

DIABETESCLOSEUP

A little Irish luck...

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From the Editor

Happy St. Patrick's Day, a day late! This has always been one of my favorite holidays, which isn't too surprising for someone born "Kelly Shaughnessy." I've lost my Irish surname but not my love for St. Patrick's Day – so belatedly, Irish luck goes out from me to you.

Things keep moving in the diabetes world – we'll be covering three conferences in the last two weeks of March alone. First, Cowen and Company's annual conference began yesterday. There will be two stellar panels on diabetes alone (and another on bariatric surgery) on Wednesday, with Dr. Howard Wolpert and JDRF's Aaron Kowalski on the device side and Dr. Caroline Apovian (an obesity expert) and Dr. David Nathan talking about drugs. We're especially eager to hear Dr. Nathan's thoughts on ACCORD. We'll be gathering updates at Cowen this week from 25 (!) of the companies we monitor for diabetes, including Abbott, Alkermes, Arena, BD, BMS, DexCom, EnteroMedics, GSK, Isis, J&J, Lilly, MannKind, Merck, Metabasis, Nektar, Novartis, Orexigen, Pfizer, Sanofi, Sirtris, Tethys Bioscience, Transition Therapeutics, Vitae, and Vivus. Whew! Part of our team is also now in Raleigh, North Carolina, at the IBC conference on targeting metabolic disease, which began yesterday as well. This meeting has some excellent speakers, including Dr. Clifford Rosen, who is on the FDA advisory panel for diabetes – very interesting!

Then, in a couple of weeks we'll be off to the American College of Cardiology meeting in Chicago, where many are awaiting Merck's taranabant data – see our preview inside on the abstract – Leerink Swann already broke the embargo, so this is just our commentary on that. This hasn't been a drug class that has overly excited us, and these data don't change that even though we're very excited to see Merck expanding in diabetes. Speaking of Merck, we were privileged to speak this month to Dr. Sethu Reddy of Merck, a powerhouse scientific director in charge of diabetes and obesity. He used to run endocrinology, metabolism, and nutrition at the Cleveland Clinic, and we hope you find our interview of interest, particularly regarding the DPP-4 inhibitor class.

As many of you know, I cannot wait to get to June! We are busy planning for ADA here – two exciting updates:

- *Close Concerns will be hosting on Sunday, June 7, the Second Annual Close Concerns TCOYD Forum, where I'll be moderating a panel of true all-stars, including Drs. Steve Edelman, Wendell Cheatham, James Gavin, Bob Henry, Anne Peters, and Eugene Wright. DCU and Closer Look subscribers receive a 20% discount until April 30; sign up at www.supportTCOYD.org - subscribers can use the promotion code CC. All proceeds go to TCOYD, the incredible non-profit diabetes education organization run by Dr. Edelman.*
- *Close Concerns had a poster accepted at the ADA and, in addition to covering mountains of research at the meeting, we look forward to discussing some of our original research on the trajectory of diabetes care in the US.*

'Til then, our best wishes to you for an excellent start to spring and please send us the same. We'd love it if you could send us special luck this month – many of you know that John and I have a little baby boy

who is coming our way soon, a bit on the early side, so we would love your special thoughts sent his way and my way so that everything stays safe and good!

Yours Truly,



Kelly L. Close

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- Novocell reports exciting type 1 stem cell research in mice – page 16**
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Blogwatch

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

- **March 14:** Cool DexCom news (we love the new manual calibration); TolerX + exenatide!?!)
- **March 13:** Glycemic variability - staying in "the zone" + Yay for NAVIGATOR

Besides writing our own blog, we also write a blog for Revolution Health called “Up Close and Personal” on life with diabetes. You can find it at www.revolutionhealth.com/blogs/kellyclose

- **February 21:** Is the US experiencing a recession..... of A1cs?
- **February 11:** More on ACCORD - and Drs. Val and B.

Coming soon in DCU...

We’re going to be interviewing Dr. Judith Fradkin of the NIDDK – send us your questions! Also look out for our previews of AACE and our reviews of this month’s meetings: Cowen & Company, IBC’s Targeting Metabolic Disorders, and the American College of Cardiology.

1. Quotable Quotes in Diabetes

“Over the past several months, we have conducted a thorough review of all aspects of our efforts to develop our AIR Insulin product and have now made the decision that it would be inappropriate for the company to continue development activities in connection with this project...”

—John Lechleiter, Ph.D., Lilly president and chief operating officer, discussing the company’s decision to discontinue the development of AIR Insulin on March 7, 2008.

“Pfizer’s experience [with Exubera] does change things for us. I think the fact that Pfizer got Exubera approved shows it can be done. We’ve learned from Pfizer and made several improvements... We continue to believe AIR Insulin will be a very successful product.”

—Dr. Lechleiter, on AIR Insulin’s prospects at the JP Morgan Healthcare Conference on January 8, 2008.

"We were as surprised as you were to get the announcement (that Pfizer was dropping inhaled insulin). I think this does not diminish the enthusiasm for the product. We need a more convenient mealtime administration for the product. The approach we have is more convenient, easier to use. We're not backing away an inch from our program in mid phase 3 or our plans to file in 2009. We'll have to see how it shakes out. This is not a signal that this is not an opportunity for the right company. We will have health economic data at launch, a more convenient device and better dosing. We have leveraged some of the learnings from Pfizer's difficulties."

—Dr. Lechleiter, on AIR Insulin’s prospects during Lilly’s 3Q07 earning call on October 18, 2007.

“It is my plea that the companies work together to come out with consolidated devices, so that patients do not have to travel around with hardware all over their real estate.”

—Dr. Satish Garg, speaking about the development of combined sensor-pump systems at ATTD in Prague, Czech Republic.

“If you can make a meter that is super reliable on the low end – not the high end, but the low end - you’ve got a winner. That’s what patients really want to see.”

—Dr. Garg, speaking about the high accuracy of the Abbott Navigator at ATTD.

"What then of the original question, ‘Can gut hormones reduce appetite and prevent obesity?’ The answer at present seems to be a cautiously optimistic ‘yes.’”

—Dr. Owais Chaudhri and colleagues, discussing the treatment of obesity with gut hormones in an article in Diabetes Care (February). The article is titled, “Can Gut Hormones Control Appetite and Prevent Obesity?”

"He took his first shot last night before supper, had very bad nausea/heartburn, which however passed in a couple of hours. I administered that shot. This morning he administered his own. Given his history of needle-shyness and dropping drugs after bad effects, he's demonstrated an almost unprecedented commitment to the therapy. Henceforth he shall be called Lizard Lips..."

—Spouse of a person with type 2 diabetes (both anonymous), discussing his experience using Byetta in an online forum.

“We’ve looked at correlations between golf performance and blood glucose. Those with good control during golf perform better. Golf is a precision sport.”

— Dr. Peter Adolfsson discussing pump use during exercise at ATTD in Prague, Czech Republic.

“The problem with treating type 1 teens is that they really have two diseases. Fortunately, only one is chronic.”

—Mr. Joe Solowiejczyk (Animas) speaking at ATTD in a session about family dynamics and management of children with diabetes.

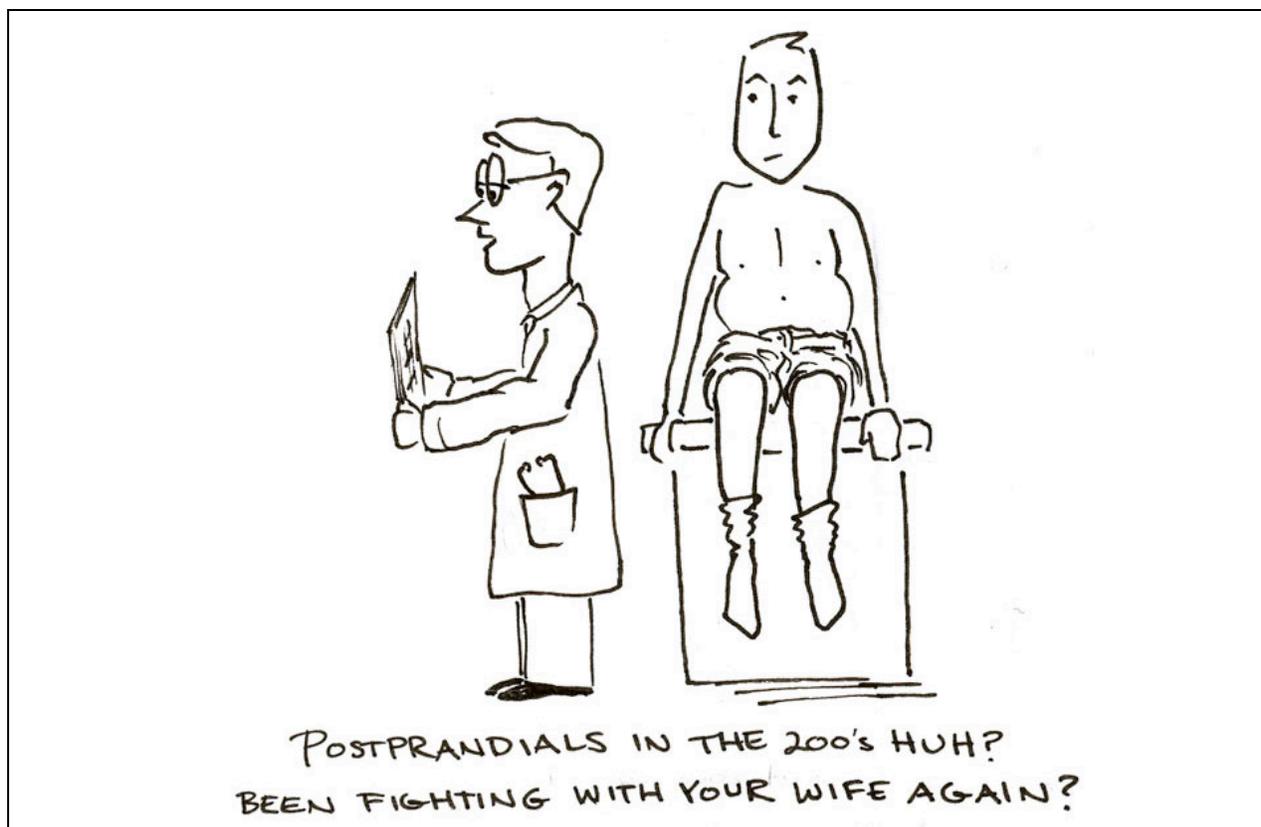
“A lot of health policy seems to remind me of religious fundamentalism. You have healthcare fundamentalists on the left and healthcare fundamentalists on the right, who agree on nothing except that they all hate the Massachusetts experiment.”

—Dr. John McDonough, speaking at the Avalere Diabetes Forum in Washington, D.C., about the Massachusetts Healthcare Reform Plan.

The diabetes caucus is now one of the largest caucuses in Congress with more than 200 members. It is a truly bipartisan caucus. Last I checked, diabetes does not strike people based on their political affiliation.”

— The Honorable Diana DeGette, U.S. House of Representatives, Co-Chair, Congressional Diabetes Caucus, speaking at the Avalere diabetes forum.

2. diaTribe FingerSticks



-by Daniel A. Belkin

3. DCU Company Watch

- **Isis—Successful partnerships across multiple therapeutic fronts:** On March 13, ISIS reported on its fourth quarter, citing successful partnerships across multiple therapeutic fronts. Of particular interest, management said they would "not be returning to Wall Street in the foreseeable future to raise money." In their diabetes pipeline, phase 2 results testing ISIS 113715, a PTP-1B inhibitor, in patients on stable sulfonylurea therapy, are expected this year. Protein tyrosine phosphatase 1B (PTP-1B) inhibitors belong to a new drug class that prevents downregulation of the insulin receptor, thus improving insulin sensitivity and insulin action. Although PTP-1B has been recognized as a potential drug target for some time, the enzyme has proved to be a difficult drug target because phosphatases are notoriously non-specific. Off target effects of ISIS 113715 include lowered LDL cholesterol and weight loss - both positive, but given the non-specificity of phosphatases, safety remains a big question in our view. Overall, we believe that this is an exciting drug class because of the need for safer, weight neutral drugs that reduce insulin resistance; as with anything early stage - not to sound like a broken record - we await more clinical data.

Management explained that release of data from phase 1 glucose challenge studies on ISIS 325568, which acts to reduce the expression of glucagon receptors, will be dependent on J&J's Ortho-McNeil, to whom it is licensed. ISIS 388626, ISIS's SGLT-2 inhibitor candidate, is currently in toxicology studies and is expected to enter clinical trials in late 2008 or early 2009. We continue to have big questions about this class given concerns about urinary tract infections, although potential weight loss would be a big plus if shown. On the competitive front, first-in-class will likely be BMS/AZ's dapagliflozin - this is currently in phase 3, and expected to be filed in 2010. Given that dapagliflozin and other SGLT-2 inhibitors in development almost completely inhibit SGLT-2, it is also difficult to imagine how these compounds could be dramatically distinguished in terms of efficacy or tolerability. As with the DPP-4 inhibitors, we would guess that safety profile (including off-target effects) and the formulation of combo pills with other anti-glycemic agents will be the main differentiating factors.

- **Transition/Lilly—Partnership agreement to develop gastrin (TT-223):** On March 13, Eli Lilly and Transition Therapeutics announced a deal to work together on Transition Therapeutics' gastrin-based therapies. Lilly will have exclusive rights and will pay an upfront \$7 million fee and up to \$130 million in sales and development milestones. We have been optimistic about the combination of gastrin (TT-223) plus GLP-1, so we think this deal could be particularly fruitful for patients if the right combination is optimized! As we note in our summary below on Transition's recent earnings call, the combination seems logical because both drugs may help to preserve beta cells and could potentially be combined into a single injection; the company hasn't discussed formulation yet but a single injection would obviously be ideal. And, actually, gastrin may well work best as an intermittent therapy, so injections may be less frequent. Gastrin has been examined in some exploratory phase 2a combo work; Lilly will initiate a gastrin-only study likely in the second half along with a phase 2 gastrin plus GLP-1 study. Although we don't believe that TT-223 is likely to be very effective at lowering blood glucose in monotherapy, the combination of TT-223 plus exenatide might in theory be effective at controlling glucose and slowing or even reversing the process of beta-cell decay - big questions of course, as this is all only potential at this stage. We think it's a brilliant idea for Lilly to test gastrin with Byetta though it is possible the company will try to use this compound to differentiate its own GLP-1 analog that is in very early testing. We're less positive about that idea because it would take longer, and we think the chance is greater that it would provide Lilly with more profits but not a better medicine for

patients. We look forward to hearing more from Transition Therapeutics in its talk at Cowen on Tuesday morning.

