DIABETESCLOSEUP

*The Leading Source of Diabetes Business News*

**Triple Threat: Obesity, Diabetes, and CVD** **December 2008 • No. 86**

## From the Editor

*This year has been a rollercoaster of change, both positive and negative, in all areas of diabetes. Of course, over the past few years (and this year in particular), we feel that the discussions and realm of diabetes have really broadened to include obesity and cardiovascular disease (CVD). Or, as well like to call it, the triple threat!*

*On obesity, we give you not one, not two, but three conference pearls this issue! Even more amazing is that all three conferences (which took place within three weeks of each other in the late fall) reflected many new insights into bariatric surgery – never before have we seen QUITE this much interest in the field. As we noted in the conference commentary for the Annual Meeting of the Obesity Society in October in Phoenix (NAASO), we could not recall so much new data being presented in the span of five days. There were two key focuses at these conferences: combination therapies and bariatric surgery. On combination therapy, there were data releases from Vivus (Qnexa), Amylin (pramlintide/metreleptin), and Orexigen (Empatic and Contrave) – whew! The other conferences we write about in this report include the Cleveland Clinic Obesity Summit and 1st World Congress on Interventional Therapies for Type 2 Diabetes, which took place in Cleveland and New York, respectively, both in October.*

*We also saw a surge of interest, higher than ever before, in bariatric surgery — including gastric banding, laparoscopy, gastric bypass, gastric sleeve gastrectomy, and gastric trans-section. Surgery for weight loss has become more prevalent in the last couple of years, presumably because it is the most effective method at the moment – some studies have shown patients' weight loss to be 30%-plus, maintained over time. The perception of bariatric surgery among medical professionals and the public has also changed over the last few years, and it is now widely perceived as an effective health intervention rather than a cosmetic intervention. There is now very convincing data regarding the efficacy of bariatric surgery in resolving diabetes and other co-morbidities and reducing overall mortality. Long-term (or as we call it,* long *long-term) safety and efficacy will need to be shown before the NIH guidelines on bariatric surgery are relaxed to include a wider population, but the biggest hurdle with bariatric surgery at this stage is, of course, that it is impossible to apply for the general population.*

*As we often mention, we still believe that diet and exercise should come first. However, we know getting people to modify their lifestyle is extremely challenging (we thought about characterizing it with the word "futile" and thought the better of it, but that's what it feels like) and requires support from all levels of society, from the individual to the government. We have not yet seen the government or managed care as an industry step up particularly (read: really, at all) in this area, but we hope things will change with the new administration.*

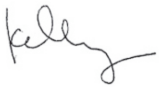
*We were lucky enough this month to interview Robert Kushner, MD (Northwestern University, Feinberg School of Medicine), the new President of the Obesity Society. Interestingly, Dr. Kushner noted that this year was the first time in the US that both the Democrats and Republicans had included obesity in their political platforms, which demonstrates the increasing visibility of the issue. Dr. Kushner expressed his desire to continue working closely with the new administration in order to help stem the obesity and*

*diabetes epidemic. In fact, there have been a lot of discussions about the dangers of obesity – 100 Fortune 500 CEOs brought together by the Wall Street Journal termed obesity the biggest public health problem of our time and the area that deserved the most action[1]. As we understand it, many obesity clinics were very moved by the visibility and attention and thought "Finally!" We sort of have that feeling too. Let's see…*

*Meanwhile, the FDA has put out its official word on cardiovascular outcome trials – we think the agency is at risk for stifling innovation. The updated full guidance document is at http://www.fda.gov/cder/guidance/8576fnl.pdf. We were surprised and disappointed that the document did not reference the UKPDS 10-year follow up data (Holman, NEJM, September 2008) as we think that is the most relevant of the papers to come out this year in terms of thinking about type 2 diabetes and cardiovascular complications. We agree risk should be managed; we just don't think risk should enable an agency to slow industry down to the extent it has. Noted regulatory experts with whom we spoke estimated that of the 100+ companies that received the new guidance in a letter from the FDA, over ninety would be on a slower, considerably more expensive path to approval and that over a dozen programs would be halted – we're all for halting programs that are too risky, but this is overkill, in our view.*

*We're sorry to end 2008 on such a down note, especially when there are over eight million patients in the US alone that are failing their diabetes therapy, and when, at last count, $58 billion was spent annually on treating preventable complications. One silver lining is that there are drugs that will likely emerge from this initiative as cardioprotective, which would be a first, and certainly a positive for patients and healthcare providers. In the meantime, we've fervently hoping the FDA doesn't throw out the baby with the bathwater.*

*Sincerely,*



*Kelly L. Close*

## Major Headlines



[1] While there is always the worry this is lip service, we've still come a long way to get that kind of attention. We hope that the obesity portfolios do get some renewed interest and that regulatory issues at FDA don't prompt a wholesale move by investors and companies out of obesity therapies.

## In This Issue



## Blogwatch

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

- **December 14:** Diabetes Causes More Amputations than Landmines — Are You Scared Yet?
- **December 13:** Your Love of Junk Food May be Inherited — and Our Nation's Obesity Epidemic is Being Passed on to the Next Generation.
- **December 12:** New Physical Activity Guidelines for Americans — Get in Your Hour per Day …

- **December 10:** Problems at FDA Prompting Slowdowns in Development — Should Patients Accept This?
- **December 8:** TV Ads Contribute to Childhood Obesity

## Videos

Below is our favorite video in diabetes this month:

- "Governor Perry Challenges Governors to Participate in 'Capitol Steps'" http://www.youtube.com/watch?v=DMxs4WCALyM

## Coming soon in DCU…

This past quarter has been a whirlwind conference season, and we will be taking a break before reporting from the JP Morgan conference in January 2009. Stay tuned…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## 1. Quotable Quotes in Diabetes

**Obesity and the regulatory environment**

*I am very concerned about the current regulatory climate regarding approval of obesity and diabetes medications. The need to conduct long-term clinical trials regarding cardiovascular and neurologic/psychiatric risk will significantly hinder investment in R&D for new agents. At a time where we are facing an epidemic of obesity and diabetes, I fear that pharmaceutical companies will choose not to launch new clinical trials. We need to work with the FDA to revisit cost and benefit issues.*

— Robert Kushner, MD (Northwestern University Feinberg School of Medicine, Chicago, IL), the new head of the Obesity Society, characterizing his reaction to new drug agents and the current regulatory climate.

**Focusing on meal estimation**

*"With the amount of time and money spent on insulin, we really should be spending more time on meal estimation given the emphasis on matching insulin to meals."*

— Jonas Kildegaard, PhD (Kildegaard Consult, Frederiksberg, Denmark) discussing the impact of real life variables within therapy tools, patient physiology, and patient compliance at the 8th Annual Diabetes Technology and Therapeutics Conference.

**Early intervention**

*"If provocative tests were performed before full onset of diabetes, we could detect metabolic abnormalities early."*

— Wayman Wendell Cheatham, MD, FACE (US Navy, Bureau of Medicine and Surgery, Washington, DC) noting during his presentation at the 8th Annual Diabetes Technology and Therapeutics Conference that earlier detection would allow earlier intervention.

**Reimbursement lacking for obesity treatment**

*"Similarly, physicians are often not reimbursed for the care of patients who are being treated for obesity. These are essentially out-of-pocket expenses and knowing that obesity is associated with over 40 medical problems affecting nine different organ systems, it is ludicrous that obesity is not covered as a health benefit for preventive care and primary care."*

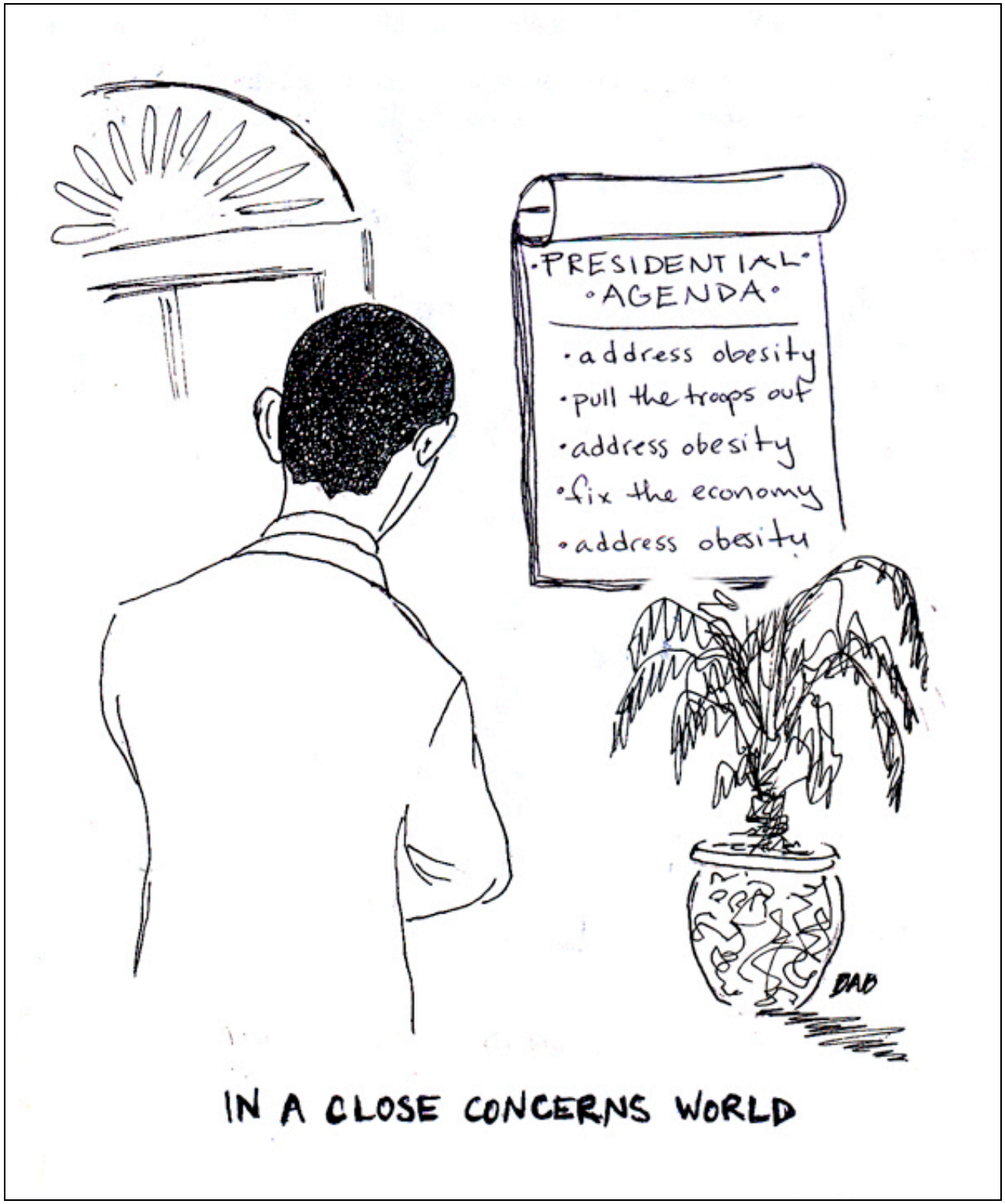
— Robert Kushner, MD (Northwestern University, Chicago, IL) commenting on the need for greater reimbursement for physicians who treat obesity.

**What is the safety bar?**

*"Unfortunately there isn't clear guidance about safety like there is with efficacy. I think what we've learned from going through the FDA's past decisions, is that the FDA's all about risk-benefit. If you have a very large benefit, they'll be able to accept a greater amount of risk."*

— A comment made during the Vivus, Orexigen, Genaera, and Athersys session at the RBC capital markets day in response to a question on what safety bar the FDA has set for obesity pharmacotherapy.

## 2. diaTribe FingerSticks




*-by Daniel A. Belkin*

## 3. DCU Company Watch

- **Arena — R&D update on lorcaserin progress and GPR119 (GDIR) agonist:** Arena provided an update on its R&D programs with a particular focus on the progress of its lead obesity candidate, lorcaserin, on December 15. Phase 3 data from the BLOOM trial is scheduled for release in March 2009 with results from the BLOSSOM trial following about six months later. The NDA filing will include 16 studies. The two pivotal trials will be BLOOM and BLOSSOM. It will also include supportive and dose-finding studies (phase 2a and phase 2b), an ECG study, an abuse liability assessment, and several safety PK/ADME studies. Two future studies will be included as well: BLOOM-DM and a mechanism of action study. These latter studies are not considered critical path for NDA filing. In response to the recent turmoil over CB1 antagonists, Arena is also carrying out depression/suicidality assessments. BLOOM-DM is expected to be completed by June 2009 while data from the mechanism of action study is anticipated by the end of 2009.

  During the call, Stephen R. Smith, MD (Pennington Biomedical Research Center, Baton Rouge, LA) suggested that lorcaserin was leading the field in terms of proximity to market with commercialization expected at the end of 2009. On the chart shown by Dr. Smith, Orexigen's Contrave (naltrexone and bupropion) was expected in 2010 followed closely by Vivus's Qnexa, Orexigen's Empatic (zonisamide and bupropion), and GLP-1 analogs in 2011. When asked in Q&A about GLP-1 for obesity, management said that the GLP-1 system is not as potent in body weight change. Management also pointed out that GLP-1 requires an injection, which it characterized as "a potential negative in the obesity space." The last pharmacotherapy on the chart presented was pramlintide/metreleptin in 2012. Arena management was keen to note during Q&A that lorcaserin was by no means an attempt to develop a "safe Fen-Phen," though they did indicate that they would consider a phentermine combination post-approval. Safety questions represented a major part of Q&A; management said that it was looking to rule out a small deleterious effect of lorcaserin on valvulopathy and that it would likely need both BLOOM and BLOSSOM data to prove non-inferiority conclusively – many had expected previously that could be done with BLOOM alone.

  Dr. Dominic Behan gave an update on Arena's G protein-coupled receptor (GPR)119 agonist (GDIR agonist), a receptor expressed on beta cells. GPR119 is another cell receptor that potentiates glucose-sensitive insulin release in beta cells and acts as an incretin secretagogue in the small intestine, where it improves both GLP-1 and GIP secretion. Coinciding with the call, Arena released a press announcement that Ortho-McNeil Janssen, its partner for APD 597, a GDIR agonist, has moved this candidate into phase 1 clinical trials. As a reminder, it dropped APD668, another in the same class earlier this year.

