipated session, Greet Van den Berghe, MD (University of Leuven, Leuven, Belgium) will discuss the "state of the art" of blood glucose control in the intensive care unit. Mikhail Kosiborod, MD (Mid America Heart Institute of Saint Luke's Hospital, Kansas City, MO) will discuss glucose intervention specifically in the coronary care unit. The final presenter, J. Hans DeVries, MD (Academic Medical Center, Amsterdam, The Netherlands), will explore the topic of hypoglycemia and glycemic variability in the intensive care unit.
- **The A session of oral presentations will feature nine ten-minute presentations on various topics** including discussions on closed-loop insulin delivery by Roman Havorka, PhD

(University of Cambridge, Cambridge, UK) and noninvasive CGM using dielectric spectroscopy by Joerg Schreiber, PhD (Physical Logic, Zug, Switzerland), among several others.

- **The B session of oral presentations will be chaired by Fran Kaufman, MD (Keck School of Medicine, Los Angeles, CA, and Medtronic, Inc.) and Yariv Yogev, MD (Tel Aviv University, Tel Aviv, Israel) and will feature sixteen ten-minute presentations.** Continuous subcutaneous insulin infusion will be discussed in several of the talks, but far-reaching subject matters, such as encapsulation technology for beta cell therapy, and telemedicine, will also be covered.
- **Continuous Glucose Sensing: Beyond Expectations.** This DexCom-sponsored session will feature speakers Jay Skyler, MD (Diabetes Research Institute, Miami, FL), Satish Garg, MD (University of Colorado Denver, Denver, CO), Thomas Danne, MD (Children's Hospital at Hanover Medical School, Hanover, Germany), and others. The session will focus on the DexCom Seven-Plus and issues related to improving patient care with CGM.

Friday (February 12)

- **Closing the Loop.** This session will be chaired by John Pickup, MD, PhD (King's College London School of Medicine, London, UK) and Tadej Battelino, MD, PhD (University Children's Hospital, Ljubljana, Slovenia) and will include topics such as algorithms, pilot studies, and FDA perspectives on the artificial pancreas.
- **New Applications and Advances in Technology for Diabetes.** In this Medtronic-sponsored session, Paolo Pozzilli, MD (The London School of Medicine and Dentistry, London, UK) will present with other speakers on topics including using technology in underserved populations, professional CGM, and the role of data management.
- **Prandial Insulin Therapy: Options for Optimization.** This session will be held in the afternoon. Sol Steiner, PhD (Biodel, Danbury, CT) will join several other speakers in presenting on new prandial insulins in development and techniques for improving insulin absorption.
- **Non-Invasive Glucose Monitoring: Is There Anything New?** Several corporate sponsors (AiMedics, Integrity Applications, RSP Systems, Sensile Medical, & Solanis Monitoring) will sponsor this interesting session, which will include discussions surrounding using autonomic nervous system responses to detect hypoglycemia, combining technologies and using multiple sensors among several other topics.
- **Modern BGM Technology: Simplifying Diabetes Self-Management.** In this Bayer-sponsored session, Anne Felton, RN (Federation of European Nurses in Diabetes, London, UK) Irl Hirsch, MD (University of Washington, Seattle, WA), and Antonio Ceriello, MD (Warwick Medical School, Warwick, UK), will each present on different aspects of SMBG and will participate in a joint case discussion of pattern management using technology.

Saturday (February 13)

- **This morning session will be dedicated to the ATTD 2009 Yearbook, featuring a star-studded roster of speakers who will review technology in the year 2009.** Speakers will include Bruce Bode, MD, FACE (Piedmont Hospital, Atlanta, GA), Satish Garg, MD (University of Colorado Denver, Denver, CO), and Thomas Danne, MD (Children's Hospital at Hanover Medical School, Hanover, Germany), among several others. Technological areas to be reviewed will include CGM, pumps, closing the loop, new insulins and other topics.