- **Orexigen—Contrave enrollment initiated in all four trials:** During the Orexigen 4Q07 earnings call, management announced that enrollment has been initiated for all four planned phase 3 clinical trials for Contrave - and completed for one, very good news. Management spent much of the call reviewing highlights of 2007, including the presentation of phase 2b data for Empatic and Contrave. Net losses for the quarter ended December 31, 2007, were \$19 million, as compared to a net loss of \$23 million for the same period in 2006. Net losses for 2007 were \$58 million, up from \$41 million for 2006. Management said during the call that it expects a cash burn of approximately \$75-\$80 million in 2008; after its recent public offering, it has cash and cash equivalents of \$161 million. We continue to be impressed by the efficacy and tolerability of Contrave and Empatic, and we believe that the introduction of a slow-release formulation may further reduce side effects such as nausea for Contrave in phase 3; however as we have said before we continue to have reservations about long-term safety given the CNS mechanism involved. We found the Q&A very interesting, especially a question about the recent guidance document for diabetes. Management said that in the past the FDA was adamant that weight loss could not be used as a claim for diabetes. As has been made clearer of late, the FDA has revisited this issue and is willing to allow a weight loss agent to receive approval for diabetes if it can show favorable changes in glucose control. It will be interesting to see what emerges in Orexigen's type 2 diabetes studies, such as 304. Management noted, "*...if we find that people who didn't lose much weight did receive a drop in A1c, that could be quite compelling.*"
- **Merck – Taranabant phase 3 results disappoint:** The *Journal of the American College of Cardiology* pre-released abstracts for the upcoming annual meeting of the American College of Cardiology (ACC) including the highly-anticipated phase 3 results for Merck's cannabinoid-1 receptor (CB1R) inverse agonist (blocker) obesity candidate, taranabant. This drug seems very similar to Sanofi's rimonabant, at least by this comparison. The 52-week trial of taranabant randomized approximately 2,000 subjects to placebo, 2 mg, 4 mg, or 6 mg taranabant doses, all with continued diet/exercise. However, before the completion of the trial the Data Safety Monitoring Committee of the trial recommended re-randomizing patients taking the 6mg dose to the 2mg or placebo arm early in the trial due to a higher incidence of adverse events, the nature of which were not specified. Grimace. At 52 weeks, the most common adverse events were gastrointestinal in nature and were statistically more common in both the 2mg and 4mg arms in comparison to placebo. Perhaps more worryingly, psychiatric adverse events occurred in 40% of the 4mg arms, twice the 20% incidence in the placebo arm (the 2mg arm was 28%). Weight loss was also disappointing – only the 4 mg dose produced over 5% weight loss relative to placebo, and given the observed side effects at this dosage, we question whether this dose is clinically sustainable in most patient populations. Patients in the placebo, 2 mg, and 4 mg dose lost approximately 2.6 kg, 6.6 kg, and 8.1 kg, respectively, from a baseline of ~100 kg (amounting to about a 4% and 5.5% weight loss for the 2 mg and 4 mg dose, relative to placebo). We look forward to reporting on the full results from this trial after they are presented at the ACC at the end of the month in the Windy City.
- **Abbott—Navigator approved and CGM field poised to expand:** Following years of wrangling with the FDA, Abbott gained approval for the Navigator on March 12. The Navigator was developed by TheraSense, which Abbott purchased in 2004 for \$1.2 billion on the promise of Navigator as well as for TheraSense's FreeStyle blood glucose monitoring system (Abbott's blood glucose monitoring has in that time grown from \$700 million to \$1.3 billion – quite a leap!). We see the Navigator approval as a positive for the industry as it will contribute to more discussion

and focus on continuous monitoring, which is still in its very early days in patient adoption and healthcare provider support. We believe Abbott's strong marketing on the merits of continuous monitoring will help advance the whole field.

To date, Abbott's Navigator has the best peer-reviewed published accuracy results among the three currently available products, although recent abstracts have shown comparable results for DexCom and Medtronic, whose products have seen improvement on this front. Abbott's predictive arrows that help to alert patients of impending hypoglycemia or hyperglycemia are characterized as an advantage from many patients and HCPS, while the DexCom Seven has other advantages including length of wear (seven or more days vs. five days for Abbott), smaller size, calibration time (2 hours vs. 10 hours), and ease of insertion (27-gauge for DexCom versus a lower gauge for Abbott and Medtronic). Medtronic has the advantage in terms of pump integration, which has been a key driver for the company, and it is widely viewed as having the best software (Carelink), which is a major positive from the perspective of many healthcare providers - they can guide patients better. From our perspective, all three companies realize that ease of use and user-friendliness are key, and we expect them all to aim to innovate faster on these fronts. It will be fascinating to see who generates the earliest and the best improvements.

We would anticipate that the Abbott FreeStyle Navigator will have its launch at ADA (June 6-10, San Francisco), though there should be some excitement at AACE as well. On pricing, as we understand it, the system will cost about \$1,000; "actual" daily cost varies depending on how long users wear the sensors but we would assume retail cost per day would also be comparable to DexCom and Medtronic, in the range of \$8.50 - \$10 per day. We look for a pediatric indication to be the next area of focus for Abbott. The Navigator is currently available in Germany and the Netherlands, and the next EU countries to launch will be Sweden and France - reimbursement varies throughout the EU of course, and we look forward to learning more on uptake at EASD in Italy in the fall.

- **Home Diagnostics—Challenging quarter; co-agreement signed with Rite Aid:** On March 12, Home Diagnostics reported the results from a challenging 4Q07 in a call led by CEO Dick Damron. Revenue for the quarter was \$28 million, down 12% from \$32 million in 3Q07 and up marginally (~3%) from \$27 million in 4Q06. Total revenue for 2007 was \$116 million, an increase of 3% from \$113 million in 2006. In specific channels, retail sales dropped 2% (compared to a 5% increase in 3Q07), distributor sales decreased 1% (compare to a 2% increase in 3Q07), and mail service sales decreased 3% (compared to 5% increase in 3Q07). Management attributed the drops to retail consolidation; specific isolated bad customers; and tough mail order comparisons. We think all these reasons are valid, but most are probably not that predictable – one of the problems with this market. While US sales sagged, international sales increased 46%. Management attributed this increase to expansion into Canadian retail and distribution markets, strong sales in the UK and Germany, additional market share gains in Australia, and continued growth in Latin America – during Q&A, it did also acknowledge stocking in Germany.

On a brighter note, Home Diagnostics recently signed an exclusive co-brand agreement with Rite Aid, the third largest retail pharmacy chain in the US. Management expressed confidence that the newly launched test strip platform, TRUEtest, as well as the accompanying no-coding meters, TRUE result and TRUE2go, would be available in 2H08. We continue to feel that the gap has narrowed between top glucose monitors and "store brand" meters from companies like HDI. However, even with new features like no-coding, HDI is still fairly far from attracting the highest frequency strip users to its brands. While pharmacies may have a financial incentive to sell more HDI meters as profitability with these meters is higher, we think this is successful mainly with

uninsured and underinsured patients; other customers who have insurance will likely go with a branded meter.

- **Smiths Deltec—Voluntary recall of ~1,000 pumps:** Deltec initiated a voluntary recall on March 10 of ~1,000 pumps sold between November 2007 and January 2008. Although it appears that the faulty component, isolated to a specific lot number, hasn't caused any problems to date, Deltec smartly initiated a voluntary recall for pumps made with this component so patients will not have to worry. Because of this problem, the company stopped shipping on February 2 but began shipping again in early March, contrary to rumors that the company was closing.

As we have written in the past, we believe pump therapy today is in expansion mode between Medtronic, Animas, and Insulet, and this is tough competition for anyone else in the market, including Deltec. It sounds like CGM will likely be a part of the company's next-generation pump, which we were happy to hear – we would imagine that this will come in the next couple of years but no dates have been promised. We estimate Deltec's share of the pump market at about 6%, with about 7% share of upgrades and under 5% of new pumps sold; our estimate of 3,500 pumps sold annually by Deltec was said to be conservative by the company. We believe its strength is in the pediatric set though it is also picking up some type 2s, we assume due to the relative user friendliness of its system. One credible industry rep with whom we spoke thought that there were well more than the 30,000 type 2 pumpers quoted by Medtronic last year (100,000 type 2 pumpers was the number he gave!) - good source, no quantitative data.

On the pediatric front, data from a poll taken by the great CWD (www.childrenwithdiabetes.com) early last month (n=435) shows that Medtronic has the largest market share with CWD pumpers at 43%, followed by Animas and Smiths tied at 24% each. In the last year, the biggest moves have been Medtronic gaining 3% share points, presumably driven primarily by CGM integration, and Insulet gaining 5% share points to reach 6%, presumably on the strength of no tubing/easier insertion/user friendliness/easy training. We remember seeing Insulet at CWD, where it launched its pediatric campaign - clearly some of the effects are seen here. Animas has lost a bit of share, but we also know that its pumps have the most refined basal rate, a very popular feature with parents of children and infants as this population takes insulin in much smaller doses than adults.

As we have previously noted, Animas was in impressive expansion mode late last year, with sales up 30-40% in the second half of 2007, due, we believe, to some very strong relationships with key opinion leaders. Roche has minimal share at 4%. In the larger market, we would put Deltec's pump share at around 6% though we note that it is very, very hard to get good information on its sales - but 6% would be reasonable given a run rate of about ~3,500 pumps a year (we've basically annualized the 1,000 pumps sold in November-December-January and brought that number down a bit).

One other interesting note about the CWD poll is that the percentage of respondents saying that they don't have but would like a pump has gone from 14% in 2004 to 6% this year; reimbursement has clearly improved and if patients want pumps, at least in this group, it does sound like they are being reimbursed. Going forward, we think CGM will really start to drive pump sales once reimbursement for the technology emerges. CGM availability has *already* been increasing pump growth for Medtronic, and this trend should continue as reimbursement continues to improve. Broad reimbursement will hinge on positive trial results (at least improvement in hypos) in the JDRF and STAR3 trials, but we also think there will be legal issues that arise if payors try to avoid paying for CGM. If someone proves that a payor said no to CGM and then the patient had a big car accident, we wouldn't want to be in that payor's shoes.

- **Lilly/Alkermes—RIP, AIR Insulin:** Lilly confirmed the termination of development of AIR Insulin, its phase 3 inhaled insulin product partnered with Alkermes, on March 10. Clearly, in doing a 180-degree turn, Lilly was concerned about the commercial potential of AIR insulin – competing priorities were probably critical, since Lilly is at work on so many other interesting potentially high-risk, high-reward projects in diabetes. Although the inhaler device was significantly smaller than Pfizer’s Exubera, and very consumer-friendly and portable, the insulin itself was not differentiated, in our view, in terms of efficacy or safety or simplicity. Notably, given Pfizer’s failures, it was unclear that the product made any significant strides toward reducing the hassle of inhaled insulin (including lung function testing) or perhaps more importantly, that it was easier to teach or use than just plain mealtime insulin.

We look for Lilly to redirect resources toward the development of a basal insulin analog to co-market with Humalog, toward international expansion of Byetta, toward exenatide once-weekly development – particularly long-term outcomes trials and testing for pre-diabetes, and to the development of gastrin (see Transition Therapeutics deal above). Overall, we believe Lilly’s reputation with investors and on the smaller company partnership front could be a bit damaged from this about-face. That said, we have written extensively about challenges with mealtime insulin and we can understand that Lilly would want to put resources elsewhere – this just wasn’t optimal communication and it’s unfortunate to halt phase 3 trials in our view unless there are safety issues. . While this is at the face of it unfortunate for partner Alkermes, we think the once-weekly exenatide program with Lilly could be truly transformational (as long as it is patient and HCP friendly, which we look forward to hearing more on.) Notably, we believe Lilly’s inhaled insulin move validates Novo Nordisk’s decision several months ago to halt its inhaled insulin program. MannKind’s Technosphere Insulin (TI) is now the last company standing among the late-stage inhaled insulin products.

In the span of less than three months, both Novo Nordisk and Lilly have dropped the development of inhaled insulin due to concerns about commercial potential rather than safety profile. However, TI’s claims have always been much bolder than those of Lilly and Novo Nordisk. During MannKind’s March 4 earnings call, Chairman and Chief Executive Officer Alfred Mann urged listeners not to compare Technosphere insulin to [Lilly’s inhaled insulin] because “...only TI will show clinical benefits not achievable with SC insulin.” MannKind claims a first-phase insulin response, fixed dosing, little or no dosing titration, no carb counting, no glucose monitoring, etc. On the face of it, it sounds too good to be true, but if some of it were true, especially the first phase insulin response and the ease of use, we believe the product could garner some market share. As a reminder, every share *point* for rapid acting insulin is currently worth nearly \$30 million in revenue.

- **Vivus—Ahead of schedule on phase 3 Qnexa trials:** During the Vivus 4Q07 earnings call on March 6, management indicated that there would be significant Qnexa dataflow in 2008. Notably, the company has completed enrollment of the 700-patient EQUATE study (OB-301) ahead of schedule, with results expected before the end of 2008. This is a 28-week randomized controlled trial with subjects who have BMIs ranging from 30 to 45 (this includes the lowest end of obese – overweight BMI is 25-29.9). Enrollment continues for the larger EQUIP (OB-302) and CONQUER (OB-303) studies, and management said that both should complete enrollment by the end of the second quarter. This is also earlier than previously stated. EQUIP is a 56-week study that is enrolling 1,250 morbidly obese patients with BMI that equals or exceeds 35. CONQUER is a 56-week study enrolling 2,500 patients with BMIs ranging from 27 to 45 and two related co-morbidities. Data from OB-202, a phase 2 study of Qnexa for the treatment of type 2 diabetes, will be presented at the ADA this June. Vivus initiated a six-month follow-up trial for OB-202 (called

DM-230) in which patients will continue their medication (control or Qnexa) in a blinded fashion; data on this will be available later in 2008. The company expects to spend approximately \$50 million on R&D for Qnexa in 2008.