- **Vivus — Encouraging results from EQUATE and DM-230 Qnexa trials:** On Friday, December 12, at its annual analyst day, Vivus announced results from two big trials of its weight loss candidate Qnexa (phentermine and topiramate CR): its 28-week, phase 3 EQUATE trial and the phase 2 DM-230 trial. The EQUATE study demonstrated superior weight loss with Qnexa as compared to the individual components of the drug and placebo. Subjects treated with full-dose (15 mg phentermine/92 mg topiramate CR) and mid-dose (7.5 mg phentermine/46 mg topiramate CR) Qnexa had weight loss of 9.2% and 8.5% respectively (19.8 lbs and 18.2 lbs), while the placebo group saw 1.7% (3.3 lbs) weight loss. Qnexa was reportedly well tolerated, and no serious drug-related AEs were seen in the study. The results from the year-long DM-203 study demonstrated the efficacy of Qnexa in improving glycemic parameters in obese type 2 diabetics. Patients treated with the full dose of Qnexa showed an impressive A1c decrease of -1.6% over the year, while the placebo group saw a -1.1% decrease (baselines: 8.8% Qnexa, 8.6% placebo). This was accompanied by a 9.8% decrease in body weight. The company was predictably optimistic during its analyst meeting and confirmed that an NDA filing would take place by the end of 2009. They plan to pursue a diabetes indication once the

obesity filings go through. Overall, we do believe combination therapies are the way to go to treat obesity, and we are intrigued by the idea that tolerability will be better due to lower dosing than would otherwise be given, but questions still remain in our mind about long-term safety.

- **Athersys — Lead obesity compound remains stuck:** President and COO William (BJ) Lehmann led a presentation on Athersys at the Lambert-Edwards SMID-West Stock Conference on December 11. The lead product candidate for the treatment of obesity is ATHX-105, a 5HT2C receptor agonist. An IND to move ATHX-105 into phase 2 trials was filed in 3Q08, and the FDA responded with a request for additional information putting the program on partial clinical hold. Three possible outcomes were suggested: running additional studies, suspending the study, or terminating further development. Lehmann also briefly mentioned the possibility of developing their MultiStem, undifferentiated human stem cells obtained from bone marrow or other non-embryonic tissue sources, product for use in treating diabetes. Currently, it is being developed for use in bone marrow transplant support, acute myocardial infarction, and stroke. The company hopes to expand this product to treat other autoimmune diseases, including diabetes, to help modulate the immune system response. The ability of the MultiStem cells to minimize the inflammatory reaction has applicability to a wide range of diseases: immune system disorders, autoimmune diseases, oncology, and others. Notably, in this tough economic environment the company has capital to last them into 2011.

- **Edwards Lifesciences — Valuable details provided on DexCom work:** Carlyn D. Solomon, Corporate VP, Critical Care discussed Edwards' ongoing work in glycemic control within the critical care setting during an investor call on December 11. We believe this area is extremely important and we are glad to see work moving ahead. Tight glycemic control improves clinical outcomes of critically and noncritically hospitalized patients, reducing the occurrence of mortality and complications such as infection. Despite strong evidence supporting intensive glycemic control in hospitalized patients, the majority of patients with diabetes and stress hyperglycemia in the ICU are treated with sliding scale insulin coverage, a practice that has repeatedly been shown to produce poor results. We believe continuous glucose monitoring in the ICU could help address this major unmet need.

  Solomon estimated the market for glucose monitoring in critical care settings at $200 million annually, adding that if Edwards is able to bring a good product to market, this figure could double. Edwards estimates that the current critical care glucose monitoring market was made up of 2.5 million patients in Europe and US. Solomon suggested that with a good Edwards/DexCom product on the market, the growth rate of this market could expand significantly. Edwards plans to complete clinical studies in 2H09 and introduce a first generation product in Europe by 4Q09. Characterizing the bottom line impact of the DexCom partnership, Edwards management said it expects meaningful sales and earnings contribution from 2010 onward. In our view, this partnership could move Edwards' critical care franchise into an advantageous position given the extensive opportunity for cross learning that DexCom brings to the table from its ambulatory CGM segment. Likewise, DexCom could increase the efficiency of the production of ambulatory sensors based on transferable learning from production of the hospital sensor.

- **XOMA — New pre-clinical data contributes to acceleration towards phase 2 for XOMA 052:** At the RBC Capital Markets Healthcare Conference in New York on December 10, XOMA management discussed positive preclinical data on the use of XOMA 052, an anti-IL1 beta monoclonal antibody currently under investigation for the treatment of type 2 diabetes. Management showed that treatment with XOMA 052 increased insulin production, proliferation of insulin-producing islet cells, decreased islet cell death, reduction in peripheral insulin resistance, and lower cholesterol levels. Additionally, these preclinical data were obtained in the absence of weight gain and hypoglycemic events. With current preclinical and clinical data, management felt confident enough going forward to announce publicly that 2Q09 is the target timeline for initiation of phase 2 clinical

studies. During the November 11, 3Q08 call, the company had only indicated that phase 1 clinical data should be available by mid 2009, but phase 2 trials would be initiated soon after. This new 2Q09 target certainly appears to show that XOMA 052 development is proceeding well ahead of schedule in our view.

Regarding anticipated commercial use of the drug candidate, President and CEO Steven Engle suggested that XOMA 052 would likely start out as a more tertiary treatment. However, if it is indeed able to reduce/prevent islet cell loss and is validated as a disease modifying therapy, the idea is to move it to first line therapy where use in pre-diabetes could potentially preserve beta cell function and delay the onset of type 2 diabetes. The question is whether you can go far back enough in the disease continuum such that there is a pre-diabetes opportunity. On this question, Engle noted that they would need to be a lot further in to the marketing and launch of the drug before performing that kind of study. He noted that the company was planning to look at a type 1 application of the drug in the future.

- **Eli Lilly – Exenatide once-weekly still on track for 1H09 submission:** At the company's analyst day on December 10, Dr. Steven Paul, EVP, Science and Technology, indicated that recent discussions with the FDA supported the use of data from the ongoing extension of the DURATION-1 study (using commercial scale exenatide once weekly) to demonstrate comparability of intermediate scale product produced at the Alkermes facility to commercial scale product being produced at Amylin's Ohio facility. As a result, the NDA submission for exenatide once weekly (EOW) remains on track to be completed by the end of the first half of 2009. This is a win on both regulatory and economic/cost savings fronts and clearly comes as welcome news as it significantly lowers the regulatory risk associated with performing a de novo study. Dr. Paul also noted that DURATION-2 completed enrollment last quarter and that results are expected in mid 2009. As a reminder, this 500-patient superiority study compares EOW with TZD and DPP-4 inhibitor therapy. DURATION-3 enrollment is also complete. This 450 patient trial is comparing EOW with Lantus; results are expected in 3Q09. Finally, in 4Q08, DURATION-4 enrolled its first patients – as a reminder, DURATION-4 compares EOW as monotherapy to metformin, TZD, or DPP-4 inhibitor therapy.

  Dr. Thomas F. Bumol, VP, Biotech Discovery Research, discussed Eli Lilly's earlier-stage pipeline including the company's GLP-1 analogs and basal insulin. GLP-1 Fc (LY2189265) is a novel engineered Fc fusion protein. It is currently in "seamless" phase 2-3 clinical trials for diabetes that began earlier this year. This method of carrying out a trial, Dr. Bumol explained, combines elements of a phase 2 dose ranging study to a phase 3 safety and efficacy study. The second candidate, GLP-1 PEG (PEGylated GLP-1) is in phase 1. Both candidates are intended to be once-weekly diabetes therapeutics, highly water soluble, and formulated for pens and small gauge needles. It is notable in our opinion that both of Eli-Lilly's in-house GLP-1s are analogs of human GLP-1, rather than exendin-4. Therefore, it is reasonable to expect that these drugs will have relatively different properties than exenatide once weekly and will be more similar to Novo Nordisk's liraglutide and Roche/Ipsen's taspoglutide, which are also GLP-1 analogs. We will be very interested to see if Lilly's in-house GLP-1s are a back-up strategy to EOW or whether they will someday compete – for now we would assume they are quite far behind and that a 2% A1c reduction will be hard to beat – although if they had significant ease of use or tolerability advantages, that would be a plus for Lilly.

  Dr. Bumol also outlined exciting details for the company's next generation basal insulin currently in phase 1: less glycemic variability, less hypoglycemia risk, and better patient control overall. The absence of a long-acting analog has been a major gap for Lilly as Sanofi and Novo Nordisk have built up this class to over $3 billion in sales – Lilly sounds like it is very focused on developing this compound. In general, it's excellent seeing that the insulin companies are again working on next-

generation products, after the introductions of Humalog (Eli Lilly), Novolog (Novo Nordisk), Lantus (Sanofi), Apidra (Sanofi), and Levemir (Novo Nordisk) in 1996, 2000, 2001, 2004, and 2005.

On the inflammation front, an area receiving a fair amount of attention by pharma/biotech, Eli Lilly is developing an anti-IL1 beta antibody for which positive proof of concept has been clinically achieved. It is currently in phase 2 planning.

- **Cerep — Enters licensing agreement with Sanofi-Aventis for development of NPY-1:** On December 10, Cerep entered into a licensing agreement with Sanofi-Aventis for development of its Neuropeptide Y (NPY)-1 receptor antagonist, which is currently in preclinical studies. Under this agreement, Cerep will receive milestone payments linked with the development of the drug as well as reimbursement for certain costs. No further details were given by either company. Cerep has developed an in vitro screening method to help identify the most promising drug candidates early on. NPY is a peptide found in the brain and autonomic nervous system associated with energy balance. In particular, NPY-1 receptor and NPY-5 receptor are known to stimulate feeding, and Shionogi is developing a NPY-5 receptor antagonist for treatment of obesity. Interestingly, Cerep and Sanofi will be developing its NPY-1 receptor antagonist for treatment of type 2 diabetes although the role of the NPY-1 receptor in diabetes has not been extensively studied. At least in the US, the majority of individuals with type 2 diabetes are obese, and it appears that it is this arm of the disease that the NPY-1 receptor antagonist is meant to target.
- **Merck — Moves three Januvia franchise compounds into phase 3:** Merck held its Annual Business Briefing on December 9, during which Dr. Peter Kim, President, Merck Research Labs, provided a number of interesting updates in the company's diabetes and obesity pipeline. Overall, Merck appears to be further strengthening its focus on patient and HCP convenience by emphasizing combination compounds and once-daily dosing. As of 3Q08, the stellar global marketing and sales execution was running at full steam as the Januvia franchise annualized $1.9 billion in its eighth quarter on the market; Merck is investing enormously in this franchise while relishing its status as the sole DPP-4 inhibitor approved in the US. The three compounds that have entered phase 3 at the end of 2008 include: 1) the fixed dose combination sitagliptin (Januvia) with pioglitazone (Actos) (MK-0431C), which has an anticipated FDA filing date of 2011; 2) extended release Janumet (enabling once-daily dosing) with an anticipated FDA filing date of 2011; and 3) a Januvia/simvastatin (MK-0431D) combination with an expected 2010 FDA submission date. Trials for the latter two will officially begin in 2009. Simvastatin (aka Zocor) is a now-generic statin that was developed by Merck. Merck also showed an updated pipeline with a number of early-stage and undisclosed diabetes drug candidates, including two in phase 2 for diabetes, four in phase 1 for diabetes, and one in phase 1 for obesity. The phase 1 obesity compound is the sole clinical obesity drug in development at Merck after taranabant was dropped in phase 3 earlier this year. By our accounting, Merck continues to optimize the pipeline; it dropped three phase 2 compounds in the last year (two diabetes and one obesity) and three phase 1 compounds.
- **Amylin — Monotherapy delayed but regulatory news improving:** Amylin, the makers of Byetta, released a statement with Eli Lilly on December 8 saying that the FDA review of Byetta for use as a monotherapy is not likely to be complete by the end of 2008 and may extend into 2009. This news does not come as much of a surprise as Amylin currently has several label decisions on the table with the FDA: a pancreatitis warning, Byetta as a monotherapy, data from adolescents on Byetta, and data on Byetta taken with oral contraceptives – we assume at least the first two will be taken together and given that the FDA is resource-constrained, we don't expect they would address both of these by the end of 2008. Importantly, it sounds like the company has not received any requests for additional studies in connection with Byetta monotherapy. We believe that the delay may be connected to the FDA's efforts to integrate the pancreatitis studies with the monotherapy approval process, and we do

not see this delay as damaging for Byetta in the long term. We also continue not to be worried about pancreatitis as we believe the FDA is getting some real data from healthcare plans that will be beneficial in showing no increased risk of pancreatitis with Byetta.

In other news, we understand that Amylin was asked to do a CV meta-analysis with Byetta as was most of the rest of the industry that has a diabetes drug in clinical trials or has been submitted for approval. Unlike many companies, this is one hurdle Amylin should be able to clear rather easily as we are fairly certain that by using Byetta data, Amylin could easily prove "no harm" without any additional trials. In fact, based on limited data from ACCORD, we believe the drug may even be cardio- protective, which would be a major positive for the company given the current regulatory environment.

- **BMS/AZ — Enter development and commercialization agreement for dapagliflozin in Japan:** On December 8, Bristol-Myers Squibb and AstraZeneca announced the expansion of the scope of their collaboration on dapagliflozin, an SGLT-2 inhibitor, to include development and commercialization of the drug candidate in Japan. Under the terms of the agreement, AstraZeneca will have operational and cost responsibility for development and regulatory activities while BMS will be responsible for manufacturing and booking sales of the drug. Both companies will market the drug in Japan sharing commercialization expenses and splitting profits equally. In our view, the expanding collaboration in drug development between these two companies indicates things are moving ahead of this and their DPP-4 inhibitor (Onglyza) partnership – also, the diabetes-related opportunities in Japan certainly appear to be expanding. Having a co-development partner is beneficial from a risk mitigation standpoint - we will be eager to watch the companies working together the closer to market they come.

- **Arena — Mediocre phase 2b data on lorcaserin:** On December 8, Arena announced the publication of complete phase 2b data for lorcaserin, a selective 5-HT2C agonist, in The Obesity Society's journal, Obesity. Top line phase 2b data had previously been released at the ADA meeting in 2006 and showed dose dependant weight loss with three doses tested. This 12-week study achieved its primary endpoint of change in body weight from baseline to day 85 in all groups. The proportion of completers achieving ≥5% of initial body weight were 12.8%, 19.5%, 31.2%, and 2.3% in the 10 mg daily, 15 mg daily, 10 mg twice daily, and placebo groups, respectively. There was no exercise component to the trial. In our view, it is disappointing that such a low percentage in each group achieved this low 5% weight loss threshold and that less than 20% in the once-daily options achieved this goal. Taking into account the caveats with doing comparisons between separate trials (with different mechanisms of action, different enrollment criteria, different populations, different lengths), we note for context that pramlintide/metreleptin phase 2a data (24 weeks) showed average weight loss of 12.7% (N = 139) in completers. Even in the ITT-LOCF group, pramlintide/metreleptin users achieved an average of 10.8% weight loss (N = 177). We would also characterize the primary endpoint of this study as a very low threshold. The study was powered to detect a 3 kg difference in mean weight change from baseline for each dose. On adverse events, headache, nausea, and dizziness were the most frequent ones observed. Nine patients in the 15 mg twice-daily group, five in the 10 mg twice-daily group, one in the 10 mg daily group, and three in the placebo group withdrew due to adverse events. Five patients withdrew due to lack of efficacy.