- **Glucose Management in the Hospital**. This session, which will feature Irl Hirsch, MD (University of Washington, Seattle, WA) and others, will delve into the best use of technology, and the best methodologies for glucose management in the hospital among other topics.
- **Stem cell therapy and immune interventions in type 1 diabetes.** Peter Jones, BSc, PhD (King's College of London, London, UK) and Jay Skyler, MD (Diabetes Research Institute, Miami, FL) will present.

— by Jessica Swienckowski

7. Conference Preview: American Diabetes Association 57th Annual Advanced Postgraduate Course

February 5-7, 2010 • San Francisco, CA •
http://professional.diabetes.org/Congress_Display.aspx?TYP=9&CID=68277

Each year, we look forward to the ADA's Postgraduate Course, a long-standing annual educational session for healthcare professionals involved in every aspect of diabetes care. Centered on translating the latest in diabetes research into clinical practice, the meeting often serves as more of a broad "big-picture clinical view" than the organization's headlining Scientific Sessions – topics this year certainly offer insight into the big picture themes of 2009, spanning from the results of large-scale cardiovascular outcomes trials, to in-hospital glycemic control, incretin-based therapies, the role of A1c testing in diabetes diagnosis, and the impact of healthcare reform in diabetes care. Held this year in San Francisco (the venue switches each year between New York and San Francisco), we expect the same intimacy as we have seen in previous meetings, with numerous "meet-the-expert" sessions and presentations led by leading faculty in the field – our anticipated highlights are presented below. Close Concerns is currently in the midst of planning a casual gathering so please let us know if you will be in our fair city by the bay and we'll send details your way!

Highlights

Friday (February 5)

- **Glucose Lowering and CVD Outcomes in the Trials.** This presentation will overview the results from recent large-scale cardiovascular outcomes trials – we suspect ACCORD and VADT, which headlined ADA's 2009 Scientific Sessions, will be discussed in detail. Given the convoluted nature of those trials, we will be interested to see how presenters Drs. Peter Reaven and Carl Hayden (VA Medical Center, Phoenix, AZ) translate results into practical advice for clinicians, especially now that we have a better understanding of the controversial 2008 headlines.
- **Treatment of other CVD Risk Factors and CVD Outcomes in the Trials.** Often a less discussed aspect of these trials, we will be interested to hear conclusions on the treatment of non-glucose factors in diabetes care. In general, we have noted trends away from the "glucocentric" treatment of diabetes and will be curious to see how this is reinforced to clinicians – led by highly regarded ADA Chief Scientific and Medical Officer Dr. David Kendall, this is sure to be an engaging session.
- **Hypoglycemia and other Adverse Consequences of Glucose-Lowering Therapies in the Trials.** Now that new ACCORD analyses dispute the notion that hypoglycemia was responsible for the excess mortality observed in the intensive treatment arm of the trial, we will be paying close attention to how hypoglycemia is framed in this session. Of course, hypoglycemia still remains a great concern for clinicians, so we will be looking out for calls for more

individualized treatment and more use of treatments with low risk of hypoglycemia, as we have heard in greater volume this year. Dr. Stephen Davis of Vanderbilt is an excellent speaker and we look forward to this talk very much.

- **What are the Implications of These Trials for Practice?** Finding the practical takeaways from these trials is sure to be a challenge – likely why ADA President Dr. Richard Bergenstal was tapped to lead this session. ACCORD and VADT analyses in 2009 suggested that some patients could safely achieve A1c levels below 7% using intensive therapy, so we expect a more optimistic – and nuanced – view – and we, as always, expect to learn a great deal from Dr. Bergenstal.