Although we've been very impressed by Qnexa's efficacy in previous clinical trials, we continue to have hesitations about the drug's safety profile, especially in light of the FDA's recent meta-analysis showing a doubling of suicide risk for epilepsy drugs including topiramate, one of Qnexa's two components. We realize it is a much lower dose and will look forward to seeing data, but particularly in the aftermath of rimonabant we believe that the agency will be extremely sensitive to CNS side effects in obesity drugs. Management characterized the new FDA guidance as a positive development for Vivus because while A1c remains the primary endpoint for diabetes drugs, greater consideration will be given to weight loss and cardiovascular risk factors. We agree that the FDA's shift away from an A1c-centric view is a positive development for diabetes drugs that cause weight loss and improvements in cardiovascular risk factors. However, there are other parts of the guidance that we would not view as positive for Vivus. In particular, the new guidelines raise the safety bar further for new drugs generally, as reflected by the increased number of patients required for diabetes clinical trials. Topiramate has previously been studied for obesity but was dropped by J&J after phase 3, presumably due to inability to find a dose that was safe and effective. Topiramate is currently available in dosages up to 400 mg/day, and importantly, from our view, the highest dose being studied in Qnexa contains less than 100 mg/day of topiramate. By comparison, Orexigen's lead weight loss compound Empatic (which contains an anticonvulsant called zonisamide, also implicated in the FDA's epilepsy review), is being tested in doses up to 360 mg/day. In light of the FDA's heightened focus on safety, we question the chances of approval for both Qnexa and Empatic. Vivus has often suggested that because the individual components of Qnexa are FDA approved, it is natural that Qnexa will also be approved; we question this assumption because the FDA's risk tolerance for obesity drugs is much lower than its risk tolerance for epilepsy drugs.

- **Pfizer—Accelerating investment in DPP-4 inhibitor candidate:** During the Pfizer analyst day presentation on March 5, management listed diabetes/obesity among six “disease area priorities.” Importantly, the company disclosed that it will accelerate development of PF-734200, a DPP-4 inhibitor that is currently in phase 2. Management said that it had reviewed all compounds in development across Pfizer's portfolio, terminated 24 compounds, and accelerated 20 compounds including PF-734200. Pfizer plans to have PF-734200 in phase 3 by December 2009 – a surprising statement in our view, given that published results on the compound include testing in only 27 healthy subjects thus far. This 27-subject clinical study was published in the February 2008 issue of *Diabetes, Obesity, and Metabolism*. Given that other DPP-4 inhibitors already inhibit DPP-4 by about 80% and are relatively indistinguishable from placebo in adverse effects, it seems unlikely in our view that PF-00734200 will distinguish itself with regards to either efficacy or tolerability. We continue to believe that the DPP-4 inhibitors will primarily be differentiated as combination products – i.e., Merck's sitagliptin/metformin, and potentially Takeda's alogliptin/pioglitazone or AstraZeneca/BMS's saxagliptin/dapagliflozin. Pfizer has not been historically strong in the diabetes sector – notably, there was nothing said on the call about inhaled insulin or insulin – but in the aftermath of Exubera, we believe Pfizer is now eager to accelerate PF-734200 in order to gain a foothold in the growing diabetes market. Management reaffirmed that CP-945598, its CB1 antagonist in phase 3, would continue to be developed “with vigor.”
- **MannKind—Awaiting phase 3 results with continued interest:** During the 4Q07 earnings call on March 4, management reiterated its goal of filing Technosphere Insulin (TI)

before the end of 2008; two of the pivotal phase 3 trials are expected to finish in September 2008. During the call, Chairman and CEO Alfred Mann briefly discussed MannKind's plans to conduct an ambitious post-marketing trial for TI to demonstrate superiority over rapid acting analogues (Humalog will be used). CGM will be used to measure changes in glycemic variability and rate of hypoglycemia – we would guess MannKind would use the SEVEN sensor due to the fact that Al Mann and DexCom CEO Terry Gregg used to run MiniMed together but there were no specifics given. The ease of use for CGM in type 2 trials will be important so that there are no screw-ups. In our view, this trial is an indication of MannKind's confidence in TI's profile and demonstrates the increasing recognition in the diabetes community of glycemic variability as a potential A1c-independent risk factor. It's terrific from our view that glycemic variability can be used in trials; from a healthcare provider perspective and a patient perspective, seeing the "percent of time" in euglycemia of two different treatments in any trials will be easy to understand and potentially very compelling, depending on results, how the trials are powered, etc.

New news on the call included details on the timing of four key trials:

- 1) Results for 009, a 12-month study comparing TI to a rapid-acting insulin analog as add-on to basal insulin in 500 type 1 patients, will be announced 3Q08;
- 2) Results from 102, an efficacy study in 650 type 2 patients comparing TI to premixed insulin, will be released before the end of 2008 – these results will be interesting because currently premixed insulin is used largely for its "ease of use" (twice-daily injections);
- 3) Study 030, a two-year pulmonary function safety study comparing TI vs. injected and/or oral therapy, will finish in "early September" with results to be included in the filing package or possibly to be made available earlier; and
- 4) Results from 103, a label expansion study testing TI alone or in combination with metformin in 500 newly diagnosed type 2 patients, will be released after the NDA filing. We wonder if this study will put forward that dosing and glucose monitoring are not needed with TI, as we have heard management say over time. Certainly there is a push for earlier, more aggressive use of insulin and if the results are favorable, which we think is likely, this would be a very smart, if ambitious trial to have designed. It should be extremely interesting to see the effect of insulin in such recently diagnosed patients, as we have heard that early insulin use can "reset" the pancreas. We hope these patients will be followed over the long term so that the effect of early insulin use on long-term complications can be followed (even if not as a randomized controlled trial – just seeing observational data would be very interesting).

Also in the pipeline, results from MannKind's phase 1 clinical trial of inhaled GLP-1 will be given at ADA; the company is planning to initiate a second phase 1b trial of inhaled GLP-1 as well. The biggest news on inhaled GLP-1 was the rapid bioavailability and the absence of nausea – we look forward to seeing these data, as GLP-1 without any nausea would be truly differentiated. Key parameters to compare, in our view, will be A1c drop, weight loss, nausea, and ease of use for both the patient and the prescribing physician.

In terms of the finances, fourth quarter net losses were about flat compared to last year at \$75 million; net losses for the year increased to \$293 million from \$232 million at the end of 2006. Management indicated that cash burn could further increase over the next two to three quarters due to increased clinical costs and the expansion of a manufacturing facility for TI; it has funds to finance the company through the end of 2009, with cash at year end 2007 at \$368 million. No

new news on partnerships for TI – we assume the talks will start up again when there are phase 3 data to share.

- **Bayer—Hitting a home run on strength of Ascencia Contour:** Bayer reported its 4Q07 results on February 28, with a truly stellar quarter in Diabetes Care. Revenues grew 18% to nearly \$1.5 billion, with strength stemming from the Contour (currency-adjusted, blood glucose monitoring increased 24%). Diabetes Care was not mentioned in the prepared remarks for the conference call but during the final question in Q&A the management team took the opportunity to praise the Ascencia Contour brand of BG meters, noting that they were “proud to be the fastest growing diabetes company in the world in 2006” and even more so after having “increased that lead in 2007.” They went on to say that they had fundamentally rebuilt the diabetes franchise over the last three years, grounding its strength in Bayer’s in-depth understanding of the interface between physician and consumer, and that accordingly the Ascencia line was growing at 2-2.5 times the regular market rate. We note that for the blood glucose monitoring industry, Bayer and J&J do seem to be the big winners in 2007 in sales expansion; J&J 4Q results rose 17%, whereas Abbott and Roche were both up well less than 10%. Still, overall, the blood glucose monitoring industry showed greater strength in 2007 than 2006, which is great to see as we believe this is the cornerstone to successful diabetes management for millions of patients. We also think that the key to success here is expanding the market and increasing testing frequency, not stealing share – we want to check back in on the Diabetes Care Coalition since we think industry could do more as a group than individually in promoting the upside of testing.
- **Merck—Label expansion for Janumet:** On February 28, two new indications for Janumet (Januvia/metformin) were added to the drug’s label – we continue to be impressed by the regulatory progress for this franchise, given that the first Januvia approval came only in October of 2006 and the drug has already sold over \$700 million (with Janumet) since then. As of the current label expansion, Janumet is now approved as a *frontline* therapy for type 2 patients poorly controlled by exercise and diet alone, and as an add-on therapy to a sulfonylurea when a patient is poorly controlled by the combination of a sulfonylurea and metformin. Studies added to the labeling showed that Januvia in combination with metformin produced similar efficacy as metformin plus a sulfonylurea for patient poorly controlled by metformin alone, with the advantages of improved weight profile and a lower rate of hypoglycemia. On page 18 we provide an interview with Dr. Sethu Reddy, US- Scientific Director for Diabetes & Obesity at Merck, about the implications of the expanded labeling for Janumet.

In January, the European Medicines Agency approved expanded labeling for Januvia including use for dual and triple therapy with a sulfonylurea or a sulfonylurea plus metformin. Janumet is currently approved in seven countries, and had worldwide sales of \$44 million during 4Q07. According to Merck, more than 4.25 million prescriptions have been written for the Januvia franchise (Januvia and Janumet), and Januvia is now available in 65 countries. Before Januvia was approved, there was much speculation that reimbursement would be poor for this drug, but in fact, Merck’s reimbursement progress has been very impressive from our view, at least relatively speaking. In the US, Januvia has reimbursement coverage in the 2nd tier in more than 200 million lives across managed care commercial formularies. Notably, Merck plans to launch a direct to consumer advertising campaign in the US in 2008 for Januvia.

- **Arena—Discussion on lorcaserin dominates earnings call:** Arena President and CEO Jack Lief led the company’s 4Q07 conference call on February 27, which was dominated by queries about Arena’s lead compound, lorcaserin, for the treatment of obesity. Notably, the data safety monitoring board (DSMB) review of 12-month data from the ongoing two-year phase 3 BLOOM trial was broadly discussed; a positive reports did emerge recently, putting to rest many

fears! The company also discussed other regulatory items on the call, including the initiation of two additional phase 3 pivotal trials, BLOSSOM and BLOOM-DM, in December of 2007. Lief said that while enrollment in BLOSSOM has been faster than expected, the same cannot be said for BLOOM-DM, which must compete with other trials to recruit diabetes patients (a reflection of the many compounds in or nearing phase 3 development). However, he said that this is not expected to change the NDA submission timeline (at least not at this point). He also insisted that lorcaserin would not run into the same stumbling blocks as rimonabant did at the FDA.

Taking a lesson from the advisory panel convened on rimonabant, Arena has implemented prospective monitoring for adverse CNS events (depression and suicidality), a positive move in our view. Arena will be holding a lorcaserin-focused R&D day on April 15 in New York. There was no new information in the call regarding Arena's diabetes partnership with Ortho-McNeil in developing its GDIR agonist, APD668. The compound is still on hold and no further information was provided on the new, ostensibly more powerful (but much earlier stage) Arena-discovered GDIR agonist in preclinical development.

On the financials side, Arena reported revenues of \$19 million for 2007, down 40% from 2006. Revenues for both years came from partnerships with J&J's Ortho-McNeil Pharmaceuticals and Merck. R&D expenses for 4Q07 were \$41 million reflecting an increase of ~7% from 4Q06 (up 26% from last quarter). Net loss for the year of \$145 million represented a 65% increase from a net loss of just over \$88 million in 2006. This reflects the increased costs of clinical development and R&D personnel for the lorcaserin phase 3 development program, and to a lesser extent, the costs of developing APD125 for the treatment of insomnia.

- **Nektar—Hoping against hope on Next Generation Inhaled (NGI):** During its 4Q07 earnings call on February 27, Nektar's management gave a succinct update on its inhaled insulin franchise. Notably, Nektar's 2008 guidance did not include any contribution from inhaled insulin, but the company is maintaining the technical capability to partner on the franchise. Management indicated that a partnership for either Exubera and/or Nektar's Next Generation Inhaled (NGI) product technology is expected in 2Q08. In the meantime, costs to keep the program going are about \$2 million per month "which won't be spent indefinitely." In the absence of a partnership for Exubera and/or NGI there will be no forward motion on the inhaled insulin franchise, and investment in this area will be halted. Overall it is hard to know whether a partnership will come through - there is no real upside for having a lot of confidence, however, though management certainly seemed to.

We think inhaled insulin is incredibly challenging due to all the barriers surrounding mealtime insulin, period (without even adding on the lung function testing, etc.), though the technology could present an opportunity for an educated company to provide a therapeutic alternative for patients who desire it. It will likely depend on the business model and the experience of the company - we wonder how much discount Sanofi could get for buying it back. This is probably difficult for anyone to take on, given the opportunity costs, but it is clear that Pfizer was not an optimal partner and we wonder how much that worked into the equation. Management tackled questions about Exubera head on and very confidently during the Q&A, maintaining conviction in their NGI product and even going so far as to say, "We all know Novo's Aradigm technology was not the ideal technology to deliver inhaled insulin. It's obvious why Novo didn't want to proceed with their mealtime insulin program." Whew! Management also emphasized that Nektar owns the dominant patents in inhaled insulin and is thinking (partner pending and long-term probably) about inhaled GLP-1 and basal insulin. We note that Novo Nordisk is working in these areas as well and has a few candidates in early stage development.