- **Alkermes — Focused on exenatide once-weekly for near-term growth:** Chairman Richard Pops presented an update on Alkermes at the JP Morgan SMid Cap Conference on December 5. For near-term growth, Pops focused on exenatide LAR, which has completed phase 3 studies. He characterized it as a "potential blockbuster for type 2 diabetes" (we agree – the combination of the A1c drop, the weight loss, the glycemic dependency, and the blood pressure drop is unprecedented) and highlighted the extensive safety and efficacy data that has been collected. As a reminder, LAR

prompted an impressive 2.0% A1c reduction from an 8.5% average baseline in pivotal phase 3 trials. It bodes well for exenatide LAR that exenatide was included in the recently-revised ADA/EASD guidelines – we believe earlier, more aggressive therapy will be one major outcome from the new guidelines as will combination therapy sooner and over a longer period of time. And that's interesting – earlier, aggressive therapy won't ensue because it's a new idea. It will ensue for three reasons in our view: it's captured the imaginations of thought leaders who are talking about it in a big way and there are now easier-to-take therapies (especially Januvia and Byetta, at least in the US) that have a much more tolerable side effect profile than have other therapies in the armamentarium and most importantly, ten-year follow up data from UKPDS showed conclusively the value of metabolic memory. So, it's now easier to persuade patients to start earlier. We think when LAR comes out, as long as the hassle factor isn't too high, the once-weekly application will convince a whole new set of patients to step up. And Alkermes surely wins - notably, LAR will be profitable for Alkermes from the first sale as the company will receive royalties based on the agreement made with Amylin/Eli Lilly. There is a lot of excitement about this drug launch, especially after Lilly, Amylin, and Alkermes calmed those worried about the submission, noting that the FDA was fine with the partners demonstrating comparability through DURATION-1 data. More on that above (See Eli Lilly Company Watch).

- **Merck — $2.4-$2.7 billion in Januvia worldwide 2008 sales expected:** A call led by CEO and President Dick Clarke and CFO and Executive VP Peter Kellogg on December 4 that preceded the annual analyst meeting (see above) reaffirmed guidance for 2008 and provided guidance for 2009. Management emphasized that Januvia and Janumet have performed well in the market, and 2008 worldwide sales are expected to be between $2.4 and $2.7 billion. By way of comparison, it took the top-selling diabetes drug on the market today, Lantus, nine years (34 quarters) to reach sales of this magnitude, compared to 13 quarters for Merck, or about three years. And Lantus is the biggest success story in diabetes launches in modern times – we expect Januvia to take this coveted top-selling diabetes spot after 4Q08 results come out – it is fighting neck and neck with Takeda right now. After the third quarter, Sanofi's Lantus has sold $2.66 billion to date, where as Takeda's Actos had sold $2.68 billion. Could anything be closer!? Now the wild card is currency – we're using average 90-day currency rates to get to dollar equivalents, but those are just estimates.

  Clarke indicated that Merck expects strong product growth for Januvia and Janumet in 2009, but expects this growth to be offset by the difficult economic climate. On a related note, we recently learned that Merck is planning a large trial to assess the effect on long-term treatment with sitagliptin (Januvia) cardiovascular outcomes in patients with type 2 diabetes and baseline A1c between 6.5%-8.0%. This study is expected to enroll an impressive 14,000 patients and will start in December 2008 with an estimated completion date around January 2015. The primary endpoint in this study will be cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina. Commitment to R&D was indicated during the financial portion of the call when Kellogg stated that Merck was going to be focusing on operations and its pipeline in 2009. We assume that there is a decent chance that Januvia could be found to be cardioprotective – we'll look forward to discussing the ins and outs or this trial over the next seven years (seven years! That is longer than Close Concerns has even been around) and we can't wait to see what it is named, who is enrolled, etc. Enrollment is a particularly interesting question – ACCORD made the study design choice (an error, in our view) of enrolling patients with pretty advanced diabetes, guessing that this population would have cardiovascular events faster, thereby enabling fewer participants and a shorter trial duration. As it turned out, the population they enrolled probably wasn't generalizable. The size of Merck's trial should enable them to enroll a patient population with lower baseline disease incidence; we assume that Merck will use at least some part of the population who has a short duration of diabetes, so that it can show results in that population. The challenging part, of course, is that it will take a long time

before events emerge in that part of the population – this is great overall as it means people are getting on therapy earlier and staying healthier longer, but it is difficult from the perspective of the company trying to prove reduced complications.

- **Home Diagnostics — Reinforcing what is known about the company and the market:** On December 2, Home Diagnostics (HDI) CEO Dick Damron gave a presentation that was mostly a general overview. There were three key new tidbits we picked up from the presentation: 1) they have increased prices on meters and strips; 2) they have submitted for approval in the EU and expect to be distributing products there starting in 2010; and 3) Damron mentioned that HDI will grow faster than the market due to managed care gains - we are surprised at this, since we view HDI as strongest in uninsured and underinsured patients. When asked if it is benefiting from the current weak economic environment, since it is the "value" player, Damron said yes that anytime there is pressure on the healthcare system, HDI stands to gain, but he did not go into details. Overall, his talk was reinforcing what is known already about HDI and the market. He emphasized the size of the blood glucose meter market and said that HDI has a unique co-branding strategy that he believes can help the company make inroads against major branded meter companies. He mentioned the strength of the company's pipeline, which has enabled the release of a new product every 24 months and called HDI the "value" player in the market. Damron emphasized that the release of the new 'no-coding' meters was a big step for the company, and he puts them at or above the level of branded players. Lastly, he spoke about the company's growing strength in emerging markets (today representing 11-12% of the company's revenue), which he views as a major source of growth in the future.

- **DexCom — Update on third generation sensor, expansion, reimbursement, and partnerships:** CEO Terry Gregg presented at the Piper Jaffray Healthcare conference on December 2 in New York. In a stirring talk, Gregg provided a timely update on ambulatory sensor development, noting that the PMA supplement for the third generation DexCom sensor has been filed and a response from the agency is expected in 1Q09. The combination Animas pump/DexCom sensor is expected to be available as soon as the middle of next year (if they achieve this timeline, from our view, that is really quite something, given that the agreement was just signed in January, 2008). We expect both new products to prompt greater demand – it's been hard to compete against Medtronic's integrated pump-sensor combination and there are elements of the new system that will be viewed as major positives by users – things like trend arrows, user-settable alarms, etc. We also expect the Insulet combination product to follow after Animas. Regarding recent CE Mark approval and European expansion, Gregg noted that sensors should ship to the EU later this month. In addition to regular CGM use, we believe an international market exists for part-time CGM use (diagnosing patterns, medicine efficacy, etc.) as well as CGM use in clinical trials. Though he would not give specifics as to which countries, we assume Western Europe would be a major target.

  CFO Steve Pacelli offered further detail on the recent agreement with Edwards Lifesciences for the hospital glucose sensor that was announced during the 3Q08 call. In aggregate the deal provides DexCom with $37 million over the next two to five years. Over the next 18 months, $10.5 million will be paid to offset R&D costs for the first and second-generation hospital sensor programs, aiding cash flow management. On receipt of CE Mark, FDA approval, and Japanese approval (for the second generation product) another $13 million will be paid; timing was estimated in mid/late-2009 to 2010. In terms of the back end commercialization aspect of the deal, we see two possibilities with either DexCom or Edwards manufacturing the sensors. The current likely scenario has DexCom manufacturing sensors and will involve a transfer price (which we assume would be at least equal to the cost of the sensors) and 10% profit sharing. This is higher than we had originally anticipated since we hadn't realized a mark-up would be reflected in the transfer price. With expanded manufacturing capacity, if Edwards takes over manufacturing, DexCom and Edwards will switch from a profit

sharing system to a royalty system with 6% royalty on top-line, worldwide sales of disposable sensors paid to DexCom.

- **MannKind — Anticipating positive new Afresa data in mid-December:** In a discussion at the Piper Jaffray Healthcare Conference on December 2, CEO Al Mann led a discussion on the development of its inhaled insulin drug candidate, Afresa. As always, Mann sounded optimistic about the 16-week MKC-TI-117 study comparing Afresa to Humalog in subjects on Lantus basal insulin. This study is intended to show a more accurate comparison of the A1c effect of Afresa versus Humalog for patients on Lantus in patients with type 1 diabetes. As a reminder, this trial will use CGM to obtain data about time spent in zone – we think it is fantastic that the company is using CGM as this will enable much better analysis of when the patient is in the zone. On the partnership front, Mann noted that serious negotiations will not begin until after NDA submission (expected by January 2009). He characterized building the sales and marketing approach for Afresa, and making progress in the rest of the world market (presumably this means regulatory and reimbursement advances) as two major focus areas for the company. During Q&A, Mann mentioned that MannKind has not received any FDA letters regarding meta-analyses/clinical trials to evaluate cardiovascular risk of new type 2 diabetes drugs – if we remember correctly from the meeting, insulin was exempted from this FDA requirement. MannKind has funding for 1.5 years, barring additional expenditures, which Mann cited as the reason they were not rushing to partner. In a follow up announcement, MannKind revealed that positive results were achieved for their two-year Afresa safety study (MKC-TI-030) and their one-year efficacy trial in patients with type 2 diabetes (MKC-TI-102). Results are expected to be released in mid-December. NDA submission is planned for early 2009 (slightly later than its end-of-2008 forecast, though not by much), and negotiations with the FDA are reportedly proceeding on track. (Ed. note: Mannkind presented phase 3 results on December 18 for studies 102 and 030 – it proved non-inferiority but did not show a superior A1c – that is not said to be required for approval but some had been led to expect it. More details to follow in DCU #87.)

- **ConjuChem — New data announced on PC-DAC GLP-1:** On December 3, ConjuChem announced phase 2 results for its PC-DAC GLP-1 program. In short, the best placebo-adjusted results from two phase 2 trials were a 1.0% A1c reduction (baseline between 8.0% and 8.6%), weight loss of 2 kg vs. a 0.4 kg reduction in placebo, and moderate nausea for 23% of the treated group. The two trials tested two doses: a once-weekly trial and a twice-weekly trial. Overall, the company seemed to cite tolerability as the biggest advantage. We found the results less compelling than results for other GLP-1 programs including Amylin's LAR, particularly from an efficacy perspective (the A1c drop for LAR was 2.0% as a reminder) although we did view the 31-gauge needle as a positive, and we also believe significantly lower nausea would be a major advantage for a competing GLP-1. Moving into phase 3 would be the next step, which the company seemed ready to announce but didn't. They mentioned on their conference call that they had received CV guidance from the FDA but did not speculate on how it might affect their phase 3 plans. ConjuChem also announced a supplier partnership with Novozymes Biopharma, in which Novozymes would supply its recombinant human albumin, Recombumin, for the development and commercialization of ConjuChem's PC-DAC:Exendin-4.

- **Novo Nordisk — Continues trend of donating insulin to children in Africa:** Novo Nordisk announced on December 3 a major donation, including free insulin, to 10,000 children in Africa, Asia, and Central America over the next five years. The program, called "Changing the Future for Children with Diabetes," will first take place in Uganda, Tanzania, Guinea-Conakry, and the Democratic Republic of Congo and will later expand to Mozambique, Haiti, Cambodia, Laos, Nepal, and Madagascar. Novo Nordisk quotes an estimate that 38,000 children under 15 in Africa have type 1 diabetes. Although type 1 prevalence is low there, these children are particularly vulnerable with most having a life expectancy of less than a year after diagnosis due to lack of insulin. Average A1c in Africa

exceeds 10.0% (the measure has only been available for a little over a year in such regions). Notably, the program appears aimed at building long-term solutions for improving overall conditions for children with diabetes: availability, accessibility, and affordability were cited as priorities. When asked whether blood glucose monitors would also be supplied (a virtual necessity for those taking insulin), Novo Nordisk responded that it was in the midst of negotiations with external suppliers. We will be interested to see which suppliers move forward with this important opportunity. We expect partnerships to form with various entities in the field including governments, diabetes associations, regional chapters of the International Diabetes Federation (IDF), and doctors and other healthcare providers. We were particularly moved by this announcement because it was given in the context of human rights: December 3rd was the 60th anniversary of the United Nations Universal Declaration of Human Rights.

- **Halozyme — New approach towards a rapid acting insulin with hyaluronidase enzyme:** We were intrigued to hear a discussion about Halozyme working on a formulation of PH20 (recombinant human hyaluronidase enzyme) with insulin during the Piper Jaffray Healthcare Conference on December 3. This program is moving into phase 2 and sounds like it has attracted some meaningful partnership interest. The focus of the discussion was on combining PH20 with insulin and creating a rapid-acting insulin similar to Biodel and Mannkind but through a different mechanism. Hyaluronidase can temporarily disrupt local connective tissue, facilitating the absorption of other drugs. ISIS is studying a premarket approval (PMA) supplement in three different areas: endocrinology, oncology, and dermatology. The hope is that a faster meantime insulin profile can more precisely mimic physiological insulin secretion, leading to reduced glycemic variability and, potentially, improved glycemic control. The company, which characterizes the combination as a best-in-class subcutaneous insulin, would like to report top-line data at the ADA 2009 meeting this upcoming June. We found this approach potentially compelling because PH20 as an enzyme has been shown to be very safe, lowering development risk; additionally, one of the key goals with improving insulin therapies is making the profile more physiological, which this approach could accomplish perhaps better than any other insulin currently available. Though development is still in a very early phase, we are excited to see more safety and efficacy data from this approach.

- **Arena — Lorcaserin development for obesity treatment remains top priority:** In a call led by CEO Jack Lief on December 3 during the Piper Jaffray Healthcare Conference, Arena reviewed the status of lorcaserin development, which continues to be the company's top priority. Arena is committed to an NDA filing for lorcaserin in late 2009 following data releases from BLOOM and BLOSSOM, its two main phase 3 trials. Phase 3 data from the BLOOM trial is scheduled for release in March 2009 with results from the BLOSSOM trial following roughly six months later. Discussions about partnerships for lorcaserin are ongoing. Separately, the company noted its belief that J&J had validated APD668, Arena's GDIR agonist currently in preclinical development. On a positive note, management said it expected the current cash to last until the filing of the NDA for lorcaserin next year.