Saturday (February 6)

- **Glycemic Control in the Hospital.** In-hospital glycemic control strategy continues to be a highly debated issue, particularly in the light of the NICE-SUGAR study, whose design has now been widely criticized. We will be very interested to hear presenter Dr. Mary Korytkowski's (University of Pittsburgh, PA) conclusions on NICE-SUGAR; we also look forward to a detailed explanation/justification of the new ADA guidelines, which put forward less stringent targets than prior recommendations. (See this month's Quotable Quote by Dr. Jamie Krinsley on page 5.)
- **Bariatric Surgery for Diabetes: New Lessons.** Clearly, 2009 was a big year for bariatric surgery, with many proponents framing the treatment as "the cure for diabetes." We look forward to summaries of new data and updates on the latest developments and technologies in bariatric surgery – as well as potential discussion on which patients are suitable for the procedure – led by Dr. Lee Kaplan (Massachusetts General Hospital, Boston, MA).
- **What's New in Incretin-Based Therapy?** The incretins and specifically long-acting GLP-1 analogs have been front and center in many of the major meetings in the past year. Data continues to collect in support of the secondary benefits of the GLP-1 analogs (most recently the potential cardiovascular benefits seem to be drawing the most attention), so there will certainly be a lot for presenter Dr. John Buse (University of North Carolina School of Medicine, Chapel Hill, NC) to cover – with Novo Nordisk's liraglutide just approved and Amylin/Eli Lilly's exenatide once weekly FDA decision just around the corner, we most look forward to hearing his opinion on the next generation of GLP-1 agonists as he has studied them at great length.

Sunday (February 7)

- **Health Care Reform and Diabetes Practice.** While it is unlikely that there will be any solid developments in healthcare reform by the time of this talk, the role of diabetes and obesity in the nation's healthcare policy is certain to garner attention in 2010 and we're very excited to hear this presentation. With the most recent estimates estimating 44 million people with diabetes and $336 billion in diabetes-related healthcare costs by 2034 (read that again, slowly – unbelievable), we suspect some discussion on cost-effectiveness and preventative care in this session, led by the very highly regarded Dr. Robert Ratner (MedStar Research Institute, Bethesda, MD) whom we have missed while he's been on sabbatical – it will be good to hear his refreshed take.
- **Role of A1C Testing to Diagnose Diabetes.** Just on the heels of the ADA's revised clinical practice recommendations, we look forward to a more detailed explanation of the adoption of A1c as a diagnostic measure. While clearly not perfect, we have heard great support from physicians for the implementation, due to the convenience and reliability of the A1c test – we are still interested to see how this development could impact diabetes care, as it will likely increase the chances of early diagnosis.
- **Sleep Apnea and Diabetes.** This area is getting more and more attention and we look forward to hearing Dr. Esra Tasali's (U Chicago) take. From what we have recently heard, research now

shows that apneas worsen type 2 by increasing insulin resistance – certainly if evidence showed that diabetes progressed faster with sleep apnea, we would think we would see a bigger focus on detecting and reducing sleep apnea. We look forward to doing and following more research in this area.

— by Eric Chang and Kelly Close

8. Diabetes Comings and Goings

- **Joe Jimenez** will assume the CEO position at Novartis on February 1, 2010. After 14 years leading the company, former CEO Daniel Vasella has decided to pass on the torch to Mr. Jimenez; however, Mr. Vasella will remain the chairman of the board of directors for Novartis. Jimenez joined Novartis in 2007 as the head of its pharmaceuticals unit.
- **Michael Tillman**, president and CEO of Roche Diagnostics, will step down on Monday, February 1, 2010. At the time DCU #98 went to press, the company had not announced the successor.
- **John Mullen** has been appointed Vice President and General Manager of NxStage, a new position that will involve managing international business development and growth initiatives. Mullen has significant experience in the medical device industry and was previously Global VP, Sales & Marketing for Cayenne Medical.
- **Linda Higgins** was appointed Chief Operating Officer at InteKrin Therapeutics in September. Dr. Higgins joined InteKrin in 2007 and served as the Chief Scientific Officer since late 2007.