- Ipsen—Following partner Roche’s lead in developing GLP-1:** In a February 27 call led by Chairman and CEO Jean-Luc Bélingard, management made many allusions to Ipsen’s GLP-1 program (R1583) but nothing as concrete as what we heard from its partner, Roche, in late January. This likely reflects the fact that Roche leads the R&D effort and, with the deeper pockets, is the deciding voice on how much to disclose. Ipsen cautiously positioned the next step after release of positive phase 2 data at the ADA in 2006 as “potential phase 3 initiation” whereas pharma CEO William Burns stated a goal of best-in-class for R1583 during Roche’s 4Q07 call, adding, “We know that we’ve got a clear dose effect, we know that we’ve got the possibility of a once-weekly product, we know that we’ve got a molecule that can be delivered with a very fine needle... and much more conveniently than some of the other work that’s going on in this class from competitors.” We would think they would want to wait until they had results (maybe they already do) on weight loss, nausea, and A1c reduction before claiming a lofty best-in-class profile. Roche management did say that plans called for phase 3 trials to start in 2H08. As a reminder, in October 2003, Ipsen granted Roche an option of exclusive license to the rights to develop and market Ipsen’s GLP-1 portfolio in all countries except Japan and France. Ipsen’s Japanese partner, the Teijin Group, has co-exclusive rights in Japan for the development of BIM51077, also a GLP-1 analog. Explicit mention of Teijin’s BIM51077 development was not made during the Ipsen call; to the best of our knowledge, it is undergoing additional phase 1 testing. However we did see a slide that indicated transfer of BIM51077 development to Roche, which indicates Roche has exclusive rights to ex-Japan and ex-France development of BIM51077 (in addition to sharing co-marketing rights with Teijin in Japan; Ipsen maintains co-marketing option in France). Also in the Ipsen pipeline was an MC4 agonist in its melanocortin program targeting obesity and the metabolic syndrome. This candidate remains at a very early preclinical stage.
- Sirtris—Expanding the pipeline in SIRT1 activation:** During the Sirtris 4Q07 earnings call on February 25, CEO Dr. Christoph Westphal emphasized the potential of SIRT1 activators in type 2 diabetes as well as new developments in the company’s preclinical pipeline. He began by reviewing some of the progress that Sirtris made during 2007, including the completion of a phase 1b study of lead compound SRT-501 and preclinical work with new chemical entities (NCEs). Dr. Westphal reiterated that SIRT1 activators have the potential to be frontline therapy options for type 2 diabetes because all available data suggest that they are tolerable, safe, orally available, weight neutral, lower glucose, and sensitize the body to insulin. Although from our view it is early to comment on safety, we continue to believe that the commercial prospects for simple and tolerable agents is very high (see Merck, \$300 million-plus for Januvia in 4Q07).

Some of the important new developments that Dr. Westphal discussed include: 1) One of the company’s SIRT1 activator NCEs will enter the clinic in mid-2008; 2) Sirtris is investing in new research into SIRT3 as a metabolic disease target; and 3) Sirtris may enter a strategic partnership in the next 12-18 months – this is the first time to our knowledge that Sirtris has provided a timeline on partnerships. The company has filed over 140 patent applications including broad mechanisms of action claims, and this will drive company valuation as well as, of course, new data. On a separate note, Sirtris is also looking into oncology diversification for its products. On our part, we’re looking forward to reviewing the results of another phase 1b study of SRT-501 (results expected 1H08 – ADA?) and the phase 2a data for SRT-501 plus metformin (three months, 65 patients per arm, metformin +/- SRT-501, data in 2H08), but we continue to believe there is a reasonable probability that this compound will be dropped (for type 2 diabetes, but not necessarily other diseases) in favor of one of the more powerful NCEs that are currently in preclinical testing. At the end of 2007, Sirtris had cash and cash equivalents of \$118 million, compared to \$50 million at the end of 2006. Net loss for 4Q07 was \$9.1 million, compared to a net loss of \$4.4 million for 4Q06. Net loss for 2007 was \$31 million, compared to a net loss of \$17

million for the prior year. Most of this increase in net loss was due to increased R&D expenses, which totaled \$29 million in 2007 as compared to \$14 million in 2006. At the projected burn rate, Sirtris has enough cash to last approximately three years.

- **EnteroMedics—Continuing enrollment of Maestro pivotal trial:** During EnteroMedic's 4Q07 call on February 20, CEO Mark B. Knudson of newly public EnteroMedics provided background information on the company's product under development, the Maestro System, which uses electrical signals to block the vagus nerve near the stomach as a treatment for obesity. Knudson described the product as something that would fill the gap between current surgical options and pharmacotherapy and reaffirmed that the company plans to complete enrollment of the 300-patient pivotal EMPOWER trial in 1H08, with the goal of commercializing the Maestro System in 2010 in the US. However, he gave no new information on enrollment, which was surprising. He said that EnteroMedics plans to file for a CE mark around the middle of 2008 – we assume commercialization overseas would depend on a partner. EnteroMedics had a net loss of just under \$9 million in 4Q07, and a total net loss of ~\$21 million in 2007. At the end of 2007, EnteroMedics had cash and cash equivalents of \$57 million, enough for about six more quarters at the current burn rate, which sounds reasonable through 2008. EnteroMedics should have sufficient cash until results emerge validating the technology – mid 2009 – and then it would rely on positive results to raise more capital.

We were surprised to hear management say during the Q&A that there was no competition in vagus nerve stimulation on the way. In December of 2007, J&J's Ethicon Endo-Surgery acquired exclusive rights from Cyberonics to patents and patent applications pertaining to vagus nerve stimulation (VNS) for the treatment of obesity. Ethicon has not announced explicit plans regarding vagus nerve treatments, but we imagine that plans are in the works. Although there is certainly tremendous upside in the bariatric surgery arena, and we believe that patients are eager for safer opportunities for substantial weight loss, we expect significant competition from established companies. It also seems fair to question whether EnteroMedics will receive regulatory clearance with one year of clinical data given the current regulatory environment; we do note this trial is a double blind randomized placebo-controlled trial rather than an open label trial. In our view, it's a tradeoff for the FDA between addressing the obesity epidemic sooner and ensuring safety of a new device. Though less invasive than bariatric surgery, implantation of the Maestro System is still a fairly invasive procedure for the treatment of a condition for which the FDA has very high standards for safety.

- **Novocell—Curing type 1 diabetes in mice with human stem cells:** Novocell reported February 20 that it has succeeded in turning human embryonic stem cells into cells that released insulin in mice in a glucose-dependent manner. The paper describing this work was published online in advance of print in the journal *Nature Biotechnology*. In the reported study, immature beta cells derived from human embryonic stem cells were injected into mice whose islet cells had been destroyed using a chemical treatment with streptozotocin. Over the course of a few months, these cells developed into glucose-responsive beta cells capable of protecting against hyperglycemia in a majority (92%) of the mice. If these findings could be translated to humans, they would represent a critical milestone in the development of a renewable source of islet cells, though at present considerable technical hurdles remain.

In the study, seven of the 105 mice that received the stem cells developed tumors from the treatment; the authors suggest that better techniques for purifying the stem cells are needed. In addition, even if a reliable, safe, and renewable source of beta cells is established, we still need new techniques to protect these beta cells, once they are implanted, from the original type 1 diabetes autoimmune response that caused the disease. Unfortunately, the immunosuppressants

that are currently used post-islet transplant have deleterious effects on the body and are especially toxic to beta cells. An alternate strategy, encapsulation of beta cells, has been in development for 25 years or more, and Novocell and TheraCyte continue to push this technology forward. Although studies have verified that islet cells can survive and be protected through this technique, the viability of encapsulation remains uncertain. We believe that given these challenges, it will likely take years before human trials commence. Still, we see the study as a potential triumph, and we are eager to see how reproducible the work is. On a broader front, although we note numerous disappointments over the years related to this sub-sector of diabetes treatment and to Novocell specifically, we do note that the company has made impressive strides on the leadership front, especially with recent additions to its BOD – it also has an excellent SAB (led by Dr. Jeffrey Bluestone of UCSF), and we are excited about the next steps there.

- **Lilly—Pushing the pen market with Kwikpen:** Lilly continues to show innovation on the mealtime insulin front with its Kwikpen launch, which began early February in the US following the pen's October FDA approval. It's our understanding that US pen penetration overall has increased to about 17%; while progress seems painstakingly slow compared to many parts of the EU, we definitely see penetration increasing, particularly with insulin analogs for patients with good reimbursement. Lilly estimates pen penetration among insulin analogs at 33%, higher than we would have guessed, although we know Novo Nordisk has certainly been extremely successful in increasing pen penetration in the US with FlexPen in particular. FlexPen and Kwikpen are both disposable. Although there is growing focus by some patients on using refillable pens because their environmental impact is lower, disposable pens are still the primary format here. We do believe reimbursement remains a barrier. In our view, increased compliance with pens should be an excellent argument for payors, but some old fashioned ones still try to position pen benefits as convenience only - looking at the short term but not the long term implications of mealtime insulin use. We continue to believe simplicity and ease of use have been the primary drivers behind the long acting analog market (no dosing, less monitoring, easier titration, no carb counting, etc). Lilly has been aggressive on the pen front over the last year, reflecting its solid attempts to energize its Humalog franchise. Long acting analog growth was considerably higher than rapid acting analog growth in 2007. In 2006, sales of each were at about \$2.5 billion, while in 2007 long acting analogs grew to \$3.3 billion, up 34%, compared to \$2.9 billion for short acting analogs, closer to 16% (difficult to say exactly since Sanofi's Apidra isn't disclosed though we assume this is low). Lilly is certainly responding by moving the ball forward with its new pens, and we assume Kwikpen would be the most popular of the three (Memoir and Luxura are more specialty in focus: Memoir's memory feature makes it attractive in segments like the retired engineer set, while Luxura, with half unit dosing, is good for children and type 1s who are particularly insulin sensitive). Overall we like seeing the innovation and will be eager to see how this continues to affect penetration and mealtime insulin analogs overall.
- **J&J—Diabetes Franchise revenue has blowout quarter:** On January 22, J&J's Diabetes Franchise (LifeScan and Animas) reported 4Q sales of \$643 million, up 19% worldwide. Sales in the US were \$337 million, up nearly 17% and \$306 internationally, up 21%. Animas had a particularly standout quarter, with sales up over 40% (following a 30% increase last quarter!). For 2007, worldwide sales for the Diabetes Franchise reached nearly \$2.4 billion, an increase of 14% from 2006. This reflected \$1.26 billion in US sales, up 10%, and \$1.11 billion in sales overseas, up 20%. Particularly from such a high base, these are truly standout results. Management also mentioned that the low cost OneTouch Horizon BG monitor was for sale in emerging markets wherever cost is an issue - good news for underserved markets.

Elsewhere on the call, management mentioned Ethicon Endo surgery was a major contributor to growth, so we assume the bariatric surgery business is doing well, particularly with the recent US approval. J&J's clear commitment to comprehensive care is clearly good news for patients and healthcare providers alike. Of interest, J&J will be an Olympic Sponsor for the 2008 Olympics. This is likely to increase visibility for the company around the world, where the incidence of diabetes continues to accelerate and now approaches 10% of the worldwide population.

—by Kaku Armah, Kelly Close, Jenny Jin, and Mark Yarchoan

4. Interview with Dr. Sethu Reddy, US- Scientific Director for Diabetes & Obesity at Merck

Dr. Sethu Reddy is the US Director for Scientific Affairs for diabetes and obesity at Merck. Dr. Reddy has an extremely impressive background; before joining Merck, he served as the Chairman of Endocrinology, Diabetes, and Metabolism at the Cleveland Clinic and has authored or coauthored more than 120 articles, abstracts, and book chapters concerning diabetes and/or obesity. He has received numerous prestigious awards including the distinction of Mastership in the American College of Endocrinology and the Florence Nightingale Award by Cleveland Clinic for Physician Collaboration. Dr. Reddy earned his MD at the Memorial University of Newfoundland, in Newfoundland and completed his fellowship in endocrinology and metabolism at the University of Toronto. He carried out his research fellowship in cellular and molecular physiology at Harvard Medical School and the Joslin Diabetes Center in Boston. Dr. Reddy's research interests are primarily devoted to clinical endocrinology, including obesity and the epidemiology of diabetes and its complications. Dr. Reddy has received more than \$1 million in research grants and support for studies related to diabetes and cardiovascular risk factors. Kelly Close and Mark Yarchoan had a far-reaching discussion with Dr. Reddy in early March, in which Dr. Reddy discusses the expanded labeling for Merck's DPP-4 inhibitor/metformin combination, Janumet, the impact the Januvia franchise is having on the diabetes landscape, and his thoughts on new drug classes more broadly speaking.

Kelly Close: Thank you so much for taking the time to speak with us today, Dr. Reddy. Congratulations on Merck's expanded indications for Janumet. As we understand it, the expanded indications include initial monotherapy - that's quite something! To start, could you talk a bit about the new label for Janumet and how it has expanded the potential indications for the combination?

Dr. Reddy: The add-on to sulfonylureas and initial combination therapy indications are the highlights. One of the broadening indications is the add-on to sulfonylurea, definitely. There's also now the comparison to glipizide in people failing metformin. Of course the label is also appropriately updated with respect to hypoglycemia and hypersensitivity reactions, similar to the sitagliptin information... But the main thing probably is the add-on to sulfonylurea and the language around initial therapy.

Mark Yarchoan: Could you talk a little more about the implications for initial therapy and what that means for patients and providers?

Dr. Reddy: Yes. So if a patient with type 2 diabetes fails diet and exercise, then Janumet may be an option. From a clinical perspective, this would be considered initial combination therapy. This offers a powerful combination for the appropriate group of patients.

Kelly: Right. Very compelling for patients to know they have that as an option right off the bat - they don't have to fail this or that first.

Dr. Reddy: If you were a purist you would say, "Well diet and exercise is the initial therapy." And all medical therapies would be considered second, third, fourth, and so on. But I think most practicing physicians probably would think of that first medical therapy as the initial therapy.

Kelly: Yes, definitely. Plus, the ADA algorithm doesn't actually suggest "diet and exercise" first anymore – our sense is they absolutely recommend it, but the first thing when someone is diagnosed that they think the person should move to is metformin, as that has shown significant benefit, whereas compliance with diet and exercise hasn't been high. One would hope, of course, that patients would combine diet and exercise with therapy. It just doesn't always happen. We think the drive toward earlier, more aggressive therapy is good, of course, because this helps avoid long-term complications.