  As a reminder, three phase 3 trials looking at the safety and efficacy of lorcaserin are underway. The first trial, BLOOM (n=3,200), is evaluating a twice-daily 10 mg dose of lorcaserin over two years in obese patients (BMI = 30-45) with or without co-morbid conditions and overweight patients (BMI = 27-30) with at least one co-morbid condition. BLOOM is continuing phase 3 studies following a review from the Echocardiographic Safety Monitoring Board in March 2008, which concluded that more monitoring for increased risk of developing valvulopathy was required. BLOSSOM (n=4,008) is evaluating a once-daily or twice-daily 10 mg dose of lorcaserin over one year in obese patients with or without co-morbid conditions and overweight patients with at least one co-morbid condition. Top-line data from this trial is expected six months after results from BLOOM are released. BLOOM-DM is

a non-pivotal phase 3 trial focusing on the effect of lorcaserin in type 2 patients that will be added as an amendment to the NDA proposal. BLOOM-DM is evaluating a once daily or twice-daily 10 mg dose of lorcaserin in obese and overweight patients with type 2 diabetes. BLOOM-DM is expected to enroll approximately 600 patients. BLOOM-DM has generated substantial interest because a diabetes indication would significantly improve the economic value of lorcaserin over a weight management/obesity indication, at least in the short-term, despite the smaller market due to a lower reimbursement hurdle.

- **Metabasis — Dedicated to developing its FBPase inhibitor MB07803:** During a presentation at the Piper Jaffray Healthcare Conference on December 2, Metabasis emphasized its dedication to building its metabolic pipeline with its key product MB07803, a fructose-1,6-bisphosphatase (FBPase) inhibitor. A review of the Metabasis pipeline revealed four other candidates being developed for metabolic diseases. MB07811 is a TRβ agonist in phase 1b for hyperlipidemia. In addition, three undisclosed products are in preclinical stages: a glucagon antagonist, a TRβ agonist, and an AMP kinase activator (in partnership with Merck). During Q&A, management was asked about recent FDA follow up letters sent. The response was surprisingly muted in our view: the company characterized the letter as a "very reasonable response."

  Phase 2a data was presented at the end of October 2008 by Dr. Alan Garber on 60 subjects who took MB07803 for 28 days. Four doses were tested: 10 mg, 50 mg, 100 mg, and 200 mg. Individuals were not on any background therapy. Dr. Garber concluded that the results demonstrated that once-daily administration of MB07803 resulted in a clinically meaningful reduction in FPG, and improvement of glycemia beyond what was attainable by prandial regulation alone. MB07803 was also safe and well tolerated.

| | Placebo | 10 mg | 50 mg | 100 mg | 200 mg |
|---|---|---|---|---|---|
| **Baseline A1c** | 8.1% | 7.9% | 8.1% | 8.6% | 8.2% |
| **Baseline FPG (mg/dl)** | 185.0 | 177.7 | 174.8 | 187.6 | 206.4 |
| **Change in FPG (mg/dl)** | 8.2 | 7.4 | 5.3 | 8.1 | -20.7 |

- **Genaera — Trodusquemine phase 1b trial started:** On December 1, Genaera began its multiple ascending dose phase 1b for trodusquemine (MSI-1436) in overweight and obese individuals with type 2 diabetes. Trodusquemine is a protein tyrosine phosphatase 1B (PTP-1B) inhibitor. The goal of this phase 1b study is to gather more safety data as well as study multiple dose pharmacokinetics of trodusquemine. This study will include 21 subjects: five subjects at each of three planned doses (3, 6, and 10 mg/m$^2$) and six subjects on placebo (two for each dose level). Trodusquemine will be given every three days over a 23-day period. Data is expected around the first half of 2009. As we have mentioned previously, PTP-1B sounds like a promising target because it can increase insulin sensitivity as well as reduce body weight. However, development of PTP-1B inhibitors has been difficult, because they are notoriously non-specific, and other similar molecules are involved in a wide range of physiologic processes, making side effects a major concern. According to CEO Jack Armstrong, early data suggests that Genaera's PTP-1B inhibitor is several fold more specific than others under development. If this increased specificity translates into a wider therapeutic window in patients, we would see this as a major positive. Efficacy has been observed in preclinical models, and if trodusquemine proves to be as effective and safe in humans, it could emerge as a novel drug class to treat diabetes in the future. Furthermore, other studies have indicated that PTP-1B inhibitors may be cardioprotective, particularly in cases of heart failure. Considering the current FDA regulatory environment and emphasis on cardiovascular neutrality or benefit, any drug that shows cardioprotective effects should have a significant advantage in the development process.

- **Aetna — Very positive revision to diabetes clinical policy bulletin reflect results of favorable JDRF CGM NEJM article:** Aetna released a revision to its Clinical Policy Bulletin on November 30 stating that the long term use of continuous glucose monitoring systems is now considered medically necessary (as an adjunct to fingersticks) in adults over the age of 24 years with type 1 diabetes. Previous iterations of the policy approved the use of short-term (up to 72 hours) diagnostic use of continuous glucose monitoring (CGM) devices in type 1s not responsive to insulin dose titration, with repeated consistent hypoglycemia and hyperglycemia, or with hypoglycemia unawareness. This is a major shift in our view: Aetna is a big deal and to say that adults should get this without any hassle is significant. Technically, some history of severe hypoglycemia is a requirement though based on conversations with reimbursement experts, we don't expect this to be a barrier for any type 1s. Overall, we view the favorable change to Aetna's policy as a major positive for Medtronic, DexCom, and Abbott since it suggests that further analyses stemming from the JDRF CGM trial data are likely to rapidly influence payor decisions on CGM.

  The main trial results for the JDRF CGM study were released in September at EASD 2008, and this revision came roughly two months later – a speedy turnaround. We will say that from our view, success wasn't about age, it was about who wore the sensor, but we assume that that result will emerge eventually. If confusion over the JDRF CGM results exist, at least the shift is starting to happen in adults. The revision text is as follows, "This CPB [Clinical Policy Bulletin] is revised to state that prolonged use of continuous glucose monitoring systems is considered medically necessary in adults greater than 24 years of age with type 1 diabetes."

- **Novo Nordisk — Building up an insulin manufacturing facility in China:** On November 11, Novo Nordisk announced a $400 million (one of the company's biggest investments ever, outside Denmark) investment to build an insulin (NovoMix 30 and NovoRapid) manufacturing facility in Tianjin, China. Construction of the 22,500 $m^2$ facility is to be completed in 2010, followed by two years of process run-in and validation, aiming for the plant to be operational by 2012. It will be the fifth strategic production site (the others being in Denmark, France, Brazil and Clayton, NC) for Novo Nordisk. Novo Nordisk insulin sales in China have been growing on average more than 35% per year over the past five years, and it is expected to continue to grow by 20% in the coming years. China now has 40 million people with diabetes and Novo Nordisk is clearly seeing increased demand for its products.

- **Sirtris/GSK — Update on Sirtris Research Activities:** At the 2008 Boston Biotech R&D Conference on October 22, the CEO of GSK-owned Sirtris Pharmaceuticals, Dr. Christoph Westphal, provided background information about sirtuins and an update on the company's current and planned research activities. Of note, Dr. Westphal showed a timeline of ongoing and planned clinical research studies for Sirtris through the year 2011. Sirtris has initiated the first phase 1 trial of its more potent second-generation SIRT1 activator, SRT2104. This is one of the company's new chemical entities (NCEs)that is many-fold more potent than the company's lead SIRT1 activator, SRT-501 (a proprietary formulation of the compound resveratrol). Assuming successful completion of the phase 1 study for SRT2104 in early 2009, phase 2 studies investigating the drug's effects in treating metabolic diseases will begin in mid-2009. Additional phase 1 trials are now planned for three yet-unnamed SIRT activators in 2009, 2010, and 2011. Clinical research on SRT-501 continues, with results expected from a key phase 2a diabetes trial in early-2009; phase 2a studies in MELAS (a rare mitochondrial disorder) and oncology are expected in mid 2009 an early 2010, respectively – important steps towards Sirtris's stated goal of developing a "sirtuins drug platform." Overall, we believe that Sirtris's acquisition by GSK has accelerated the pace of SIRT1 research in diabetes as well as a myriad of other diseases. At the time of Sirtris's acquisition, it was several years ahead of competition in studying this drug target, and we imagine that GSK's lead over competitors has further

accelerated. The theoretical advantages of SIRT1 activation is that it provides a weight neutral, anti-inflammatory, non-hypoglycemic means of effectively lowering blood glucose. Of course, many questions remain about the safety and efficacy of SIRT1 activators in treating a broad range of diseases, but we believe that it is likely that GSK's acquisition will someday seem shrewd.

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

## 4. DCU Interview with Dr. Robert Kushner, President of the Obesity Society

*Fortuitously, we were able to speak with Robert Kushner, MD (Northwestern University's Feinberg School of Medicine, Chicago, IL) who was recently named as the new President of the Obesity Society. He is Clinical Director of the Northwestern Comprehensive Center on Obesity and holds an appointment as Professor of Medicine at Northwestern. In addition to being an author on over 140 peer-reviewed scientific articles on obesity and nutrition, he is also the author of Counseling Overweight Adults: The Lifestyle Patterns Approach and Toolkit. Dr. Kushner is also an editor for several publications including Obesity and Obesity Management. We were keen to hear about how Dr. Kushner hopes to move forward in expanding the reach of the Obesity Society, particularly in regards to increasing obesity awareness and working with the new administration. We were very grateful for our time spent with Dr. Kushner and discussing a broad range of themes, which included bariatric surgery, the future directions of obesity research, and the current regulatory and reimbursement environments.*

**Expanding the influence of the Obesity Society**

*Melissa Tjota:* Dr. Kushner, thank you so much for taking the time to talk to us. It's a privilege to have this opportunity. Before we start in earnest, could you share a bit with us about your background?

*Robert Kushner:* I am physician trained in internal medicine with a postgraduate fellowship in clinical nutrition and a master's in clinical nutrition. I have been involved in the clinical care, education and research areas regarding nutrition and obesity for over 25 years. I devote my time providing clinical care in our Center for Lifestyle Medicine, teaching at Northwestern University's Feinberg School of Medicine and conducting clinical research trials. Since October, I have had the privilege to serve as president of The Obesity Society.

*Melissa:* Congratulations on becoming the next president of the Obesity Society! We have noticed over the past few years that the annual meeting of the Obesity Society has been garnering more attention, and we think this increase in visibility is incredibly important as obesity has become one of the biggest public health problems of our time, at least in the US and increasingly around the world. What are some of your plans for the upcoming year in your new role, and what are the steps you are taking to expand the reach of the Obesity Society?

*Dr. Kushner:* To start with, our society initiated a five-year strategic plan process that was approved last year by our Council. There are three pillars regarding the future direction for our society. The first is research, both basic and clinical; the second is clinical care; and the third is advocacy. Those are the three areas in which we are taking a leadership role.

When it comes to research, the role of the society is rarely to do the basic research; rather, it is to provide a home for interaction, collaboration, and networking of

investigators in order to further basic clinical research and population science research. Our society was initially formed as a research society and as a home for cutting-edge research. This is an important continued goal for our society and a major focus of our annual meeting.

**Thoughts on Bariatric Surgery**

*Melissa:* An interesting thing we have been seeing more often on the research side are studies on bariatric surgery and how it effects changes in gut hormone levels. Bariatric surgery has gained even more visibility this year both at ADA and at NAASO, and there continues to be great excitement in the field because of its ability to reverse co-morbid conditions and actually resolve diabetes. However, it is obviously not a treatment that you can practically apply at the population level, at least for all of the millions of individuals who are obese and have diabetes. What are your thoughts on bariatric surgery?

*Dr. Kushner:* For those of us who are clinicians and treating patients with clinically severe obesity or moderate obesity with co-morbid conditions, bariatric surgery has become an extremely exciting and successful treatment option, particularly for patients with obesity and diabetes. There is a great deal of exciting work being generated that is helping us understand the immediate metabolic effects that occur following different bariatric surgical approaches regarding the way the body regulates glucose and insulin sensitivity. It is exciting not only from a clinical point of view but from a research point of view as well. The dramatic and immediate changes in glucose tolerance and insulin sensitivity that you see following bariatric surgery could potentially open up new avenues for other types of treatments.

*Kaku:* In your opinion, how close are we to actually bridging that understanding of how bariatric surgery leads to those changes?

*Dr. Kushner:* The Roux-en-Y gastric bypass procedure has been in use in this country since the 1970s. For decades, it has been observed by clinicians that diabetes improves very quickly with this procedure, but it is really only in the past five years or so that endocrinologists, surgeons, and other clinical researchers have focused on the mechanisms involved. It is the first time that animal models are being used to study the effects of gastric bypass. There was a recent consensus conference in New York on bariatric surgery and diabetes where some of the latest information was reviewed and summarized.

*Kaku:* At that meeting, I felt that there was a great deal of controversy regarding the BMI cutoffs where bariatric surgery should be considered. Do you think that it is a simple matter of cut points or are there more complex thresholds that we should be thinking about?

*Dr. Kushner:* There are two things you need to take into consideration here. By surgically manipulating the gastrointestinal tract, we now have a better understanding of the role of the GI system and GI hormones on the regulation of blood sugar and insulin sensitivity. From a research point of view, it is a fascinating model, and from a therapeutic point of view, it could be a lifesaving treatment. Where it gets more controversial is who do you offer the surgery to, at what cut point, and who is going to pay for it? The denominator grows exponentially the lower you drop the BMI. Do we offer bariatric surgery to patients with diabetes irrespective of their BMI? There it gets

much more complex when you think about the application and the translation into clinical care. Currently there is a consensus that we should uphold the NIH guidelines — an individual who has a BMI of 35 or greater with diabetes — they should be considered a candidate for bariatric surgery. That alone is an important message since many patients who meet that criteria are not being offered bariatric surgery.

**Pharmacotherapy for Obesity**

*Melissa:* On the other end of the treatment spectrum, obesity pharmacotherapy has been in the news a great deal lately. Could you share with us what you think are the most promising treatments right now, especially in lieu of all the controversy surrounding the CB1 antagonist class in the past couple of months? Where do you see pharmacological treatments for obesity going?