9. DCU Stock Chart and Final Thoughts

	31-Jan-10	31-Dec-09		31-Jul-09		31-Jan-09		IPO		Market Cap
ALKS (Alkermes)	10.94	9.41	16%	10.32	6%	11.76	-7%	5	119%	1B
AMLN (Amylin)	17.98	14.19	27%	14.71	22%	11.80	52%	14	28%	2.5B
ARNA (Arena)	3.12	3.55	-12%	5.10	-39%	4.29	-27%	18	-83%	289.3M
BIOD (Biodel)	4.01	4.34	-8%	4.93	-19%	4.70	-15%	15	-73%	95.8M
DXCM (DexCom)	9.06	8.07	12%	6.46	40%	3.36	-	5.33	70%	448.7M
ETRM (EnteroMedics)	0.59	3.90	-85%	3.31	-82%	1.15	-49%	12	-95%	21.9M
GSK (GlaxoSmithKline)	39.01	42.25	-8%	38.29	2%	35.11	11%	8	388%	101.2B
HALO (Halozyme)	5.42	5.87	-8%	7.06	-23%	6.08	-11%	-	-	496.7M
HDIX (Home Diagnostics)	6.12	6.10	0%	6.79	-10%	6.46	-5%	6.27	-2%	103.6M
HGSI (Human Genome Sciences)	26.47	30.58	-13%	14.30	85%	2.38	1012%	7.68	245%	4.4B
ISIS (ISIS Pharmaceuticals)	11.16	11.11	0%	18.28	-39%	14.22	-22%	21.5	-48%	1.1B
MBRX (Metabasis)	0.31	0.39	-19%	0.48	-35%	0.47	-34%	10	-97%	10.9M
MNKD (Mannkind)	10.12	8.76	16%	8.03	26%	3.69	174%	2.31	338%	1.1B
NVO (Novo Nordisk)	67.43	63.85	6%	58.39	15%	53.77	25%	14	382%	47B
OREX (Orexigen)	6.36	7.44	-15%	8.18	-22%	4.32	47%	29.2	-78%	299.2M
OSIP (OSI Pharmaceuticals)	34.22	31.06	10%	33.79	1%	36.39	-6%	12	185%	2B
PODD (Insulet)	13.63	14.28	-5%	6.70	103%	7.93	72%	170	-92%	419.7M
TTHI (Transition Therapeutics)	2.75	3.60	-24%	4.79	-43%	4.63	-41%	15	-82%	63.8M
VVUS (Vivus)	8.45	9.20	-8%	7.41	14%	4.68	81%	1.25	576%	680.6M
XOMA (XOMA Limited)	0.62	0.70	-12%	0.90	-32%	0.70	-12%	14.25	-96%	122.5M
S&P 500	1073.87	1115.10	-4%	987.48	9%	825.44	30%	-	-	-
NASDAQ	2147.35	2269.15	-5%	1978.50	9%	1494.43	44%	-	-	-

Index Value = 152.1

Overall, there was considerable volatility in diabetes and obesity stocks this month, as the S&P 500 and NASDAQ trended downward. The diabetes/obesity index was up slightly from 147.7 at the end of December 2009. On the upside, Amylin and Alkermes both had very positive stock movements this month (up 27% and 16%), likely connected at least in part to coming closer to the PDUFA date for EQW (exenatide once weekly) – Alkermes also had positive news elsewhere in its portfolio. As expected, EnteroMedics continued to fall (from a low base) due to disappointing results from the EMPOWER trial. MannKind stock jumped 16% this month; the majority of this increase can be attributed to speculation in the days prior to the PDUFA date of January 16, 2010 - the decision has since been delayed. Obesity companies trended downward, particularly those with late-stage obesity candidates (Arena down 12%, Orexigen down 15%, Vivus down 8%); we suspect that the recent results of the SCOUT trial, which prompted the EU to pull sibutramine off the market, led to much of the decline. DexCom had a particularly impressive run in the first half of the month (~20% gain) reflecting its strong 4Q09 results announced at JP Morgan; its announcement to sell $3.5 million of shares eroded the gains a bit though the stock still ended the month with a notable gain of 12%. As usual, we look forward to trial results, partnerships, and regulatory decisions to drive the index in the coming months.