Dr. Reddy: The FDA does allow that initial combination therapy or maintenance of combination therapy should be individualized and left to the professional healthcare provider. But then it goes on to detail the specific indications. One is failure of diet and exercise. Two is failure of metformin alone. Three is failure of sitagliptin alone. Four would be people that are currently taking sitagliptin and metformin separately and want to convert. Five is actually the triple combo: sitagliptin, metformin, and sulfonylurea. And typically I guess that scenario is where patients are taking metformin and a sulfonylurea and are thinking about adding sitagliptin. One could substitute the metformin with Janumet instead of adding a third pill.

Kelly: Okay. That's pretty powerful. It sounds like *officially* Janumet isn't initial therapy, because it would be supplementing diet and exercise, is that right?

Dr. Reddy: Yes. Data in the expanded label supports a new regimen for Janumet as initial therapy in patients inadequately controlled with diet and exercise alone. Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider.

Kelly: And before it wasn't, right? Before, patients did have to be failing metformin or sulfonylurea, if I recall correctly.

Dr. Reddy: Right. In the original label, the wording was that Janumet is indicated as an adjunct to diet and exercise when people are not doing well on metformin or sitagliptin alone, or in patients being treated with the combination who wanted to switch. So this would be a broadening where potentially that initial combination therapy is allowed.

Kelly: So this is a big change, in the scheme of things! It makes it clear to PCPs that if somebody presents with type 2, they can put them on Janumet right from the start.

Dr. Reddy: Right. If somebody presents at their clinic with a very high hemoglobin A1c, then they might think about this early combination therapy with the rationale, of course, that neither of these medications cause much hypoglycemia; so there is very little danger of a patient developing serious hypoglycemia.

Kelly: We think that's terrific that a glycemic-dependent agent can be prescribed right off the bat because that makes having more aggressive goals – or some would just say normalized goals - easier from the start. We've been impressed with Merck's execution of Januvia . . . , whether it be the fast regulatory process, the early effective work on reimbursement, the sampling programs, the international expansion, etc. In the scheme of things, it's not so surprising to see this do so well commercially given the ease of use; we think this speaks to how simple to teach and learn Januvia is what a favorable side

effect profile it has. For this drug, all those pieces almost outweigh the fact that Januvia actually isn't highly efficacious in monotherapy compared to other drugs, especially insulin – that is to say, the A1c drop is good but not great – but the side effect profile is great, not challenging (relative to all other classes besides incretins).

Now, the efficacy with metformin is much more profound, so much so that we were wondering why Janumet actually hasn't been stronger commercially? Of course, the franchise has done incredibly well overall, and execution seems positively textbook, as long as safety holds. So on the Janumet question, has Januvia done so much better commercially (so far) because doctors felt that they wanted to just try Januvia first because that's what was approved first? Or, is it to the benefit of starting two different drugs separately? And if that is right, we would be expecting a steeper growth curve ultimately for Janumet, right?

Dr. Reddy: Janumet just got launched late last year, so that's why it's probably going to be a little bit slower tracking than another new medication in the same class. Our data in Study 36 showed the greater efficacy of the combination compared to the individual drugs, but most doctors typically think that with combination therapy you don't get the equal bang from both medications. You usually get a little bit less. Here it appears that sitagliptin and metformin seem to deliver equal bang for the buck or certainly an additive effect, but I think that data probably isn't as publicized yet. It will take a while for that to get ingrained in people's minds, I think. When they see that combined efficacy, people will start using Janumet.

Dr. Reddy answers science questions about Januvia and the DPP-4 class:

Mark: Is there anything else that you think that isn't well understood well about Janumet?

Dr. Reddy: I think there is some data that metformin also raises GLP-1 levels modestly and that in healthy people, at least, there appears to be a further increase in the active GLP-1 levels with sitagliptin plus metformin together.

Kelly: And that's in the label?

Dr. Reddy: Yes. It's in the clinical pharmacology part of the label. So that is of scientific interest, I think, in terms of how these medications might have an additive force at work together. There's still a lot of research that needs to be performed, especially in type 2 diabetes patients.

Mark: I want to make sure we understand the mechanism correctly. Metformin increases the *total amount* of GLP-1 produced, while sitagliptin increases the *percent* of the total amount of GLP-1 that is active, is that correct? So when you combine the two in healthy subjects, what we are seeing is a dramatic increase in the ratio of active to total GLP-1, as well as a substantial increase in the overall pool of GLP-1.

Dr. Reddy: Correct.

Kelly: Right, and so it seems like the two mechanisms are synergistic, not just additive, actually – is that right?

Dr. Reddy: We're can't say synergistic because scientifically it means that you have more than an additive effect, and we don't want to overstate or over-claim. We just have to be very precise in our language.

Kelly: The average A1c drop from metformin is about a point, right?

Dr. Reddy: Right, 1.1% or 1.2%.

Kelly: Well, we know if metformin drops 1.1-1.2% and Januvia drops less than that and there are some studies showing over a 2.2% drop with Janumet so ... it looks like synergy, but we'll accept for the moment you prefer to say the effects are additive.

Mark: There has been a powerful response to this drug. It's clear that insulin initiation is really complicated for our healthcare system to address, and a lot of the other drug classes are either also complicated or have daunting side effect profiles. Januvia or Janumet are clearly differentiated on both of those fronts. Can you talk a little bit about trials that you are doing that might open up the class to more people?

Dr. Reddy: Well, we're anticipating some results from a geriatric study. We're also anticipating the results of a study with Januvia as combination with bedtime basal insulin. That question comes up quite often. And then the other triple combo, of course, would be Januvia plus metformin plus TZD, which is also an ongoing trial.

Kelly: That's interesting – one would think the results to that might be quite powerful because you have the TZDs working on insulin resistance while Januvia and metformin work on insulin secretion, among other mechanisms.

Dr. Reddy: And there have been two large trials of international studies looking at patients with either modest renal impairment or severe renal impairment.

Mark: That's interesting – clearly no rest for the weary on the trial front! I know there have not yet been data showing beta cell preservation or regeneration but obviously for populations that have suffered some renal impairment, that could be particularly important.

Dr. Reddy: Yes. So clearly right now for the DPP-4 inhibitors as well as exenatide, there appears to be some reasonable animal data that there are some beneficial effects on beta cell mass and beta cells versus alpha cells. But there is no human evidence yet for any of these medications. Certainly we don't want to make any allusions or claims to that effect. I have a feeling that a lot of physicians are very hopeful and they are dreaming and they are trying to imprint that dream, that hope, on these new therapies. But I think we just have to be cautious.

Kelly: How would you actually determine if it was having some effect on beta cells; if it really could be construed to regenerate beta cells? At some point can you just take a surrogate – “this has kept A1c low for four or five years”? Are there studies that are ongoing?

Dr. Reddy: The difficulty we have is that we do not have good imaging technology for the beta cells.

Kelly: Right.

Dr. Reddy: At least in humans, it's going to be very tough to study. How could you show it? Well, so what you might do is treat the patient early, possibly during pre-diabetes, with the medication. Then if you improve their blood sugars and so on, theoretically if you stop the drug and watch them, if you have restored the beta cells to some normalcy in terms of mass and function, you would be looking at a long-term effect of the drug after cessation. However, if there appears to be a failure of the insulin or the glucose starts rising relatively quickly after you stop the medication, it would suggest that you are not having too many long-term effects on the beta cell mass itself.

Dr. Reddy speaks about the growth of the DPP-4 class and about how Januvia will be differentiated in the future:

- Kelly: Switching gears, is there anything you can say about testing Januvia or Janumet in people with pre-diabetes?
- Dr. Reddy: That certainly has been widely discussed and suggested, and we continue to discuss it within Merck. As you probably remember we have formally announced that we are doing a cardiovascular outcomes study.
- Kelly: We've been thinking more and more about pre-diabetes, particularly from a public health perspective, given that diabetes is arguably the biggest public health crisis of our time. Januvia strikes us as the first real therapy that would be simple enough for people with pre-diabetes to take.
- Dr. Reddy: Yes, obviously it's once a day and gets renally excreted and doesn't cause hypoglycemia or weight gain. So in that regard it could be a viable option, but only a clinical trial studying the efficacy and safety in pre-diabetes would confirm that.
- Kelly: Of course. What about head-to-head studies, say, versus GLP-1?
- Dr. Reddy: Amylin may be doing a head-to-head study versus Januvia.
- Mark: We want to pick your brain about something else. There are, of course, a lot of DPP-4 inhibitors that are coming on the market— or that are trying, at least. It's been very hard for us to figure out if there are any meaningful differences between them. It seems like mechanistically they all seem to inhibit DPP-4 pretty well, and there are these various rumors about different side effects, but nothing concrete. Do you have any particular thoughts about how these DPP-4 inhibitors might be different from one another?
- Dr. Reddy: Some experts have proposed that once you inhibit the enzyme to a certain amount, you aren't going to see differences in efficacy. So I think the differentiation might be in terms of safety and the long-term experience.
- Kelly: Right, if there is any differentiation.
- Dr. Reddy: I think we'll just have to wait and see what happens. We have a wealth of experience that physicians will feel comfortable with. Safety is obviously going to be an ongoing issue.
- Kelly: Yes although with safety that's all about time so we would think you would have at least a couple more years in the US before there is another DPP-4 inhibitor approved – if then. Can you say a little more on safety?
- Dr. Reddy: So we're being cautious in that we need to continue to monitor for safety and be pharmacovigilant. I think we have been fortunate in terms of our selectivity and specificity, and, with the post-marketing surveillance as well. Nothing unexpected has happened to date.
- Mark: Right. Looking at the published data it seems that among the DPP-4 inhibitors, Januvia appears to be a little bit less potent at inhibiting DPP-4, although our understanding is that the difference is not meaningful because anything more than that wouldn't really give any additional increase in GLP-1 levels. Do you think that's accurate?
- Dr. Reddy: Well I think our data shows that there is 80 percent inhibition seen 24 hours after the first dose. I think that's a pretty reasonable inhibition of DPP-4. Now remember, all of these assays that you see from different companies, including ours, are of the peripheral

DPP-4 levels, but as you can imagine, the real scene of the action might be in the gut right after GLP-1 and GIP get released.

- Mark: Right. And of course that's probably not the easiest thing to measure in people.
- Dr. Reddy: Exactly. I think the astute person will probably say, "Well, the bottom line in all of these mechanisms and so on is: what is the main A1c reduction?" And in that, too, we have to compare apples to apples. They have to be at similar baseline A1c values and similar duration of diabetes and all of these other factors that are in play.
- Kelly: Have you thought about using continuous monitoring in any of your trials so that you could actually show reduced glucose variability?
- Dr. Reddy: Yes. I can't say where, but we are sponsoring an investigator-initiated study. They are looking at sitagliptin with CGM.
- Kelly: That sounds quite powerful, potentially – I know from a patient perspective, seeing the time spent in euglycemia is pretty compelling – very easy to understand, vivid from a patient point of view. We'll be interested in seeing the results of that study. You must speak to so many clinicians who have had success with Januvia. What's been the most compelling factor that has contributed to the success of the Januvia franchise? Is it the glucose dependency or the weight neutrality or the once-a-day dosing? Or that it doesn't cause edema and has no association with CHF or fractures? What is swaying opinions?
- Dr. Reddy: Well I think for the specialists it's clearly the basic science behind the action of Januvia. I think there is a great interest in the fact that, okay, here is a scientific discovery in terms of gut peptides and how they regulate beta cells and alpha cells, and here is a medication that takes advantage of that physiology. Many of the CME programs that Merck has organized in the last year have had great attendance because there was just a great deal of interest in the science behind the medication. That science, of course, relates to all those factors you mentioned: glucose dependency, lack of edema, lack of weight gain, etc.
- Kelly: I see.
- Dr. Reddy: When patients are not tolerating metformin or failing metformin, or if metformin is contra-indicated, then physicians will consider Januvia as a possible choice. It's the leveraging of this very interesting biology that people really like.
- Mark: Just a question about the ADA algorithm. Do you have any sense of if or when Januvia will be added to the algorithm? I know that currently the algorithm just recognizes the fact that Januvia exists, but it isn't actually on the main chart.
- Dr. Reddy: Right. That's a great question. Basically we're all waiting for long-term outcome data on a number of products, which may take three to five years. In the meantime, the reality is that most practicing physicians have to individualize, and they can't necessarily afford to wait. These are FDA approved medications, so they are available. I think most physicians understand that the algorithm doesn't mean that one shouldn't use these other medications. An alternative is the AACE roadmap, which is a little more current.
- Kelly: On a related note, do you have a sense of how much the incretins - Januvia and Byetta - might be delaying insulin initiation? Or, how might they be starting people off on therapy earlier such that more people ultimately get to advanced therapy, even if there is a delay?
- Dr. Reddy: Obviously we don't have those kinds of studies.
- Mark: What is your feeling, just on a gut level (so to speak)?

Dr. Reddy: In the UKPDS where sulfonylurea, metformin, and Ultralente insulin were used, it was clear that patients did deteriorate over time. And with the ADOPT study, in all the groups the patients' A1c levels were rising, albeit a little bit slower with rosiglitazone than the other medications.

Mark: Yes.

Dr. Reddy: So I think there is a progression that's going to be irrevocable or hard to stop. I think the sooner we intervene and the more aggressive we are, the more life we will potentially get out of oral agents before needing insulin therapy. If you follow all patients long enough, I think they may need insulin eventually, but most people with diabetes would prefer oral medication to insulin therapy at this time. That may change in the future.

Dr. Reddy speaks about the safety of Januvia:

Mark: And do you think it's true that they would then prefer basal insulin? Basal insulin grew 34 percent last year compared to 14 percent for rapid-acting analogs. Do you think that's because of simplicity?

Dr. Reddy: Bedtime insulin has been around for 20 years now and daytime sulfonylurea was around a long time ago. It was called the BIDS regimen: the concept of type 2 patients taking a bedtime insulin, waking up in the morning with a great fasting blood sugar, and then using oral agents during the day. We actually found that if you start off the day with a high blood sugar, no matter how good you are with your behavior and lifestyle, you are going to go up and down at a higher baseline, whereas if you start off the day with a good fasting sugar then theoretically your lifestyle intervention and oral agents might be more effective. Now the little wrench in this is going to be the ACCORD study.