*Dr. Kushner:* For me, one of the most exciting areas is the bridging of diabetes and obesity, and for the first time, we are really looking at hormonal treatment or hormonal modulation as a treatment for both diabetes and obesity combined. There are the GLP-1 analogs and also the combination of leptin with pramlintide. Harnessing hormonal treatment for obesity and diabetes to me is very exciting. In large part the GLP-1 analogs do not appear have the CNS side effects that are starting to become problematic, at least from the FDA regulatory point of view. You also have hormonal treatment that is affecting management of diabetes, and at the same time, affecting satiety in helping with weight loss. The other intriguing treatment direction is using combination therapies. Although the use of combination drugs seems like a simple concept, it is relatively new in our treatment paradigm for obesity. It has really only over the past five years or so that we have seriously started thinking about combined therapy for treatment of obesity, and of course, that is a treatment we have been using for diabetes for quite some time. Augmenting two mechanisms of action, particularly hormonal treatment, is again a very exciting area of further research. If you want to go one step further, you can envision combining traditional bariatric surgical treatments, newer surgical treatments (i.e. intraluminal devices or gastric pacing), along with pharmacotherapies. If you take a high-risk individual, you can potentially envision two or three modalities, which is something we do with cancer therapy all the time. We recommend surgery, radiation and chemotherapy — that is quite accepted among the public for treating cancer. We have never really thought that way for treatment of obesity before.

*Melissa:* At the Obesity Society meeting, we were pleased to see data being presented on combination therapies, bariatric surgery, and other treatments being developed for obesity. From your perspective, what is the most exciting research going on right now? Can you tell us the areas of research in which you are most looking forward to seeing results?

*Dr. Kushner:* From a basic research view, it is having a better understanding of appetite control and neural regulation that governs how body weight is regulated. We need to better understand what drives metabolism, from a genetic and physiological level that will eventually lead to translational research. From a population science view, we are facing the most serious chronic disease epidemic we have ever seen: obesity. So, understanding the science behind how we actually make changes on a population level or public health level to stem the tide of obesity is critically important. There are a lot of initiatives that could be taken by the government or by industry, but we really do not have a strong research base about what is going to work. That is really where our

population science researchers can provide leadership by generating hypotheses and testing different treatment modalities on a community and population level. Of course, childhood obesity will be looked at among these studies.

*Melissa:* What do you think has been the biggest change in pharmacotherapy for obesity?

*Dr. Kushner:* It is the ones that you probably know about already. For example, a combination of pramlintide and leptin is very exciting, and I used to think years ago that an injectable drug would be a hurdle for treatment of obesity, but I no longer think that. With the technology currently available by using small needles and injectional pens, I don't think that is a significant issue anymore. If we had a drug that was safe, effective, and durable I think that would be quite acceptable to the patient population that we treat even if it was a twice daily injection.

*Melissa:* Why do you think that we have not considered treating obesity through that multiple modality method?

*Dr. Kushner:* There are probably several reasons. One is that we do not have a lot of modalities at the moment. We have basically two surgeries that are generally accepted—gastric bypass and gastric banding. When it comes to pharmacotherapy, we essentially have two drugs approved by the FDA for treatment and maintenance of weight loss since 1998. Regarding a third therapy, which would be something like an endoluminal sleeve or gastric pacing, those are in phase 2 and phase 3 trials. Unfortunately, we do not have a lot of modalities to offer. The last thing, which makes it a little more complex, is that cancer is thought of as a life-threatening illness, so you would want to use as many modalities as possible to cure the patient. When it comes to obesity, we do not really think of it in the same way, we do not think of it as a cancer, we do not think of it as life-threatening. Many people still falsely think of it as a character fault. So to provide a lot of therapy and have it paid for by companies, which it currently isn't, we have a lot of hurdles — not only social hurdles but reimbursement hurdles to get past.

**Reimbursement Issues, the Regulatory Environment, and Final Thoughts**

*Melissa:* Could you comment more on the reimbursement situation at the moment for treatments for obesity and bariatric surgery? What changes do you hope to see with the inauguration of the new administration?

*Dr. Kushner:* CMS has already made changes regarding recognition and reimbursement for bariatric surgery and that hurdle has already been tackled. However, we are very far away from reimbursement at the primary care level, which is where treatment is rendered for the general population. Currently the primary care physician, nurse practitioner and dietitian are not reimbursed for counseling. I hope our society will be able to work with the new administration regarding reimbursement issues at a primary care level. Medications are also infrequently reimbursed for obesity. We are going to need a lot of societies and coalition groups coming together to achieve these important goals.

*Kaku:* On a practical note, could you discuss the extent to which bodies like FDA and/or CMS/Medicare view obesity as a disease?

*Dr. Kushner:* CMS has recognized obesity surgery as an accepted treatment modality and does reimburse for that treatment. Many of the third party payors have followed their lead

and provide coverage for bariatric surgery as well. We now need advocates for reimbursement for non-surgical obesity care by primary care clinicians. This also includes the non-surgical perioperative care provided by physicians and dietitians.

**Increasing Awareness of Obesity**

*Melissa:* We agree, and as we have been tracking obesity, it has been daunting how quickly obesity has increased along with the rates of diabetes.

*Dr. Kushner:* Yes. In response to your comment, I would like to discuss the importance of advocacy just for a moment. Largely due to the work of The Obesity Society, this is the first year that obesity has been directly addressed in the platforms of both the Democratic and Republican parties. We anticipate that obesity care and prevention will be a major initiative for healthcare in the new administration. That is probably the most important advocacy role we have, which is to work with the new administration and have The Obesity Society as the "go-to" society regarding the science and the leadership to make important public health and clinical care changes.

*Melissa:* Speaking of advocacy, what are some things you think need to be done to bring more awareness of obesity and its associated health problems to the general population? Furthermore, along those lines of general education, what can be done to encourage people to engage in lifestyle modifications and lead healthier lives? As we have seen, lifestyle modification is one of the most difficult things to persuade people to take on.

*Dr. Kushner:* Well, I believe there are several different avenues that our society can play a role in, and I will discuss a bit more about the clinical care pillar of our strategic plan. Unlike basic research, which our society does not directly conduct, what the society can do is to provide education for healthcare professionals. From that point of view, our society is and will continue to be a leader in education on obesity for healthcare professionals. A very exciting initiative that our society initiated this past year is a multi-year project to develop a certification process and examination for physicians in obesity medicine. We started working on it in the fall of this year, so we intend to have a certification program for physicians in obesity medicine by 2010. From a provider point of view, it will be a very important and exciting initiative from our society.

Next, from a public health point of view, our society will work with the new administration to make sure that reimbursement for obesity care is front and center regarding new healthcare initiatives. For example, registered dietitians are not reimbursed for the care of patients with obesity. Similarly, physicians are often not reimbursed for the care of patients who are being treated for obesity. These are essentially out-of-pocket expenses and knowing that obesity is associated with over 40 medical problems affecting nine different organ systems, it is ludicrous that obesity is not covered as a health benefit for preventive care and primary care.

*Kaku* We're really happy to hear about the initiative to have an obesity certification for physicians, and I was wondering if there was going to be any directed focus at pushing this certification towards primary care - in diabetes, this appears to be where the one forefront of the fight against the epidemic clearly is.

*Dr. Kushner:* This is an evolving process, but the way we envision it is that a certification in obesity medicine would probably identify physicians coming from three different primary care areas. One would be internal medicine, second would be family practice, and the third

would be pediatrics. I would envision those are three primary boards where an individual would want advanced training in the care of patients with obesity ranging from lifestyle counseling to pharmacotherapy to bariatric surgery. The entire gamut would be a healthcare provider who I would identify as someone who is specialized and competent in comprehensive care of the obese patient. That is where we are heading. Of course, our goal eventually would be identification and recognition by the American Board of Medical Specialties as a conjoined board or a secondary board. That is a long-term process but that is where we will be heading.

**Final Thoughts**

*Melissa:* Lastly, could you share with us your thoughts about the current regulatory environment concerning drug development - particularly the issue facing diabetes medications in showing that they do not cause cardiovascular risk?

*Dr. Kushner:* I am very concerned about the current regulatory climate regarding approval of obesity and diabetes medications. The need to conduct long-term clinical trials regarding cardiovascular and neurologic/psychiatric risk will significantly hinder investment in research and development for new agents. At a time where we are facing an epidemic of obesity and diabetes, I fear that pharmaceutical companies will choose not to launch new clinical trials. We need to work with the FDA to revisit cost and benefit issues.

*Kaku:* We share your fears. On the subject of challenges, to close our conversation, what would you say are the biggest challenges you face in your role as President of The Obesity Society?

*Dr. Kushner:* The basic and clinical science members of our society are conducting the most exciting and cutting-edge obesity research. We will need to continue to advocate for NIH funding and mentor younger people, which is another role for our society. The second challenge is to strengthen the education arm of our society and making sure that healthcare providers are informed about the latest treatment guidelines and evidence-based modalities used to treat patients with obesity. Lastly, regarding advocacy, we need to spend a lot of time on making sure that our society will play a role with the new administration regarding healthcare. So those in essence are our biggest challenges.

*Melissa:* Once again, Dr. Kushner, thank you for taking the time to talk with *Diabetes Close Up*. We found this an incredibly informative conversation, and we look forward to seeing the Obesity Society continue to play a leadership role in not only increasing awareness about obesity but also in highlighting obesity research.

*— by Kaku Armah and Melissa Tjota*

## 5. In the News: The National Changing Diabetes Program releases new data on the economic burden of diabetes

*The National Changing Diabetes Program (NCDP) released new data November 18th on the economic burden of both diagnosed and undiagnosed diabetes in 2007. Previous cost estimates for 2007 did not include the impact from undiagnosed diabetes, pre-diabetes, or gestational diabetes. The study reported $153 billion in medical expenditure related to diabetes (diagnosed, pre-diabetes, undiagnosed, and gestational), over 30% higher than the original 2007 estimate of direct healthcare spending on diabetes*

*of $116 billion. The study also provides a breakdown of the type 2 vs. type 1 costs as well as the necessary data to calculate their per capita contributions to healthcare spending on diabetes. This ambitious study by The Lewin Group was conducted by the same authors who calculated the previous $174 billion estimate in the American Diabetes Association 2007 study and the $132 billion in the ADA 2002 study. NCDP is an initiative founded by Novo Nordisk in 2005.*

*What does this updated report mean? The data shows that costs for diabetes are higher than previously thought due to 1) costs of those undiagnosed and not previously counted; 2) costs of those with pre-diabetes that were not previously counted; and 3) larger number of people with gestational diabetes than were previously estimated. In our view, more employer and government focus would be an optimal step since all these patients, without early intervention, will ultimately present a huge economic tab to employers, especially long-term employers, and also to Medicare once the patients hit 65 – and through their post-65 life given longer life spans. The sheer volume of people that are and will be affected by diabetes strongly suggests that early diagnosis and intervention will provide for significant savings in the long-term. The cost per case only increases as patients get older, lose more beta cell function, experience increased insulin resistance, and begin to develop diabetes complications. Some argue that treating patients earlier increases longevity and still places the same burden on Medicare (or private insurers). Putting aside the morbidity of this notion for the sake of argument, it would seem to us that the difference between spending a lot of money to treat complications for a short while (before death) and spending less money on early intervention and maintaining longevity over a longer period is quite clear. You obtain better quality healthcare and happier citizens by investing early. It is far cheaper to prevent patients from developing long-term micro- and macrovascular complications.*

*We agree with the authors that a good entry point to solving this problem is to focus on large employers who are most affected by the cost of lost productivity attributed to diabetes and its related co-morbidities. Employees as well have a role and will need to actively participate in programs that employers provide. We would also lobby for greater government understanding of the future costs to Medicare. With the shrinking endocrinology workforce, apparent shortage of primary care doctors, and cutbacks in patients being seen by primary care practices, the importance of patients being diagnosed early, treated early, and taking on bigger self-care responsibility seems obvious. We also believe the importance of diabetes education is moving further front and center as the value of optimal self-care has become increasingly important. We include below some background on the studies, and we applaud the Lewin Group for the comprehensive analysis that underscores the breadth of the crisis.*

- **The biggest difference between these new data and the most recent estimates released in 2007 is that these data account for costs associated with undiagnosed diabetes and pre-diabetes.** The study estimates that the US incurs ~$153 billion in direct medical expenditure leading to $217 billion in total diabetes costs. This marks a 32% increase in direct costs from the 2007 estimate of $116 billion, and a 25% increase in total cost from the oft-quoted $174 billion figure. The following is included:

| | |
|---|---|
| Type 1 patient cost per year | $10,500 each ($15 billion total) |
| Type 2 patient cost per year | $6,406 each ($106 billion total) |
| Pre-diabetes patient cost per year | $439 each ($25 billion total) |
| Undiagnosed patient cost per year | $1,746 each ($18 billion total) |
| Gestational diabetes cost per year | $3,533 each ($636 million total) |

- **The study includes a cost analysis for diagnosed diabetes broken down into type 2 and type 1 expenditures.** It puts the direct cost associated with type 2 diabetes at $105.7 billion (n =

16.5 million), and for type 1 diabetes at $10.5 billion (n = 1.0 million). This estimate that type 1 accounts for 5.7% of diagnosed diabetes cases is at the low end of the oft-cited statistic that type 1 accounts for 5-10% of diabetes cases: the percentage of type 1 patients was expected to decline since the pace of type 2 growth has been so high in recent years. Total costs for type 2s and type 1s was reported at $159.5 billion and $14.9 billion respectively – so although the percentage of type 1s is estimated at only 5.7%, type 1-related costs are disproportionately higher than costs for type 2s and represents 8.5% of total spending on diabetes.

- **While the study found a higher per case economic burden of type 1 diabetes compared to type 2 diabetes, an interesting trend was also found with age.** Younger type 1s were found to have similar cost per case when compared to type 2 counterparts. In middle-age categories, relative increase in expense associated with type 1 diabetes occurred. However, in much older type 1s, the cost per case for type 1s increases exponentially past that for type 2s. The authors of the document note that a selection bias limits this analysis here since older type 1s have had the disease for much longer than their type 2 counterparts. Potential limitations to the estimates for diagnosed type 1s were noted. The authors note that these estimates are "sensitive to the criteria used to identify people with diabetes using claims data."

- **Data for the cost of undiagnosed diabetes was estimated from a proxy population – people within two years of initial diabetes diagnosis.** Medical cost estimates for this group for 2007 were reported at $11 billion out of a total cost of $18 billion. The study estimated that 6.3 million adults in the US had undiagnosed diabetes, which computes to $2,864 spent per person with undiagnosed diabetes. This estimate of the population of undiagnosed people with diabetes is slightly lower than the 6.6 million (2.2% of the non institutionalized US population) estimate used by the ADA in 2007.

- **The medical costs associated with pre-diabetes were reported to exceed $25 billion or $443 per adult with pre-diabetes.** Given the 57 million estimated pre-diabetic adults in 2007, the per person cost of diabetes should not be taken lightly, particularly if earlier screening of high risk individuals becomes more common. A finding reported by the research group noted that pre-diabetes was associated with excessive use of ambulatory services for diabetes-related co-morbidities such as hypertension, endocrine, metabolic and renal complications. The data also showed that two years prior to diagnosis ambulatory and hospital-based care use for complications increased. This buttresses the need for earlier intervention in the disease progression as a potential cost saving mechanism for our healthcare system. We applaud estimating the cost of pre-diabetes, and this is the first published attempt we have seen. While we don't actually think the medical costs of pre-diabetes should be included in an estimate of the overall costs of diabetes, we do think it is a valuable estimate to know as a way of underscoring the economic and societal value in preventing or delaying onset of diabetes.

- **Gestational diabetes was reported to increase national medical costs by $636 million in 2007, 94% of which went to maternal costs and the remaining 6% ($40 million) for neonatal costs.** The study notes that 36% of gestational diabetes costs are covered by government programs (primarily Medicaid), 56% are covered by private insurers, and the remaining 8% consists of self-pay and charity care. Notably, the number of patients estimated to have gestational diabetes has risen to 180,000 from 136,000, a 32% increase – definitely a group deserving more attention, given the potential savings.

- **An interesting side note:** The 2002 report had forecasted $109 billion in direct spending by 2009, whereas direct spending has already reached $116 billion as of the 2007 report. Although there are some explanations for this result (the forecast didn't take into account medical inflation, for example),

it seems clear that the overall cost of diabetes is increasing at a rate beyond that explained by changing demographics and inflation. We had an interesting conversation with the authors of the study who pointed out that additional factors likely to drive up future costs include 1) the continued high rates of obesity and the rising prevalence of type 2 diabetes; 2) earlier onset of type 2 diabetes, so the future elderly with type 2 diabetes will likely have had diabetes longer than the current elderly with type 2 diabetes, and will likely have more complications than the current elderly with type 2 diabetes; and 3) improvements in health care and medicine are leading to increased longevity for people with diabetes. The 2007 report did not make any future projections, but complications spending, judged by in-patient costs, appears to be growing at a record pace. In 2002, in-patient costs were $25 billion, and the costs increased to $58 billion by 2007. Meanwhile, spending on drugs and devices increased relatively modestly over the same period, from $23 billion to $27 billion. While we had a better data source in 2007 than in 2002, according to the authors, the pace of complications spending certainly seems sobering, from any perspective.

- **We look forward to seeing these data published in 2009 in Population Health Management.**

*— by Kaku Armah, Kelly Close, and Melissa Tjota*

## 6. Conference Pearls: The Obesity Society 2008 Meeting

*October 3-7, 2008 • Phoenix, AZ • www.obesity.org*

*There seemed to be even more happening this year at the Annual Scientific Meeting of the Obesity Society (NAASO) than in previous years, reflecting the increasing problem of obesity globally and an increasing societal interest in addressing diabetes and other chronic diseases through weight loss. Two major themes struck us throughout the meeting: the rise of both combination therapies and bariatric surgery. On combination therapy, data were released from Vivus (Qnexa), Amylin (pramlintide/metreleptin), and Orexigen (Empatic and Contrave). While we see combination therapies making strides by increasing tolerability and thus efficacy (both prompting and for some, maintaining weight loss), doctors and researchers do continue to emphasize that diet and exercise should accompany these pharmacological treatments. As Dr. Lutes stated during the conference, "I think diet is very important, and if you don't deliver it, you are missing a very important 'pill.'" However, we know diet and exercise is difficult to implement and requires support from all levels of society beginning with the individual and going up to the government. We haven't seen widespread government or managed care in the US step up particularly on that front, and without some transformational changes, we don't envision diet and exercise prompting meaningful change anytime soon.*

*The other big focus during the conference was bariatric surgery — everything including gastric banding, laparoscopy, gastric bypass, gastric sleeve gastrectomy, and gastric trans-section — bariatric surgery has never before received such airtime. Surgery has increased visibility in the last couple of years, presumably because it leads to significant weight loss that has been shown at least in some studies to be maintained over time - additionally, the resolution of diabetes has been eye-opening, as have studies that have shown additional benefits on health outcomes. Long-term safety and efficacy will need to be shown, but for now, there's no stopping surgery, at least from a low base. The major hurdle with bariatric surgery is, of course, that it will be extremely difficult, if not impossible, to apply it on a population level. Ultimately, we learned a great deal about how the treatment of obesity is changing this year at NAASO, both in pharmacological and surgical approaches. We give highlights below on the drug and surgery fronts; detailed commentary is divided among various drug classes, surgery, and other obesity teachings (more on lifestyle, etc.).*

- **Obesity is a killer disease that by some estimates results in >300,000 deaths a year:** Richard A. Lutes, MD (Central Ohio Nutrition Center, Columbus, OH) discussed the various treatments available for treating obesity. Franz *et al*, JAMA, 2007 carried out a meta-analysis that looked at the possible treatments for obesity. Compared to diet and exercise, the medications available (Abbott's Meridia and Roche's Xenical) produced greater weight loss. He then showed data from a study by Gary Foster, PhD (Temple University, Philadelphia, PA) showing that patients considered a 17 kg weight loss (-37.5 pounds) disappointing, but found a 25 kg loss (-55.1 pounds) to be acceptable. Unfortunately, none of the currently available drugs are able to prompt this level of weight loss. While drugs can be useful in helping an individual lose weight, Dr. Lutes pointed out that weight loss was also accompanied with a decrease in energy expenditure, so lifestyle modifications are also needed.

- **Lou Aronne, MD (Weill Cornell School of Medicine, New York, NY) believes that we need a 'bridge' from diet to surgery—pharmacotherapy.** Regulatory agencies currently tolerate only a very low risk profile for weight loss drugs, and as a result obese people must choose between relatively safe but ineffective therapies, and much more invasive and effective surgery. He said, "I think the problem is not having enough treatment before we get to surgery." He thinks that the medical community should be looking more at the benefits of weight loss than at the amount of weight loss. "I would argue we need 15 to 20 categories of drugs to manage obesity effectively." We assume this because there are so many pathways involved.

- **Lawrence Blonde, MD, FACP, FACE (Ochsner Clinic Foundation, New Orleans, LA) stated that there are many unmet needs associated with conventional diabetes medications.** One of the main problems is that most therapies are associated with weight gain; they fail to adequately control post-prandial hyperglycemia; they fail to maintain long-term glycemic control; and wide glycemic fluctuations often exist. Individuals on insulin also have to worry about the risk of hypoglycemia. Other common adverse effects include gastrointestinal side effects and nausea. Dr. Blonde felt that many of the unmet needs were addressed by incretin-related therapies. Studies have shown that these therapies improve weight maintenance and weight loss, have a low risk of hypoglycemia, a low risk for edema, reduce post-prandial hyperglycemia, and potentially reduce glycemic variability.

- **Frank Greenway, MD (Pennington Biomedical Research Center, LA) believes that obesity drugs can be differentiated on the basis of their effects on mood, and that the strength of these effects may be a rough predictor of efficacy.** He quickly went through a list of different obesity drugs, some in development and some approved. Specifically, he characterized Arena's lorcaserin as ineffective, and many other drugs (topiramate, phentermine, and Sanofi's rimonabant) as having unreliable effects on reward and mood. In contrast, he characterized zonisamide and bupropion as having positive effects in both of these categories, and he is heading up studies on this combination therapy for Orexigen. He pointed out that many of the drugs had negative or unpredictable effects on mood and reward, and concluded that the combination of bupropion with either zonisamide or naltrexone (Orexigen's Empatic and Contrave, respectively) might act on both homeostatic and reward systems in the brain, increasing their efficacy beyond that achievable with other weight loss medications.

- **Gaining a better understanding of the effects of bariatric surgery:** A study by Mosumi Bose, PhD (Columbia University, New York, NY) showed that the levels of the hormone ghrelin (which is thought to promote hunger and food intake), while elevated in patients who achieved weight loss through diet, were decreased in patients who underwent either gastric bypass or gastric banding. This effect may underlie the prolonged maintenance of weight loss with bariatric surgery. Blandine Laferrère, PhD (Columbia University, New York, NY) set out to study the potential gut hormone

mechanism that could favor decreased food intake following gastric bypass surgery. Overall, Dr. Laferrère stated that the increase of GLP-1 and PYY stimulated levels could be contributing factors in the control of weight loss after gastric bypass. For the gastric banding group, successful weight loss after gastric banding occurred in the absence of gut hormone changes, so the mechanism of successful weight loss may not be hormone dependent. Josep Vidal, MD, PhD (Hospital Clinic Universitari, Barcelona, Spain) reported on a study designed to compare the GLP-1 response elicited by Roux-en-Y gastric bypass and sleeve gastrectomy. The results of this study suggest that these two surgeries are largely interchangeable, at least in terms of their effects on GLP-1.

**Highlights of data presented at the meeting:**

- **Alan Moses, MD (Novo Nordisk, Princeton, NJ) gave a brief discussion of the liraglutide phase 2 obesity results.** After 26 weeks, weight loss in the highest dose liraglutide arm was ~7.4 kg (16 pounds) or 4.5 kg (10 pounds) placebo adjusted. There was 5% weight loss in ~75% of patients (N=564) treated with the 3.0 mg dose. Perhaps most notably, he reported that a striking 80% of patients had pre-diabetes remission at the highest dose.

- **Steven R. Smith, MD (Pennington Biomedical Research Laboratories, Baton Rouge, LA) reviewed the results from a study looking at the safety and efficacy of treatment with pramlintide/metreleptin.** The results from this phase 2a study were already published by Roth *et al.*, PNAS, 2008, and the focus during this presentation was more on whether or not the combination treatment improved control of eating. They used the binge eating scale (BES), which assesses behavioral and attitudinal components of the subjective experience of binge eating. Individuals treated with metreleptin had a 30% reduction in their BES score while individuals treated with pramlintide had a 24% reduction in their BES score – notably, the effect was greater in the patients on the combination therapy who saw a 43% reduction in their BES score. Dr. Smith emphasized that these results warrant more detailed mechanism-of-action studies to assess the effect of pramlintide/metreleptin on components of the energy balance equation.

- **James Robinson, MD (University of Louisiana, Baton Rouge, LA) presented results from a dose-finding study with Empatic, a combination of bupropion SR and zonisamide SR being investigated by Orexigen as a treatment for obesity.** The data showed good efficacy: about 9% weight loss at 24 weeks and 14% loss at 48 weeks, for the 360 mg/360 mg maximal dose combination, and decreased amounts of weight loss for lower doses of either drug. A large gap divided responders and non-responders, with 14% weight loss in the responders vs. 2.6% weight loss in non-responders at the maximal dose. In addition to weight loss, HDL increased, and a modest reduction in triglycerides (-24 mg/dL) and in blood pressure (about 2-4 mmHg) was observed at the highest dose. Nausea was the most frequent reason for discontinuation, with 4.6% of patients discontinuing due to nausea in the maximal dose. Overall, Dr. Robinson concluded that the SR formulation and slower titration schedule appear to have improved tolerability of the two drugs.

- **Erickson, *et al.* discussed Contrave, Orexigen's lead phase 3 compound for the treatment of obesity.** This drug candidate combines sustained release formulations of naltrexone and bupropion. In a retrospective analysis of the data from a phase 2 study, investigators applied the ATP III — abdominal obesity, atherogenic dyslipidemia, blood pressure, insulin resistance, pro-inflammatory state, and pro-thrombotic state — definition of the metabolic syndrome to the 32 mg naltrexone group, which had been found to have the most favorable risk/benefit profile during the NB-201 study. By this definition, metabolic syndrome was prevalent in 30% of subjects at baseline and decreased to 14% in the intent to treat group. From our view, reduction of pre-diabetes is a very real way to get payors' attention – although obesity isn't yet really seen as a disease, moving from "pre-diabetes" to "normal" is attention-getting.

- **Garvey, *et al.* reported new Qnexa data showing a decrease in systolic blood pressure by 3.9 mm Hg (neutral effect in placebo) and a decrease in triglycerides by 19 mg/dL (0.6 mg/dL in placebo).** These beneficial cardiovascular signals should be positive in the regulatory review process given the FDA's concern over cardiovascular safety. We have previously reported positive data on the glycemic impact of Vivus's Qnexa (15 mg phentermine and 100 mg topiramate) from the OB-202 study in 200 type 2 patients with diabetes. To recap, Qnexa was found to decrease A1c levels by 1.2% compared to 0.6% in the placebo arm after 24 weeks of treatment (8.6% A1c baseline). Body weight decreased by 8% (17 lbs) in the treatment group and 1.2% in the placebo group. Qnexa treatment caused an increased incidence of side effects, but they did not result in higher withdrawal from the study. Qnexa also reduced cardiovascular risk factors such as blood pressure and lipid levels.

**Other drug classes to keep an eye on:**

- **John McElroy (Jenrin Discovery, Philadelphia, PA) gave an overview of Jenrin Discovery's attempts to synthesize and test a non-brain-penetrant CB-1 antagonist.** Hypothetically, this drug would work on peripheral CB1 receptors in a similar way as rimonabant (Sanofi-Aventis) or taranabant (Merck), but it would not be able to enter the brain. In theory this could produce effects on weight loss and glycemic control without the negative side effects of brain-penetrant antagonists. Jenrin has a candidate compound, JD-5006, which has been shown to reduce body weight and improve lipid parameters in mice with diet-induced obesity, and does not seem to produce negative side effects in animal models like those seen with brain-penetrant CB1 antagonists. We're very interested in this approach, but are unsure if the peripheral effects of CB-1 inhibition will be effective in producing weight loss in humans. Even if the peripheral effects are insufficient by themselves, this approach may be useful as part of a combination treatment with CNS active drugs that don't have psychiatric side effects

- **Arne Astrup, MD, PhD (University of Copenhagen, Copenhagen, Denmark) discussed phase 2 results from a 24-week trial and eight week follow-up on tesofensine, a norepinephrine, dopamine, and serotonin reuptake inhibitor by the Danish company NeuroSearch.** The participants were put on diet and exercise, and at the end of 24 weeks, the change in body weight was -2.2 kg (5 pounds) for placebo, -6.69 kg (15 pounds) for 0.25 mg of tesofensine, -11.3 kg (25 pounds) for 0.5 mg of tesofensine, and -12.83 kg (28 pounds) for 1.0 mg of tesofensine. One key point that Dr. Astrup made was that ~75% of the weight loss could be attributed to body fat. The main side effects of tesofensine were nausea, constipation, diarrhea, insomnia, and dry mouth (percentages not given). The results also showed a slight increase in pulse and blood pressure, but Dr. Astrup stressed that it was not a clinically significant, abnormal change from baseline (though even a small, negative cardiovascular signal could present future problems with regulatory agencies). In the wake of the CNS side effects with rimonabant (Sanofi-Aventis) and taranabant (Merck), we appreciated hearing that tesofensine improved rather than worsened participants moods. We will be eager to see more details, especially on the percentage of patients in which side effects were seen, in order to understand the drug's overall profile more completely.