Mark: Yes, that was our next question.

Dr. Reddy: An endocrine colleague stated that some of the patients who were in the intensive arm were taking 1.6 units of insulin per kilogram. And some of these patients, of course, weighed 90 kilograms, let's say. So they were taking about 150 units or more of basal insulin at bedtime.

Dr. Reddy: With the ACCORD press release, as you heard, there is some question about maybe one should be a little more cautious with overdoing it with just the basal insulin. Trying to use some rapid-acting insulin for mealtime coverage might make sense. I have a feeling that some people are just using basal like a sledgehammer as opposed to using it judiciously to bring the morning sugar to reasonable levels. In the end, it is best to wait for the published data before idle speculation.

Mark: That definitely makes sense. Now for a question on reimbursement: It seems like you've been incredibly successful with reimbursement. You got this through very quickly. The data were really good, but it's not like there were mountains and mountains and mountains of data.

Dr. Reddy: I think it should be seen as a good thing that we were able to get it through quickly.

Kelly: Yes, that's definitely a positive and it shows perhaps payors are giving more attention to medicine that doctors can teach and patients don't mind taking. It seems very positive that you got the strongest indication you could upfront and then have been expanding since then – expanding geographically, expanding in terms of approved indications, expanding the number of patients who have access.

- Mark: Two completely unrelated questions. The first one is a few months ago there was some noise about exfoliative skin disorders including Stevens Johnson Syndrome and Januvia. However, it was never clear how many cases of Stevens Johnson Syndrome were actually observed in patients using Januvia. Do you have any update on this?
- Dr. Reddy: Unexpected side effects are always possible whenever you launch a totally new chemical compound. When Januvia initially got approved we had just had our clinical trial experience, which was extremely clean. But as you get post-marketing experience – the press release said there were over four million prescriptions to date – you will see a much more variable spectrum of patients using the medication that are on a whole bunch of other drugs and over-the-counter remedies. So I think it was anticipated that one would see some people having allergic-type phenomena to the medication. That's to be expected, I think.
- Mark: Right.
- Dr. Reddy: Stevens Johnson Syndrome was added into the post-marketing section of the Janumet and Januvia labels. So far we really haven't seen very many cases of Steven Johnson Syndrome – maybe a handful at the most. And there were no cases in our clinical program. But again, our position is that we still need to be watchful and to keep an eye out for more of these or any different kinds of side effects.
- Mark: I know some doctors or patients may be concerned about this just because the actual number hasn't been published – but that's very helpful.
- Dr. Reddy: Because these are post-marketing and volunteer reports, it's really tough to estimate rates.

Other questions abound!

- Mark: We have an additional science question for you. One of the things that has always been a little mysterious to me is that DPP-4 inhibitors increase GLP-1 levels, but they don't seem to cause the weight loss that's seen with the GLP-1s. I have heard two different explanations for this: one of them is just that the level of GLP-1 is lower and the other one is that DPP-4 also cleaves the weight-regulating hormone PYY, counteracting the weight effects of GLP-1. Do you have a sense of which of these two is correct?
- Dr. Reddy: Yes, most likely the GLP-1 levels that are obtained are in the physiological range. No symptoms of any gastric emptying problems or satiety issues have come up. Also, sitagliptin does not cross the blood/brain barrier, so it may not be expected to have any effect on the central satiety center and so on.
- Mark: But presumably if it's preventing the cleavage of GLP-1, the GLP-1 would then act on the brain, right?
- Dr. Reddy: That's true, but if it's in the physiological range, the same thing would happen if you were a non-diabetic and you ate something: your level of GLP-1 would go up. You get a similar degree of elevation with sitagliptin. Now when you are looking at exenatide I think you are getting about eight to 10-fold the physiological level of GLP-1. You are basically getting pharmacological doses. The PYY effect, as far as we can see, has mostly been shown in test tubes. It hasn't been clearly shown to be a physiological issue.
- Kelly: Okay. Thank you. Now we also wondered, can you tell us anything about new data presented at ADA on either taranabant, your CB1 antagonist, or on Januvia or Janumet?

Dr. Reddy: I think there will be at least six or eight posters from Merck at the ADA. I think half of those will be related to Januvia and Janumet. The other half is more scientific outcomes research kind of data. And at the ACC meeting coming up in late March there will be a presentation by Dr. Ngozi Erondu on phase 3 data from taranabant. He also presented some of the data at the Obesity Society meeting in New Orleans last year.

Kelly: Wonderful. We're looking forward to both of those meetings – especially the ADA, where it seems not that long ago that Merck was a newcomer, showing the first data on Januvia. You've certainly come a long way and we thank you for all you are doing for patients and families of those with diabetes and for healthcare professionals around the world. We look forward to Merck participating even more actively in diabetes and obesity in the coming years. Thank you so much for your time. We really appreciate it.

– by Kelly Close and Mark Yarchoan

5. In the news: InteKrin's SPPARM Moves Forward

On February 25, InteKrin Therapeutics announced that it is advancing INT131, a non-TZD selective PPAR modulator (SPPARM), into Phase 2b. The double-blind trial will include multiple doses of once-daily INT131 and will have pioglitazone (Takeda, Actos) as an active comparator. Although the development of PPARs has been marred with unexpected toxicities and the PPAR class as a whole has come under fire due to side effects with Actos and particularly Avandia, we are very optimistic about the prospects of INT131. Unlike many other PPARs, INT131 was actually developed to specifically antagonize the adverse effects of the TZDs such as weight gain and fluid retention without comprising efficacy. The company's extensive preclinical data has demonstrated safety multiples that are 1-2 orders of magnitude greater than the full PPAR-agonists. In a four-week phase 2a study, INT131 lowered glucose without causing fluid retention or weight gain (data to be published at ADA). With Actos annualizing at around \$4 billion in spite of weight gain, fluid retention, potential fractures, and CHF association, we believe that there is significant medical need for a drug with similar efficacy and without these side effects.

- **Background on INT131:** This is a so called “Selective” Peroxisome Proliferator-Activated Receptor Modulator (SPPARM), designed to target insulin resistance in a manner similar to Actos and Avandia, but without the associated weight gain and fluid retention. This is accomplished by unique receptor binding pocket associations, thus selectively activating genes involved in insulin resistance, without activating the genes responsible for other side effects. INT131 was actually developed to specifically antagonize the adverse effects of the TZDs such as weight gain and fluid retention without comprising efficacy. Although INT131 is a PPAR, it belongs to a different chemical class and is not a thiazolidinedione (TZD).
- **In a four-week Phase 2a study, INT131 lowered fasting glucose without causing fluid retention or weight gain (data to be published at ADA).** Interestingly, while Avandia and Actos take a long time to exert glucose-lowering effects (typically on the order of eight to twelve weeks), INT131 appears to begin acting rapidly. The company's extensive preclinical data has demonstrated safety multiples that are 1-2 orders of magnitude greater than the PPAR full agonists. Even at over 500 times the therapeutic dose in rats, INT131 did not produce weight gain or fluid retention compared to placebo. The drug was shown to significantly increase levels of adiponectin over 14 days of treatment in healthy volunteers.
- **We believe that SPPARMs will offer significant advantages over the current TZDs and over other PPARs in development.** Although a number of companies are currently pursuing PPARs including GSK, Sanofi, Metabolex, Roche, Daiichi Sankyo, J&J, Kyorin,

Plexxikon/Wyeth, Mitsubishi Tanabe/Perlegen, and Takeda, at least some of these are “full” PPAR-gamma agonists and should therefore be expected to have similar dose-related side effects as Avandia/Actos. Others are “dual action PPARs” that like the discontinued muraglitazar activate both PPAR-alpha and PPAR-gamma; a few are “pan-PPARs” and these target PPAR-alpha, PPAR-gamma, and PPAR-delta. One advantage of dual and pan PPARs is that they may offer an improved lipid profile; safety, however, remains a big question. (Many of the genes affected by these broad-targeting drugs may have unknown effects, and some experts have suggested that the broader the target of a PPAR the higher the risk of carcinogenicity. Given the recent scrutiny of the side effects of Actos/Avandia and increased regulatory focus on safety rather than efficacy (in our view), many companies have over the past several years as well as more recently halted development of full PPARs. In our view, the recent concerns regarding the current PPARs have actually created a window of opportunity for INT131 by increasing interest in a safer PPAR, and InteKrin started, in our view, far ahead of the curve by focusing on safety and selectivity.

- **The development of PPARs has been especially challenging**, with more than 50 INDs filed and all but 2 terminated before (or after) reaching the market due to various toxicities. We underscore that INT131 is in the very early stages of testing, and if history is telling, its path to market is no sure bet. But the available data is very encouraging, and based on its selectivity we believe that mechanistically INT131 is very promising. InteKrin is not the only company pursuing SPPARMs. Another company with a SPPARM in development is Metabolex, but as we have written before we are less enthusiastic about Metabolex’s lead drugs - MBX-102 (JNJ 39659100) and MDX-2044. Unlike INT131, neither of Metabolex’s lead compounds were originally designed as SPPARMs and as we understand it, MBX-102 at least is being used in very high doses (about 200 fold higher than Avandia) presumably to compensate for low potency. We question the drug’s efficacy even at these high doses and look forward to seeing the Phase 2 results for both of Metabolex’s drugs. Bottom line, INT131 appears to have a much broader safety margin.
- **The Phase 2b trial of INT131 will be placebo-controlled and double-blind, and will include various doses of INT131 once-daily, and Actos as an active comparator.** Mouse and rat carcinogenicity studies as well as animal reproductive safety studies are ongoing and will be completed by the end of Phase 2b.

—by Kelly Close and Mark Yarchoan

6. In the News II: Launch of the Silicon Valley J&J Diabetes Institute (JJDI)

We recently attended the launch of the J&J Diabetes Institute (JJDI) in Silicon Valley, CA and were very taken with J&J’s phenomenal work to create an institute that could improve the delivery of diabetes care at the community level. JJDI is a center of diabetes learning, aimed at providing comprehensive training to the nurses, physician assistants, and diabetes educators – the individuals at the forefront of day-to-day diabetes care. The vision of this momentous undertaking is to address the “acute shortage of skills training in diabetes management at the community level.”

Another JJDI has also been opened in Japan and by mid-2008, J&J plans to open similar facilities in Beijing (opening the same week of the Olympics) and Paris (opening this summer). The fact that we only heard this idea in late 2007 is nothing short of remarkable; in our view, this is J&J at its best, harnessing learnings from other operating companies (Ethicon Endo Surgery and their Surgical Training Institute is one example of how J&J has already done this well; a Vistakon training institute is another). In short, we came away with three big picture thoughts: 1) J&J is proving itself an industry pacesetter in looking holistically at diabetes care not only as a business but also as a multifaceted

problem requiring multifaceted solutions that the company is in a strong position to address. 2) The recent J&J Barometer healthcare provider (HCP) survey suggests that HCPs have a good grasp of the state of diabetes care in their communities but are constrained from bringing about major change primarily due to a dearth of healthcare and patient resources for diabetes management. 3) “Diabetes” in high-risk underserved populations continues to spiral out of control but it’s not too late to intervene – prevention, prevention, prevention, on the primary, secondary, and tertiary levels.

- **JJDI Silicon Valley opened Friday, February 29.** The first half of the presentations was more retrospective in nature discussing the scope of the diabetes pandemic. It opened with a welcome address from JJDI Chairman Dr. Kenneth Moritsugu and a remarkable video representing a call to action by a slew of well-respected diabetes care providers. Dr. Edelman presented data from the J&J-commissioned survey of 250 HCPs (see more below) detailing their concerns regarding diabetes care at the community level. These presentations were followed by self-guided tours of the impressive facility and mock classes from JJDI faculty.
- **The JJDI had received over 4,000 requests to attend from community-based professionals before the Institute opened.** We were very encouraged by this heightened level of interest in a non-CME education program. The Institute had been in touch with the major professional societies for the aforementioned HCPs to inform them of the existence of their programs and application procedures. As at the day of the Silicon Valley launch, four pilot classes had been completed with 59 providers trained. There were 3,263 registered participants for subsequent courses, 34% certified diabetes educators, 31% registered nurses, 23% physician assistants and 11% non-specified other.
- **J&J has stepped up the state of the art (in diabetes care) to meet the state of the disease.** JJDI faculty and staff will meet with front line diabetes providers every day starting March 3. The Institute’s programs are currently geared primarily towards community based-nurses, physician assistants, and diabetes educators – *truly* the front line of healthcare that helps patients deal with day-to-day diabetes management. Who better to target with training programs with which they will be equipped to most effectively and efficiently fight the front line battle against diabetes?
- **We think the most important question about JJDI is whether or not those who most need the education be exposed to it.** The fact that the Institute will cover the total cost of attendance is enormously positive given the financial and time pressure this group often faces. That said, like everything else about diabetes, data speaks louder than words. The Institute plans to measure the impact of this program by conducting on-site pre- and post-session surveys of attitudes/awareness of attendees. In addition, J&J plans to create a virtual network of JJDI alumni whose interaction will be tracked by the Institute. From our conversations, we learned that some metrics pertaining to patient outcomes at the practices of attending HCPs and we assume A1c will feature as an important measure – we hope that glycemic variability also comes into the mix. We also hope to see emphasis on blood pressure, lipid levels, and adverse cardiovascular events amongst other complications as reported metrics to determine the degree of success of this initiative and future improvements to the curriculum.
- **The center will offer twice-weekly, two-day intensive, interactive courses to educate HCPs with innovative practice models and diabetes technology.** Courses will cover practice guidelines, standards of care, blood glucose pattern management and software solutions, communication with patients and families, reimbursement for diabetes care, and insulin pump therapy – participants actually get to test drive Animas pumps. Importantly, we saw in a sample program that insulin initiation might form a part of a rubric called “Decision points in therapy.”

Granted this was but sample program, we were impressed that it included training on the idea of pumps and therapies (including Symlin!) for type 2s. Also of note were the reimbursement classes on CGM and remote monitoring suggested as part of the sample curriculum.