- **As reported in the company watch, trodusquemine is Genaera's drug candidate for type 2 diabetes and obesity that acts by selectively inhibiting protein tyrosine phosphatase 1B (PTP-1B).** Unlike other PTP-1B inhibitors in development from Akros, Ceptyr/Lilly, Isis/Merck, and TransTech, Genaera is developing its PTP-1B inhibitor for an obesity indication. In theory, PTP-1B is a promising target - increasing insulin sensitivity and causing significant weight loss. However, development of PTP-1B inhibitors has been difficult, because they are notoriously non-specific, and other similar molecules are involved in a wide range of physiologic processes, making side effects a major concern. If trodusquemine proves to be effective and safe in humans, it could emerge as a novel

drug class to treat diabetes. Furthermore, other studies have indicated that PTP-1B inhibitors may be cardioprotective, particularly in cases of heart failure. Considering the current FDA regulatory environment and emphasis on cardiovascular neutrality or benefit, any drug that shows cardioprotective effects should have a significant advantage in the development process.

*— by Kaku Armah, Brendan Milliner, and Melissa Tjota*

## 7. Conference Pearls: Cleveland Clinic Obesity Summit

*September 10-13, 2008 • Cleveland, OH • www.clevelandclinicmeded.com*

*The Cleveland Clinic Obesity Summit was a fantastic conference with a lot of great presentations by a number of pioneers and innovators in the obesity field. One of the resounding take home messages was the need for better therapies to treat obesity – drug, device, and surgical interventions. Another phrase we heard a lot was "combination therapy" which is something we typically think of regarding drug therapy and lifestyle changes. However, a push seems to be underway to place bariatric surgery into the combination therapy arsenal. As Dr. Lee Kaplan of Massachusetts General Hospital noted, the simultaneous use of multiple interventions permits the success of numerous products: "we don't need winners in this category, we need players."*

*Many speakers referred to the need for a better understanding of the underlying mechanisms by which bariatric surgery promotes weight loss and the idea of surgery changing the "set point" in energy balance seems to be broadly accepted. A good analogy to explain this conceptually is to look at weight gain as an imbalance in energy intake and energy output where the net change in energy is positive. In normal weight individuals, intake is balanced with output around a certain "set point" that is different for everybody. This set point can be visualized as a pivot between intake and output. Surgery is thought to reset the set point or pivot such that the balance favors weight loss. Although it was initially thought that surgery shifted the weight set point by physically changing the digestive tract leading to less calorie absorption, some models of weight loss following bariatric surgery have suggested that differences in calorie absorption pre- and post- surgery do not account for the difference in weight. Therefore, it is thought that there is a complex interplay at work between various hormones including incretins. The work that needs to be done involves taking this concept, clarifying its biological basis, and designing drug and device interventions that mimic the effects of bariatric surgery in a much less invasive way.*

**Highlights**

- **Donna Ryan, MD (Penington Biomedical Research Center, Baton Rouge, LA) gave an enthusiastic presentation on the positive first year results of the Look AHEAD study. Look AHEAD** is investigating whether intensive lifestyle intervention (ILI) results in improvements in weight, fitness, glucose control, and cardiovascular risk factors compared to diabetes support and education. Of several significantly positive parameters, one particular piece of data stood out: in individuals in the ILI arm achieving all three ADA goals (A1c, blood pressure, lipids) increased by 13% after one year. Four-year Look AHEAD results should be available at next year's ADA.
- **The Cleveland Clinic invited representatives from the McCain and Obama camps to come address the conference.** For reasons unbeknownst to us, the McCain campaign, having known that Senator McCain was going to be the Republican nominee for ages, was unable to send a core member of his healthcare advisory team. Basically the McCain campaign appeared to have blown off the Cleveland Clinic, which we cannot imagine! Professor Mark Votruba, PhD (Case Western, Cleveland, OH) ultimately presented the McCain healthcare policy, and he did an excellent job, although he clearly was not necessarily as enthused by parts of the policy as somebody who actually worked with the McCain campaign would have been. This fact, in addition to Dr. Krishnamoorthy's

passionate presentation of the Obama healthcare policy, led to a very lopsided debate, in our view, in favor of the Obama camp.

**Obesity Pathology**

- **In a fascinating presentation, Richard Atkinson, MD (Obetech, Richmond, VA) spoke about the role of infectious agents and microbacteria in the current obesity epidemic.** Dr. Atkinson believes that behavioral factors alone cannot explain the recent spike in obesity and that viruses and bacteria may be involved. Given the strong association between bacteria and obesity, Dr. Atkinson believes that manipulating gut bacteria to change body weight composition may have future therapeutic potential. Moreover, a number of studies have demonstrated associations between viral infection and weight gain, and a recent study published online in Nature found that specific sets of gut bacterial genes can define differences between obese and lean twins

- **Dan Bessesen, MD (University of Colorado, Denver, CO) gave an incisive presentation on energy balance and weight loss.** He started off discussing why maintaining weight loss is so hard for people and went on to highlight studies showing brain responses (via MRI) to different food stimuli in different states of hunger for obese and non-obese individuals. These studies showed that obese people had the same responses to particular food stimuli whether they were hungry or full, which meant their biological mechanisms were not preventing them from eating more despite the fact that they were full. He concluded that the reason some obese people are able to keep the weight off is because they can "override" these faulty biological mechanisms with cognitive mechanisms based on the knowledge of improved quality of life in the reduced weight state.

**Obesity Drug Development**

- **Lee Kaplan, MD (Massachusetts General Hospital, Boston, MA) gave an intriguing opening presentation in which he made the point that despite the >200 compounds in active development for obesity, we still only have two approved drugs, the last of which was approved a decade ago.** Similarly, over 800 devices have been patented, over 40 devices are in development, and only two devices (same mechanism of action) have been approved. We note our disappointment surrounding not just the number of approved drugs but also the side effect profiles that likely make adherence to the medications, which are already sub-standard, much worse. Dr. Kaplan explained the concept of the human body's efforts to maintain an energy set point using this explanation to illustrate the difficulty of dieting: the body simply adapts energy expenditure to maintain the set point. As such, he stressed the need to learn from the success of bariatric surgery in order to create pharmacologic interventions that actually change baseline physiology and alter set points. He also gave a big thumbs up to combination therapies in development.

- **Richard Atkinson, MD (Virginia Commonwealth, Richmond, VA) gave a fairly eyebrow-raising presentation in which he noted that diet and exercise was simply <u>not</u> the answer to the obesity problem.** Hurrah! We believe in it but don't think it's enough. He characterized phentermine as the best drug on the market and expressed interest in Vivus's Qnexa and Arena's Lorcaserin, and regretted that J&J did not continue with its topiramate program which showed 12% weight loss over 1 year – he remarked that the curve was still trending down at the end of the study but didn't mention side effects, which was why the phase 3 trial was halted. He advocates combination therapy using multiple drugs (not necessarily labeled for combination) as well as very low calorie diets (for rapid initial weight loss) combined with diet, exercise, and behavioral modification. He mentioned Empatic (Orexigen), Contrave (Orexigen), and Qnexa (Vivus) trials ongoing and noted he was particularly interested in the Qnexa outcomes. He characterized Arena's Lorcaserin as a possible "son of Phen-Fen" but safer. He concluded his presentation stating that drugs were the future of obesity treatment, noting at least 350 drugs in pipelines.

- **Kishore Gadde, MD (Duke University, Durham, NC) gave an expansive overview of drug therapies for obesity.** Of note, he expressed confidence in drugs targeting the endocannabinoid system and touted the value of combination therapy. On this subject, he also cautioned against the use of off-label drug combinations until we have safety data from large randomized controlled studies. He characterized liraglutide as giving impressive weight loss, exenatide (Byetta) giving modest weight loss in diabetes patients, and pramlintide (Symlin) giving mild to modest weight loss in diabetes patients. He also mentioned octreotide (Novartis), a somatostatin analogue that showed less than 2% weight loss relative to placebo in obese adults. He was not enthusiastic about this drug's viability.

**Bariatric Surgery**

- **Philip Schauer, MD (Cleveland Clinic, Cleveland, OH) discussed diabetes remission rates with gastric bypass surgery noting that biliopancreatic diversion resulted in the greatest (≥95%) remission of diabetes.** He characterized metabolic and endoscopic surgery as two types of surgery that would see more attention going forward, since the former addresses the more comprehensive area of the metabolic syndrome and the latter is less invasive than current bariatric surgery procedures. Dr. Schauer provided some Advisory Board projections on bariatric procedure volumes: 314,000 procedures projected for 2009 and expected to reach 367,000 in 2014. Dr. Schauer concluded his presentation commenting on a study on the economic impact of bariatric surgery, which concluded that after a mean investment ranging from $17,000 – $26,000, all costs are recouped within two years for laparoscopic surgery patients and within four years for open surgery patients (after controlling for observable patient characteristics). He cited Advisory Board data, which predicted that by 2014, endoscopic restriction would have overtaken laparoscopic surgery as the dominant bariatric procedure putting these less invasive procedures in greater competition with the drug market.
- **Dr. Schauer also indicated that the duodenal-jejunal bypass (DJB) is getting renewed attention as creative ways are being devised to perform this procedure.** GI Dynamics was the first to the field and presented their study results at the American Society for Metabolic and Bariatric Surgery (ASMBS) 2007 meeting in San Diego where they showed 10% excess weight loss in a very small (N=12) patient population after 12 weeks. Three of four diabetes patients in that study were reported to have had an A1c drop of 0.5%. There was also a presentation during the 2008 ADA meeting (103 OR) on a completely endoscopic DJB sleeve for the treatment of type 2 diabetes, showing rapid restoration of glycemic control independent of diet or weight loss (note that these were interim data from the first week of the 52 week study).
- **Stephanie Sogg, MD (Massachusetts General Hospital, Boston, MA) discussed what is arguably one of the most important aspects of the patient experience of bariatric surgery.** She did a thorough positive/challenges analysis of the practical, psychological, interpersonal and behavioral issues that patients deal with following such a surgical procedure. She stated that the consequences of bariatric surgery are overwhelmingly positive but stressed the need for healthcare providers to mandate long-term psychosocial follow-up to ensure patients are receiving complete care. Her conclusion, "Adjustment does not end when weight loss stops."

*— by Brittany Adler, Kaku Armah, and Melissa Tjota*

## 8. Conference Pearls: 1st World Congress on Interventional Therapies for Type 2 Diabetes

*September 15-16, 2008 • New York City, NY • www.interventionaldiabetology.org*

*The stated aim of this groundbreaking meeting was to craft an agenda of health policy initiatives and seize the opportunity offered by novel interventional therapies in diabetes and obesity treatment. A fair amount of hot debate went on at this meeting, and one of the biggest controversies was the need (and design) for randomized outcomes trials to show the safety and efficacy of bariatric surgery used in non-morbidly obese populations (BMI < 35) as a "cure" for diabetes. These long-term studies will also help answer questions on patient and surgical procedure selection criteria. These studies will also provide great insight into the mechanism of action of weight loss and diabetes remission following surgery, which can be leveraged to inform drug and device development in the field. Asked whether they thought surgery was appropriate for treating diabetes in inadequately controlled patients with BMI under 35, 55% of participants said, "Yes," 3% said "No," and the remainder said they needed more information. Note that the 1000+ member audience was comprised of 67% surgeons, 14% endocrinologists, and a mix of other healthcare professionals. Although there is growing consensus on the impressive return on investment for bariatric surgery, the issue of the substantial up-front costs if such an intervention is to be widely used as a public health tool still remains. Some questions about whether surgical intervention is the best place to make a huge investment also exist, especially in light of the majority, non-obese population that could be helped by an investment in prevention and pre-diabetes treatment by increasing access to education and basic drugs like metformin, SFUs, and insulin.*

**Highlights**

- **Paul Zimmet, MD, PhD (Baker IDI Heart & Diabetes Institute, Melbourne, Australia) described the 21st century as the most obesogenic environment in human history and the numbers continue to grow…in the wrong direction**. He stressed the need for studies to define the group(s) that will receive the most benefit from the different approaches to diabetes treatment: lifestyle intervention, pharmacological intervention, or surgical intervention.

- **Sir George Alberti, MD (Imperial College, Newcastle, UK) discussed the idea of cut-points in diabetes diagnoses and defining the metabolic syndrome.** He suggested that these cut-points were artificial and stressed the need to look for different ways of defining the condition and consistently describing diabetes remission after bariatric surgery. We agree that diabetes as a condition is a continuum; cut-points seem useful from a practical standpoint though hardly binary. He suggested including IFG and IGT in type 2 diabetes, and also suggested reducing the lower limits of these metrics. Additionally, he emphasized the importance of measuring waist to hip ratios (or waist girth) as a good metric for diagnosing the metabolic syndrome. He defined the syndrome as a cluster of conditions associated with diabetes and CVD with greater occurrence than by chance alone.

**Therapeutic Controversies – Bariatric Surgery and Diabetes**

- **Panelists in a session comparing and contrasting current therapies to investigational therapies answered a series of questions posed by moderator Harold Lebovitz, MD (SUNY Staten Island, New York City, NY).** Dr. Lebovitz touched on the lack of success with lifestyle interventions and combination hormonal therapies for weight loss, and engaged Dr. Philip Schauer in a bit of an argument on medical versus surgical intervention for diabetes treatment. The gist of the debate centered on the lack of long-term, randomized, large controlled studies showing hard outcomes after surgical intervention.

- **Francesco Rubino, MD (Weill Cornell Medical College, New York City, NY) questioned the "chronic and irreversible" paradigm of thinking about diabetes and asked that we re-think the way we look at the disease based on collaboration (not competition) across all implicated medical disciplines.** He also reviewed the benefits of surgery looking particularly at data from patients with BMIs under 35. He concluded that the benefits were similar to those for

more obese people, and further that no side effects specific to leaner people were identified. Therefore, a BMI cut-off of 35 is not a good predictor of success with bariatric surgery.

- **Dr. Rubino asked what is the ideal operation?** Many kinds of GI procedures are in use that, in preliminary studies, can ameliorate type 2 diabetes. For example, the ileal transposition bypasses most small intestine by linking the beginning of the small intestine to the end, and seems to result in increased GLP-1 levels. However, traditional (laparoscopic) gastric bypass has the most promising data at the moment. A RCT of 30 patients with BMI <35 randomized to laparoscopic sleeve gastrectomy (LSG) versus laparoscopic sleeved gastric bypass (LSGB) resulted in 7% of patients getting their diabetes under control in the LSG group, compared to 93% in the LSGB group, despite similar weight loss between the two groups.