- **The leadership at the JJDI is clearly a top-notch benefit that the Institute will leverage. RADM Ken Moritsugu, former Acting US Surgeon General is the chairman of the Institute.** Other luminaries on the faculty panel include Dr. Steve Edelman (UC San Diego, TCOYD), Dr. James Gavin (Emory University), Amparo Gonzalez (Emory University, AADE president), and Dr. Irl Hirsch (University of Washington) amongst many others.
- **A 250-person survey of HCPs commissioned by J&J and conducted by Penn et al examined current HCPs concerns. This was illuminating and covered the following:**
 - **The shortage of resources for diabetes care** – We believe that if Healthcare Economics was a prerequisite for graduation at the University of America, Lady Liberty would not graduate any time soon. 92% of the survey participants said more resources for diabetes management was the single action to best improve diabetes care in their community. 23% identified lack of funding for community education programs as the number one barrier (out of 12 others) to ameliorating diabetes care at the community level. 18% responded lack of reimbursement for patient education and 11% said financial cost associated with diabetes management. Responding to a question regarding factors affecting amount and quality of diabetes care received, 90% cited lack of preventative care, 84% said limited access to healthier foods and 80% said poor reimbursement for diabetes education.
 - **Plummeting health literacy among patients contributing to healthcare disparities** – It goes without saying that the best tool we have in our diabetes arsenal is self-management. Good self-management can only be achieved through good diabetes education from the healthcare team of which the patient is an integral part – quite cyclical if you think about it. Good education can only be achieved through effective communication, which engenders trust in the healthcare team. This is a good indicator why 52% of practitioners surveyed identified limited English language proficiency as a barrier to better care. Does it fall to the patient to learn to speak perfect English? No! It falls to the practice to be knowledgeable about its community and have bilingual and bicultural translators on hand. 54% of respondents pointed to the non-availability of culturally sensitive materials as an issue when counseling patients. Of course this takes us back to the first issue about resources – another cyclical conundrum.
 - **Difficulty in staying current with information and skills required to improve diabetes patient outcomes...** Eighty percent of respondents agreed that too many internists and general practitioners don't receive much needed specialized training. Eighty-eight percent of them voted for having timely and updated information on best practices and more courses on diabetes management in medical/nursing school. Over 90% of the HCPs surveyed added that streamlined, increased reimbursement for time spent with patient will improve the quality of diabetes care. There was almost unanimous agreement (97%) on the benefits of a multidisciplinary approach to diabetes management.
- **A resounding, unifying theme that came through loud and clear from the all-star panel was the need to have a greater focus on prevention especially in high risk underserved populations.** As Dr. Jaime Davidson (University of Texas) succinctly said, "Diabetes favors minorities." Native Americans hold one of the highest diabetes prevalence in the

world (50% by age 40). Per year, African Americans suffer more than 9,000 amputations, 4,000 new cases of end stage renal disease, 3,000 new cases of blindness and 400,000 hospitalizations. Hispanic/Latino American populations comprise the largest and fastest-growing US ethnic minority group. They have a diabetes prevalence 2-3 times higher than for Caucasians. What's worse? A growing number of cases are being reported in the second and third generation Hispanic/Latino Americans.

- **Cultural sensitivity is key in preventing and/or effectively managing/treating diabetes and obesity.** Davidson described an normal weight perception study that showed African American females and Hispanic American females defined normal weight as having a BMI of ~27 whereas white females defined it as a BMI of ~22.
- **Dr. Davidson's conclusion was simple, detect early, treat early, treat to target, prevent complications and save healthcare dollars.** If only the translation to reality were as simple! In particular, we hope that the insulin initiation sub-topic we saw in the sample curriculum really gets sufficient play despite J&J's lack of direct involvement in this arena. . All in all, we tip our hats, stomp our feet and loudly applaud J&J for it's continued patient advocacy clearly evidenced by this multi-year, multi-million dollar initiative.
- **And what does this mean for J&J's Diabetes Franchise?** Clearly, we believe the JJDI can't help but further build J&J's One Touch brand – the brand already has the ultra high awareness around – the JJDI should put awareness in the stratosphere! All deserved. Naturally, we imagine the impact of time at the Institute should leave some indelible positive marks on the minds of attendees. In addition to further building the J&J diabetes brands, this should make salesforce detailing more efficient as well. All in all, the JJDI should have the outcome of favorably supplementing LifeScan and Animas' marketing, which is already extremely strong. Training on J&J products, post-conference access to JJDI, access to faculty, updates on new products – win/win, undoubtedly.

—by Kelly Close and Kaku Armah

7. Conference Pearls: Advanced Technologies & Treatments for Diabetes (ATTD)

February 27-30, 2008 • Prague, Czech Republic • www.kenes.com/attd/

The first-annual Advanced Technologies and Treatments for Diabetes (ATTD) conference included one of the most impressive lineups of speakers of any conference this year. Exceeding our expectations, the conference brought us up to speed on recent developments in a number of exciting areas of diabetes technology, including closed loop systems, CGM and pumps, non-invasive BG meters, and even encapsulation of beta cells. This was a truly global conference, with 54 countries represented by the conference's ~700 attendees. There were five small exhibits by Animas (2020 pump), Abbott (Navigator and Lite), DexCom (Seven), Medtronic (Paradigm), and Roche (Accu-Chek). Below are our highlights from the meeting.

- **Throughout the conference, we were provided with a possible roadmap toward closed-loop systems.** According to Mr. Chuck Yerich (Medtronic International), the next step will be systems that suspend insulin when glucose levels are low (we've heard that Medtronic hopes to introduce such a system in the coming year in the UK - this is one of the easier regulatory pathways). During the conference, Dr. Bruce Buckingham (Stanford) showed that reliable and useful pump-suspension systems are already possible. After that, systems will be introduced that are closed-loop at night and open-loop during the day. Later, Dr. Eyal Dassau said that hybrid closed-loop systems may

be introduced that allow users to input meal information (a feed-forward system) with a discrete meal detection backup system (a safety net that responds to a rise in post-prandial glucose even if no meal information is entered). These three steps may bridge the gap from our current open loop systems to a fully closed-loop system.

- **Dr. Thomas Danne presented data from a new 40-subject Navigator study.** Patients used the Navigator in a masked phase for 20 days, followed by a 40-day unmasked phase. In all groups, there was a significant improvement in A1c during the unmasked stage, especially among those previously in poor control. The average A1c drop for patients stratified into A1cs below 7%, between 7% and 8%, and above 9% was from 6.53% to 6.23%, 7.54% to 7.04%, and 9.02% to 7.58%, respectively. Patients also reduced frequency of SMBG with the Navigator, so increased self-monitoring was not the cause of the improved A1cs. We look forward to full data release.
- **Dr. Stephanie Amiel presented some unpublished data from 10 DAFNE centers (523 patients) – more data will be presented in the coming weeks.** The A1c drop was statistically significant, but not large (value not given, but from the unlabelled bar graphs it seemed to be on the order of 0.5% to less than 1.0%). More importantly, in Dr. Amiel's view, hypoglycemia fell dramatically. Psychological test scores showed that it greatly reduced anxiety and depression. Patients diagnosed with severe anxiety or clinically evident depression showed an especially impressive benefit from DAFNE. This is a big deal from our perspective. Less hypoglycemia could well mean fewer over-corrections, with less hyperglycemia as a result... this may not have reduced A1c but the quality of life is clearly better.
- **Dr. Amiel also said that patients and healthcare providers are “too focused on A1cs,” and sometimes fail to recognize that “low A1c with frequent hypoglycemia is not good control.”** Dr. Amiel discussed the cause of hypoglycemia unawareness based on very advanced brain imaging research, and she demonstrated that patients with hypoglycemia unawareness have both a decreased stress response and a decreased inhibition of pleasure perception as compared to patients who are hypoglycemia aware. Using PET scanning to detect metabolic rate and regional changes in perfusion in the brain, as well as other technologies, Dr. Amiel's group identified the brain regions that are activated by hypoglycemia. These areas include the amygdala, posterior thalamus, OFC, brainstem, and pituitary gland. The cortical response is actually different and impaired in patients with hypoglycemia unawareness.
- **It was reiterated at this meeting that the cost of diabetes (direct and indirect) in the US has risen to \$174 billion.** It was emphasized that most of this cost is not related to the day-to-day cost of caring for diabetes, but rather that most of the cost is related to the complications of diabetes such as retinopathy, amputations, and neuropathy. Actually, “most” is an exaggeration, but \$58 billion of the \$116 billion – exactly 50%! – of the direct costs estimated were due to complications, up from 27% (\$25 billion of \$92 billion) in 2006. That kind of increase is disgraceful in our view.
- **Glycemic variability is gaining major attention, and many presenters discussed the need for large, multi-center trials like the DCCT to settle questions such as the importance of glycemic variability and the clinical benefits of CGM and CSII.** Before such a study may be conducted, Dr. Fergus Cameron argued that the diabetes community must settle on a single gold-standard metric for assessing glucose variability that is reproducible and designed with CGM in mind. One potential problem for any trial using CGM and CSII is that the products have approximately 18-month cycles, but Dr. Satish Garg argued that short product cycles will continue for years, and if such a trial is not done, we will never achieve appropriate reimbursement for CGM and CSII. We agree. Funding would clearly have to come from some industry heavyweights, government, and nonprofits, and such a trial would take a long time to plan. While we agree that a trial to test

glycemic variability would be challenging to design, that is not reason enough not to do it. Nor are short product cycles – patients could move to new technology through the trial.

- **In an excellent talk on gut hormones, Dr. Juan Frias (Animas) explained that plasma glucose is normally maintained in a very narrow range in people who don't have diabetes.** This narrow range is maintained through multiple hormones. There is a constant flux of glucose from the liver to the tissues, and this is maintained through a low insulin to glucagon ratio in the fasting state. During the fed state, a number of coordinated events keep glucose levels stable. This response is mediated by a number of hormones, including increased insulin, decreased glucagon, increased amylin, and increased incretins. All of these hormones are mismatched in people with diabetes.
- **Dr. Frias briefly mentioned the idea of putting GLP-1 or Symlin in a pump or closed loop system to better control post-prandial glucose.** He said there may be certain advantages with respect to weight loss and glucose control to having GLP-1 and amylin spike specifically at mealtimes, which would be possible if it were administered in a pump. We know from personal and anecdotal experience that Symlin works better in a pump – this isn't surprising, because this is how the body works – we just need a patient-friendly way to do this.
- **Mr. Chuck Yerich shared some of Medtronic's market research regarding integrated CSII and CGM.** About 1,350 people responded to Medtronic's survey, and the average user had been using Paradigm for several months. Patients indicated that they most frequently used the glucose sensor on the upper abdomen, lower abdomen, sides of the waistline, and thigh. The back and arms were not used by many patients. Only 5% of patients "experienced a lot of pain," and about 16% experienced "no pain" using the sensor. A majority of the patients (51%) reporting experiencing "minimal pain." A majority of the patients reported looking at glucose information more than 20 times per day. As they looked at the glucose information, 38% looked at the value, 31% looked at trends, and 23% looked at rate of change. Most patients report changing behavior after using CGM. In the above survey, 95% patients said their behavior has changed as a result of wearing the glucose sensor. Of these 95%, more than half said that they changed the timing of boluses, and about 40% said they changed food choices, types of boluses, and BG testing frequency. In the same study, patients were asked to rank the most important benefits of a glucose sensor. Patients ranked the following in order from most to least important: provides a better sense of glucose control, a sense of security, confidence to adjust therapy, freedom/flexibility, sense of well-being, and motivation to change behavior.
- **Dr. Francine Kaufman discussed the results from a pilot sensor-augmented pump study in children.** The trial enrolled 10 subjects, with a mean age of 14.5 years. Mean BG initially increased as participants began to get used to the sensor, but it improved significantly by the seventh sensor. The participants made a lot of treatment and behavior changes in response to seeing the data. Mean A1c dropped from 8.1% to 7.8% in only 30 days. Mean glucose was reduced from 167 mg/dL to 156 mg/dL. One adverse event related to irritation was noted, and one subject experienced an infection at the sensor insertion site. All of the patients completed the study and wore all seven sensors. Dr. Kaufman reviewed individual patient data to show that many of the adolescents began to consume fewer carbohydrates at breakfast and began giving insulin boluses 10-15 minutes before a meal after observing the real-time data. Dr. Kaufman underscored that the amount of clinical benefit is highly associated with sensor use, and she said that CGM can be used as a motivational and behavior modification tool.
- **Navigator was in the spotlight throughout the conference.** Abbott's symposium about the Navigator was extremely popular. The speakers at the session - Drs. Joe Bugler (Abbott, UK), Satish

Garg (Barbara Davis Center for Childhood Diabetes, Denver), and Thomas Danne (Kinderkrankenhaus auf der Bult, Hannover Medical School, Germany) - spent a considerable amount of time discussing the Navigator's predictive arrows, and the use of these arrows in adjusting bolus rates in real-time. Performance for the Navigator is consistent over five days of use. In a five-day study, approximately 80% of Navigator readings were in the so called "A" zone for all five consecutive days. We found this particularly impressive – data are often given for the "A + B" zone and this is more difficult to gauge.

- ***In silico* testing (computer simulation) is gaining acceptance with regulatory agencies as a substitute for animal trials**, and Dr. Claudio Cobelli said that this testing mechanism has the potential to greatly accelerate development and optimization of various diabetes treatments.
- **Dr. Aaron Kowalski gave a short presentation explaining that the JDRF is now fully committed to encouraging investment in next generation technologies.** JDRF anticipates \$170 million in research funding in the next fiscal year. Approximately 60% of the funding will go to research labs in the states, with the majority of the remaining 40% going to Europe. As many readers know, the JDRF is funding a large CGM trial with the aim of increasing reimbursement and acceptance of sensors. The trial has enrolled 450 patients (two cohorts – 350 patients with an A1c above 7.0%, and 120 patients with an A1c below 7.0%). All participants are above the age of eight. All three CGMs may be used in the trial – the Paradigm, Navigator, or DexCom (STS or Seven). The trial will have multiple visits at 1w, 4w, 8w, 13w, 19w, and 26w in order to optimize CGM treatment (and therefore hopefully show greater A1c improvements). Patients will receive a phone call from a healthcare provider between each visit. A1c is the primary outcome at six months for the first cohort (patients above 7.0% A1c), and the sample should have a 90% power to detect a 0.5% difference in A1c. Recruitment for the trial was completed in December 2007.
- **Dr. Bruce Bode spoke enthusiastically about the implementation of computerized insulin delivery systems in the ICU setting.** There are clear, tangible benefits to tight glycemic control in the ICU – a previous study found that for every 50 mg/dL rise in glucose, length of stay increases by an average of 0.76 days, and hospital charges go up by about \$2800. However, many hospitals struggle to control hypoglycemia in the ICU. Use of the Glucommander computerized insulin delivery system has been shown to prevent hypoglycemia while successfully keeping hyperglycemia at bay. Another study showed that hypoglycemia early on during the hospital stay is an independent risk for mortality. The benefits of tight glycemic control are more significant for stays that are longer than three days in length. In the acute coronary syndrome arena, there is better and better evidence that mortality is really a "u-shape" and that patients need to be in the 80-130 mg/dl range to minimize mortality.
- **Dr. Zdenek Rusavy briefly presented some intriguing observational data from the Czech National Register of CSII Treatment, which was founded in 1998.** On average, patients in the registrar had a 1% lower A1c after one year of pump use, starting from a high baseline of 9.5%. The improvements in A1c were similar among type 2s and type 1s. Dr. Rusavy said that the register supports the conclusion that CSII therapy is an effective type of treatment for type 2s.

—by Kelly Close and Mark Yarchoan

8. Literature Review: Increased Testing Frequency Following Medicare Expansion

Rui Li, Ping Zhang, K.M. Venkat Narayan Peter; American Journal of Public Health, February 2008

Medicare coverage was expanded on July 1, 1998 under the Balanced Budget Act of 1997 to include glucose monitors and strips for patients with diabetes who were not receiving insulin therapy. In an effort to improve diabetes self-management, the legislation also expanded diabetes management training for patients in non-hospital settings. To evaluate the efficacy of the Medicare expansion, the authors used data from the 1996-2000 Behavioral Risk Factor Surveillance System to measure the change in self-monitoring of blood glucose after the legislation was implemented among Medicare patients with diabetes who were not receiving insulin therapy. The authors found that the proportion of Medicare patients with diabetes not on insulin who checked their blood glucose at least once a day increased from 22.3% to 35.1% after the Medicare expansion. While this is a significant improvement, it is remarkable in our view that 65% of Medicare patients with diabetes not on insulin are still not checking once per day – the absence of testing, in our view, is what leads to patients not being engaged in their care and at risk for serious long-term complications. To control for environmental factors independent of the legislation, the authors also analyzed the glucose monitoring behavior of privately insured diabetes patients not using insulin as a comparison group. Although this patient population was not directly affected by the Act, there was a small but significant increase in the probability of self-monitoring from 30.3% one year before the Act to 36.8% 30 months later among privately insured patients. Much of the improvement in glycemic control in the private sector is probably due to a spillover effect from the legislation, as well as continued education on the benefits of tight glycemic control in response to the UKPDS and other long-term outcome studies. The difference in the probability of self-monitoring between the Medicare group and the privately insured comparison group after the legislation passed was 7.1 percentage points, which approximates the efficacy of the Balanced Budget Act on the target Medicare population. This significant improvement in diabetes self-monitoring underscores the importance of financial resources as well as patient awareness and education in determining how often patients self-monitor blood glucose. We believe that it is important for Medicare to further increase strip reimbursement for insulin users as well as non-users (the current reimbursement limit is three strips per day for those on insulin and one strip a day for those not on insulin), and this study supports the notion that this might be an important step towards better control nationally, and consequently, less spending down the road on complications.

- **Before the Medicare expansion in 1998, monitors and strips were only covered for diabetes patients who were receiving insulin.** The Balanced Budget Act of 1997 expanded Medicare coverage to include monitors and strips for non-insulin users (100 strips every 3 months, or about one strip a day) as well as non-hospital-based programs that encourage diabetes self-management. The outcome of the legislation was a reduction in out-of-pocket expenses on diabetes monitors and strips from 100% to 20%. The authors analyzed whether this drastic expansion of coverage for diabetes patients not receiving insulin therapy improved disease management in this patient population.
- **The authors analyzed data from the 1996-2000 Behavioral Risk Factor Surveillance System (BRFSS), which is a well-known, highly credible telephone survey of 150,000 to 210,000 adults in the United States.** The study population consisted of 9,609 adults with either Medicare or private insurance who had diabetes and were not receiving insulin. The survey differentiated between participants using oral glucose agents and those on diet control and asked how often they checked their blood glucose. The authors also examined the effect of the time-course of the legislation on the frequency of self-monitoring. Five time periods were analyzed: 1) 13-18 months before the Balanced Budget Act; 2) 0-12 months before the Balanced Budget Act (baseline); 3) the 11 month transition period after the Balanced Budget Act was signed but before it took effect; 4) 0-12 months after the legislation took effect; and 5) 13-30 months after the legislation took effect. The authors controlled for factors that may influence the

frequency of glucose monitoring, such as age and duration of diabetes, as well as gender, race, marital status, education, and income.

- **The authors found that the percent of Medicare patients not using insulin that tested their blood glucose at least once a day (as recommended by the American Academy of Family Physicians) increased from 22.3% to 35.1% after the Medicare expansion went into effect.** An improvement in glucose monitoring was first apparent during the transition period, when the probability of self-monitoring among Medicare patients not using insulin jumped from 23.5% to 28.7%. This percent increased again to 32.9% one year after the law took effect, followed by another increase to 40.1% 18 months later, averaging a 16.6 percentage gain from one year before the Balanced Budget Act was signed to 30 months later.
- **The comparison group, consisting of privately insured non-insulin users, also showed improvements in glucose monitoring after the legislation went into effect, although to a smaller degree than the target Medicare population.** The probability of self-monitoring in the privately insured group increased from 30.3% one year before the Balanced Budget Act was signed to 36.8% during the first 30 months of the Act. This is probably due to a spillover effect from the legislation, especially because Medicare is very influential in shaping the policies of the private sector. Much of the increase in testing frequency may also be attributed to continued education on the benefits of tight glycemic control in response to the UKPDS and other long-term outcome studies showing a reduction in morbidity and mortality.
- **As testing frequency improved for both privately insured and Medicare patients, the authors conclude that the specific increase in testing frequency attributable to the Medicare expansion may be as small as 7.1%, with the rest of the increase in testing frequency for Medicare patients attributable to continued education on the benefits of tight glycemic control.** Overall, this study shows that the Medicare expansion of 1998 achieved its goal of increasing glucose self-monitoring among diabetes patients not using insulin. Although it is difficult to tease out how much of the effect of the legislation was attributable to increased coverage of strips and monitors and how much was due to the mass media campaign and the self-management training programs, it appears that both of these factors influence self-monitoring behavior. Past studies have shown that frequent monitoring is critical to maintain control over glucose levels, which in turn is protective against complications.
- **We believe that it is important for Medicare to further increase strip reimbursement for insulin users as well as non-users** (the current reimbursement limit is three strips per day for insulin users and one strip per day for non-insulin users), and this study supports the notion that this might be an important step towards better control nationally, and consequently, less spending down the road on complications. We believe that the current one or three test strips limit is especially insufficient for patients who want to measure post-prandial glucose in response to a growing body of evidence that post-prandial glucose excursions and glycemic variability is an A1c-independent risk factor. Of course, there is no consensus about the importance of glycemic variability, and in our view a DCCT-type long-outcome trial may be needed to settle the issue. However, given the significant *in vitro* evidence about the dangers of glycemic variability and clinical evidence that glycemic variability predicts mortality in adults in the ICU and in kids in the PICU, we think it is imperative for Medicare to give patients tools necessary to check post-prandial glucose levels.

—by Brittany Adler and Mark Yarchoan

9. Conference Preview: American College of Cardiology 2008

March 29 – April 1, 2008 • Chicago, IL • www.acc08.acc.org

From March 29 to April 1, cardiologists from around the world will descend on Chicago for the 57th Annual Scientific Session of the American College of Cardiology. Nearly 30,000 people are expected to attend this eight-topic track meeting. This year's meeting has a particular focus on quality and value in cardiology care.

- **The quality-of-care debate will be presented by national leaders** including Dr. Donald Berwick, co-founder and president of the Institute for Healthcare Improvement, and Dr. Mark McClellan, former administrator of the Center for Medicare and Medicaid services and former commissioner of the Food and Drug Administration. Both thought leaders are expected to discuss the need for reform in payment structures, as well as describe some of the necessary quality initiatives needed to translate our existing clinical knowledge of best practices into widespread improvement of patient outcomes.
- **In the diabetes arena, ACC'08 offers significant programming and the presentation of a few critical clinical trial results.** Some major topics of interest include:
 - “Optimizing cardiovascular disease risk reduction in patients with diabetes”
 - “Diabetes and Hyperlipidemia: 2008 perspective,”
 - “Noninvasive imaging in the evaluation of coronary artery disease in patients with diabetes,” and
 - “The Impact of metabolic syndrome with or without diabetes on prognosis in the COURAGE trial.”
- **There are more and more posters that list diabetes or obesity in the title being presented** – as of late, there is a big spillover effect from diabetes at cardiology meetings and the reverse and this meeting is no exception. One poster that discusses the protective effects of a GLP-1 degradation product against acute myocardial infarction has even been designated a candidate for Best Poster of ACC 2008.
- **Other posters will also highlight important findings in diabetes.** Dr. Douwe Pons and colleagues from the Netherlands will present data from the multi-center GENDER study, which is a prospective cohort study of effects of genetic background on cardiovascular disease. The authors found that one particular genetic allele (1863T) was associated with increased risk of re-stenosis after percutaneous coronary intervention. One suggested explanation for this association is that diabetes patients with this risk allele may have altered inflammatory responses.
- **Dr. Santilli and colleagues from the University of Rome conducted a preliminary randomized, placebo-controlled trial of acarbose, an alpha-glucosidase inhibitor that improved A1c, lowered postprandial glucose, and reduced inflammatory platelet associated factors.** While this study may confirm earlier evidence from the STOP-NIDDM trial demonstrating a reduction in coronary events in patients taking acarbose, this study will likely not create the basis for any new large-scale clinical investigations or change prescribing patterns given that the findings are not tremendously novel – this is a great example of a drug that does work well but is difficult to take due to “hassle factor” – three times/day dosing, gastrointestinal side effects, etc.
- **Companies on the diabetes front are certainly looking to influence cardiologists. The ACC will feature some fascinating symposia, including** 1) “Critical Updates The Role of Atherosclerosis, Hypertension and Diabetes in Cardiovascular Disease: Call to Action for the Cardiologist” from Merck; 2) “Taking it to the Wall 2008: Reducing cardiovascular complications in diabetes and hyperglycemia” from Sanofi; 3) “Chronic Management of Obesity: A

Comprehensive Approach to Reducing CV Risk” from Merck, and 4) “Cardiovascular risk management in diabetes: A cross-disciplinary approach to the clinical challenges” from Takeda.

- **Even beyond diabetes, obesity will garner much attention at ACC’08 as global trends of obesity continue to drive cardiovascular disease rates.** Much of the data presented at ACC’08 is epidemiological in nature and confirms various morbidities associated with obesity. Important clinical data, however, will be presented surrounding the cannabinoid 1 receptor blockers rimonabant (Sanofi-Aventis) and taranabant (Merck). Dr. Leonardo Tamariz and colleagues from the University of Miami conducted a meta-analysis of weight loss clinical trials conducted on rimonabant. They will present data confirming the weight loss effects of rimonabant, while also highlighting the significant risk of depression and discontinuation of the drug due to other adverse events observed in clinical trials. Exact data regarding adverse event epidemiology will be presented at the meeting – we will be interested in seeing these numbers. We’re also very eager to see the results from a recent clinical trial of taranabant. As well, we’re very interested in assessing the exhibition floor...

—by Arjun Venkatesh

10. Diabetes Comings and Goings and Final Thoughts

- **Jess Roper**, DexCom’s Interim Chief Financial Officer, has been named Vice President and Permanent Chief Financial Officer of DexCom.
- **Erik Verhoef** joined Tandem as VP of Marketing. He was previously at Biosite and BMS.
- **Ted Greene**, former CEO and Founder of Amylin Pharmaceuticals, recently joined Tandem's Board of Directors.
- **Dave Marver** left Medtronic Diabetes to join a private equity firm in Boston. Diabetes has lost a strong advocate, at least for the moment, though we will hope private equity will see a strong uptick in diabetes investments sometime soon.

It’s been another tough month in the market, with four companies in our diabetes universe down over 30% - MannKind, Biondi, and DexCom, and only one company up – the 2007 winner, Novo Nordisk, rose 4% and is up a whopping 60% versus a year ago. Here’s to better days in the market ...

	14-Mar-08	14-Feb-08		2-Jan-08		14-Mar-07		IPO		Market Cap
GSK	40.85	43.32	-6%	50.17	-19%	54.83	-25%	-	-	121.58B
NVO	67.50	65.03	4%	63.80	6%	42.41	59%	-	-	41.91B
AMLN	25.67	28.92	-11%	36.95	-31%	38.44	-33%	14	83%	3.47B
MNKD	5.07	7.79	-35%	7.86	-35%	14.79	-66%	14	-64%	511.65M
PODD	14.57	17.75	-18%	23.42	-38%	-	-	15	-3%	385.09M
SIRT	10.16	11.87	-14%	13	-22%	-	-	10	2%	291.59M
OREX	10.81	12.11	-11%	13.94	-22%	-	-	12	-10%	290.90M
BIOD	9.99	15.34	-35%	22.65	-56%	-	-	15	-33%	235.66M
DXCM	4.68	8.28	-43%	8.95	-48%	7.34	-36%	12	-61%	138.24M
HDIX	6.34	7.44	-15%	8.45	-25%	10.46	-39%	12	-47%	114.21M

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