- **Moderating the ASMBS-sponsored panel in the session on diabetes and metabolic outcomes of bariatric surgery, Dr. Philip Schauer asked a series of audience response questions, which produced some fascinating results.** 87% of respondents indicated they believed there was sufficient evidence to recommend that surgery be strongly considered for patients with type 2 diabetes and a BMI >35. When the same question was asked regarding BMI greater than 40 or 50, well over 90% of the attendees voted "yes" as expected. Another interesting response came when the question was posed, "Which operation has the best risk/benefit ratio for treating patients with type 2 and a BMI>35?" 1% more of the respondents selected biliopancreatic diversion as having a better risk benefit ratio than gastric banding which surprised Dr. Schauer. That said, only 8% chose "gastric banding," 79% chose "gastric bypass," and the remaining 4% selected "none of the above."

**Therapeutic Controversies – Bariatric Surgery and Diabetes Remission (Mechanism)**

- **The panel discussion on research priorities in an era of economic constraint started off with a series of audience response activities.** 50% of the audience voted "exclusion of the proximal bowel" as the mechanism of diabetes remission and pretty much everybody agreed that a multi-center clinical trial in bariatric surgery was needed. Again almost 50% chose the Roux-en-Y gastric bypass as the procedure of choice during this trial –a relatively high percentage (34%) opted for novel procedures such as the bilopancreatic diversion. Two-thirds of the audience believed optimal medical management would be the appropriate comparator in this trial.

- **The panel on minimally invasive approaches to type 2 diabetes treatment highlighted the importance of figuring out the mechanism of diabetes remission for the different types of surgery before coming to a conclusion as to which therapy (or combination of therapies) was most effective at reversing diabetes safely.** The point was repeatedly made that long-term studies were needed in order to ensure long-term efficacy of the intervention. Said Dr. Xavier Pi-Sunyer (St. Luke's Hospital, New York City, NY): "We need to figure out which patient groups derive the best risk-benefit ratio. We need to figure out which procedure matches best to which patient. We clearly do not have enough evidence. I don't care if you have a study of 24,000 patients if there is no control group. We're getting a lot of complications (bone, hypoglycemia, etc.) from people who had their surgery 2-3 years ago so we need long-term studies."

**Bariatric Surgery in Youth**

- **Francine Kaufman, MD (Children's Hospital, Los Angeles, CA) did not directly address the use of surgery in adolescents but rather outlined the problem of childhood obesity as it relates to environment**. Since she discussed school interventional programs, she seemed to lean toward avoiding surgery for adolescents.

- **Thomas Inge, MD (Cincinnati Children's Hospital, Cincinnati, OH) concluded that GI surgery was an effective treatment for adolescent morbid obesity.** There is little evidence that their condition can be reversed with non-operative therapies and "moderate" evidence that their condition can be reversed with operative therapies. So far, data has shown no greater risk in adolescents than in adults and similar resolution of comorbidities.
- **Meg Zeller, MD (Cincinnati Children's Hospital, Cincinnati, OH) is a psychologist who provided a different perspective on surgery for adolescents.** She suggested that the psychological consequences of childhood obesity are quite severe and may warrant extreme intervention. Teens for whom this is safe and effective have to be selected carefully, and more research needs to be done targeting post-operative care models for adolescents.

**Cost Effectiveness of Bariatric Surgery**

- **Professor Pierre Cremieux, PhD (Analysis Group, Boston, MA) discussed his economic study on the time to return on investment for bariatric surgery in diabetes patients.** The study reported that it took two years to return the initial investment of $17,000 for laparoscopic surgery and four years for the initial $26,000 investment for open surgery. Professor Cremieux was emphatic that this was the first time he had seen such a result for a medical intervention. In our view, such stats make it a no-brainer that the surgery should be used in at least some percentage of patients.
- **The follow-up panel on the cultural and economic implications of diabetes surgery was fascinating.** In short, while panelists were intrigued by the findings of Professor Cremieux's study, the up-front cost for an intervention like this for a large population is very daunting. Richard Kahn, PhD (American Diabetes Association, Alexandria, VA) and Dr. Harold Lebovitz both raised the argument that if we do indeed dedicate such a huge upfront investment to fighting diabetes, we need to think carefully about the most effective intervention looking at the entire diabetic population – not just the obese part of it. We think this is a foregone conclusion.

*— by Kaku Armah*

## 9. Literature Review: Arguing for a Coordinated National Strategy

**Huang TK and Glass TA (2008) "Transforming Research Strategies for Understanding and Preventing Obesity." JAMA, 300: 1811-1813.**

*In the October issue of the* Journal of the American Medical Association (JAMA)*, Drs. Huang and Glass detailed the need for a coordinated national strategy to combat the growing obesity crisis. They argue that although many people perceive obesity as an individual problem, the problems associated with excess food consumption and sedentary lifestyles can only be solved through a coordinated strategy that incorporates the social, physical, economic and policy environments. They identified contributing causes of obesity including the lack of physical education in schools and poor diets due to unhealthy food sold through schools, worksites, and other institutional cafeterias and vending machines. On the government level, the authors blame the lack of access to preventative care, which accounts for the disproportionate rate of obesity among the poor and minority. Their commentary addresses four key areas for research including cross-disciplinary approaches, policy intervention, capacity building, and taking a global perspective. Ultimately, the authors argue that obesity can only be solved through the concerted effort of the individual, the community and the national government.*

- **In the commentary, Dr. Huang (Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD) and Dr. Glass (Johns Hopkins Bloomberg School of Public Health, Baltimore, MD) stressed the need to address the**

**growing obesity epidemic.** They quoted a recent estimate that indicated that on the current trajectory, obesity will account for roughly $860 billion (or more than 16%) of health care expenditures in the United States by 2030. These numbers reflect the fact that currently one-third of children and two-thirds of adults in the United States are overweight or obese.

- **To address the obesity problem, the authors suggest a multilevel research approach that treats the disease within the broader social, physical, economic, and policy context.** They argue that the food and physical activity behaviors that result in obesity, are not merely a matter of individual choices but the result of the complex interplay between biology and socio-environmental factors. These factors occur on multiple levels, including interpersonal (family, peers and social networks), community (school, workplace, and institutions), and government (local, state and national polices).
- **To implement a multilevel strategy to combat obesity, the authors outlined four key areas of research and investments:** cross-disciplinary hypothesis and questions that examine biological and socio-environmental risk factors, policy intervention research that examines the effect of food and physical activity, capacity building in multilevel science, and a global perspective on obesity research. The first key area of research is an emerging field that assesses the effects of socio-environmental factors and how they in turn affect behavior and health. Policy intervention research focuses on food marketing controls, taxes on less healthy foods or ingredients, and incentives for health foods, along with urban design policies that promote active living. The third key area of research strives to bring together all governmental departments as well as private industries, health care systems, communities and individuals. Lastly, since obesity is not a problem unique to the United States, any approach to reducing obesity should be taken from a global perspective.

*— by Michael Dougan and Susan Lin*

## 10. Conference Preview: Advanced Technologies and Treatments for Diabetes

*February 25-28, 2009 • Athens, Greece • http://www2.kenes.com/attd/Pages/home.aspx*

*Early next year is the 2nd annual Advanced Technologies and Treatments for Diabetes conference, one of the most interesting diabetes device meetings on our calendar. The schedule is jam-packed with fascinating presentations topics on diabetes devices including insulin pumps, sensors, closed-loop systems, new insulin delivery approaches, new insulin analogs, telemedicine, in hospital glycemic control, and diabetes and obesity prevention.*

*The first day of the conference is a preliminary day of industry-sponsored symposia. We're particularly interested in the Animas workshop as new Animas pumps should be coming within a few months of the meeting and the Medtronic workshop focused on the highly-regarded CareLink management software.*

*Large blocks during the rest of the show are divided up into two "Halls" with different themes. On Thursday, Hall A is dedicated to "SMBG – Impact on Diabetic Control" and Hall B is "Patients and Technology" in the morning, the "AIDPIT and P-Cezanne symposia" and "glucose variability and clinical practice" in the afternoon. We're excited about Dr. Jay Skyler's talk on "Immunotherapy of Type 1 Diabetes" and Dr. Irl Hirsch's "SMBG Frequency and Titration Guidelines for Insulin Treated Subjects," Dr. Boris Kovatchev's talk on glycemic variability, and the DexCom workshop about issues that matter in CGM.*

*Friday's talks are divided into "Technology-Health Policy and Benefit" and "Continuous Glucose Monitoring" in the morning, and then continues as one session with the Loop Club (a well-known group of scientists pursuing closing the loop) and the Roche satellite symposium. Of particular interest is Satish Garg's talk "Health Outcomes from CGM" and Fran Kaufman's discussion of the "Promotion of Healthy Lifestyle for Children."*

*On Saturday, the last day of the conference, the AIDPIT symposium continues with "Reproducing Insulin Secretion" in parallel with a session on "Ongoing Studies." We're looking forward to Dr. Irl Hirsch's talk on "Implications of the CGM Studies," Drs. Peter Chase and Bruce Buckingham on "Pump Shut Off to Prevent Nocturnal Hypoglycemia," and Dr. Howard Wolpert on "Issues with Closing the Loop."*

**Highlights**

**Day 1: Wednesday, February 25**

- **(1:00 — 6:30 p.m.) Companies' workshops.** Includes the Medtronic Workshops, the Animas Workshops, and many that are still TBD.
- **(6:30 p.m.) Opening Ceremony**

**Day 2: Thursday, February 26**

- **(General Session) Immunotherapy of Type 1 Diabetes.** Jay S. Skyler, MD, MACP (University of Miami Miller School of Medicine, Miami, FL).
- **(Hall A) SMBG frequency and titration guidelines for insulin treated subjects.** Irl Hirsch, MD (University of Washington, Seattle, WA).
- **(Hall A) Glucose variability – clinical relevance, assessment, and control.** Boris Kovatchev, PhD (University of Virginia, Charlottesville, VA).

**Day 3: Friday, February 27**

- **(Hall A) Health outcomes from CGM.** Satish Garg, MD (University of Colorado, Denver, CO)
- **(Hall A) Promotion of healthy lifestyle for children.** Francine Kaufman, MD (University of California, Los Angeles, CA).
- **The Stanford-UCSB-Denver progress towards a closed-loop.** Bruce Buckingham, MD (Stanford University, Palo Alto, CA)

**Day 4: Saturday, February 28**

- **(Hall B) Implications of the CGM Studies: where are we now?** Irl Hirsch, MD (University of Seattle, Seattle, WA)
- **(Hall B) Pump shut off to prevent nocturnal hypoglycemia.** Peter Chase, MD (University of Colorado, Denver, CO) and Bruce Buckingham, MD (Stanford University, Palo Alto, CA)
- **(Hall B) Issues with closing the loop — critical appraisal.** Howard Wolpert, MD (Joslin Diabetes Center, Boston, MA)

*— by Brendan Milliner*

## 11. Diabetes Comings and Goings

- **Leif Bowman**, reimbursement expert, recently left LifeScan in October and joined DexCom.
- **Frank Bymaster** left his position as Vice President of Neuroscience at Orexigen in November.
- **Dr. Michael Cowley,** the Chief Scientific Officer at Orexigen, announced his decision to step down from his position in November, but he will continue to be retained as a consultant.
- **Jeff Jonas** left his position as Executive Vice President of R&D at Isis in July and joined Shire as Senior Vice President, R&D.
- **Dr. Richard Kahn**, currently the Chief Scientific and Medical Officer of the American Diabetes Association, announced his retirement effective June 2009. Although Close Concerns and Dr. Kahn have differed on some issues surrounding technology innovation, we salute Dr. Kahn for his many scientific contributions to the field.
- **Paul Laikind, PhD** resigned as president and CEO of Metabasis in December and will be replaced by Mark Erion, PhD who will also continue his role as chief scientific officer at Metabasis.
- **Jean-Claude Leroy,** the top legal and financial officer at Sanofi-Aventis, resigned in mid-December and will be replaced by CFO Laurence Debroux and General Counsel Karen Linehan.
- **Anthony McKinney** stepped down from his position as Chief Business Officer at Orexigen in November.
- **Steven R. Pacelli** was appointed to the newly created position of Chief Administrative Officer at DexCom in December after serving as Senior Vice President of Corporate Affairs since July 2007.
- **Dr. Gary Tollefson** resigned as Director, President, and CEO of Orexigen in November to focus on his recovery from acute leukemia.
- **John Varian,** currently COO and CFO of Aryx Therapeutics, was appointed to the Board of Directors at XOMA in early December.

## 12. DCU Stock Chart and Final Thoughts

| | 15-Dec-08 | 17-Nov-08 | | 17-Jun-08 | | 17-Dec-08 | | IPO | | Market Cap |
|---|---|---|---|---|---|---|---|---|---|---|
| GSK | 37 | 35.6 | 4% | 42.12 | -12% | 51.6 | -28% | - | - | 95.99B |
| NVO | 53.98 | 49.4 | 9% | 62.51 | -14% | 62.56 | -14% | - | - | 38.68B |
| AMLN | 11.38 | 6.91 | 65% | 26.2 | -57% | 37.65 | -70% | 14 | -19% | 1.57B |
| BIOD | 3.05 | 2.38 | 28% | 15.15 | -80% | 19.75 | -85% | 15 | -80% | 72.32M |
| OREX | 4.39 | 4.4 | 0% | 8.32 | -47% | 14.39 | -69% | 12 | -63% | 151.12M |
| PODD | 8.24 | 4.41 | 87% | 16.52 | -50% | 23.11 | -64% | 15 | -45% | 228.76M |
| MNKD | 3.97 | 3.33 | 19% | 2.77 | 43% | 7.78 | -49% | 14 | -72% | 403.81M |
| DXCM | 3.02 | 1.99 | 52% | 7.65 | -61% | 7.98 | -62% | 12 | -75% | 89.96M |
| HDIX | 5.09 | 6.03 | -16% | 8.04 | -37% | 7.65 | -33% | 12 | -58% | 88.98M |

The diabetes sector has continued to see enormous swings of late; finally, they are positive. Amylin and Insulet and DexCom have risen well over 50% each (up 65% and nearly 90% and 52%, respectively) in the last month, making up lost ground from previous months. Biodel and MannKind have also risen double digits; while HDI fell about 15%, and GSK and Novo Nordisk rose between 5 and 10%. Orexigen was flat –

we are assuming we will see many of these stocks move during the JP Morgan meeting next month when so many involved in life sciences descend upon our lovely city by the bay. We are looking forward!

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