

# DIABETESCLOSEUP

75 and Lots to Ponder...

December 2007 • No. 75

---

## From the Editor

**This is a special month indeed. First it's special because it's the holiday season,** and I recently watched the lighting of the Christmas tree in Union Square with my daughter Coco. These are striking moments that last a lifetime, and I hope however you celebrate the holidays, you share those same wonderful moments with family and friends.

**This is also a special month because we are publishing our 75<sup>th</sup> issue of Diabetes Close Up** (our first issue was in late 2002), and it's also our one-year anniversary in publishing diaTribe. That my job is to look and watch and help write about everything new in the diabetes world, well, I am privileged to do that with a small group of astonishingly talented people – it doesn't get better than this, so extra appreciation to all of you who have made this possible.

**In the five years since starting Close Concerns, it occurs to me that a lot has changed and a lot hasn't changed.** That is incredibly evident in our interviews this month – we bring you two big ones in honor of it being a special issue! The first is with Dr. Mary Parks, director of the FDA's Division of Metabolism and Endocrine Products, who recognizes that patients continue to do poorly and that the FDA is not exactly rich in resources. We found her candor refreshing, and we fully understand that she has one of the tougher jobs around. We're glad she's there. We also had an opportunity to speak to Dr. David Nathan about the update to the “ADA/EASD algorithm” for type 2 treatments – there is no one who packs more meaning into each sentence, that is for sure.

**We're also publishing this month the results of a survey we put together of 525 medical school students.** This is probably the most dispiriting story we've reported on in 75 issues of DCU – our main finding was that virtually none of these students plans to pursue diabetes as a specialty. There are several reasons why – the money is one thing, the hours are another, the lack of success in working with patients is yet another. We were struck not only by the declining interest in treating diabetes but also by declining interest in general medicine – where will patients go in 20 years? I don't know.

**For some eye-opening thoughts from the front line on the prospects of treating diabetes in this day and age,** see the editorial by MD and PhD candidate Michael Dougan, who had some intriguing thoughts on the matter.

**In the spirit of the holiday season, we're going to stick with the positives.** We know that patients are doing a lot more to educate themselves these days and are availing themselves of new tools – I'm convinced that continuous monitoring, for example, has hit a tipping point and that patients are digging it more than dissing it. Too, this month, we saw Amylin present some breakthrough science, and we heard about Medtronic's first steps toward a closed-loop system.

**So we hope you enjoy this issue. For now, our family is preparing for Christmas in a special way.** Before our two children go to bed on Christmas Eve, we're going to leave out a plate of cookies, a glass of milk . . . and a glucose meter. Santa's got a long night ahead of him, and we aren't taking any chances.

Appreciatively,



Kelly L. Close

## Major Headlines

**New LifeScan leadership; J&J broadens commitment to obesity – page 6**

**Novo Nordisk announces final LEAD3 data – page 8**

**Amylin hosts striking second annual R&D day – page 12**

**Medical students and diabetes: staying away in droves – page 19**

**FDA insider Dr. Mary Parks discusses the current FDA environment – page 26**

**Dr. David Nathan gives update on ADA/EASD TZD guidelines – page 32**

**Global Diabetes Summit, Columbus – Best diabetes faculty ever! – page 35**

## In This Issue

1. Quotable Quotes in Diabetes .....	4
2. diaTribe FingerSticks .....	5
3. DCU Company Watch .....	6
• <b>J&amp;J</b> —New LifeScan leadership; J&J buys rights to Cyberonic’s obesity technology	
• <b>Novartis</b> —Galvus moves forward in EU but higher h-a-s-s-l-e expected	
• <b>Merck</b> —Januvia filed in Japan, full speed ahead	
• <b>Biodel</b> —Ambitious agenda for VIAject in 2008	
• <b>Merck</b> —Talking up taranabant, with ambitious plans to file in 2008	
• <b>Novo Nordisk</b> —Positive LEAD3 data released and filing expectation moves up a bit	
• <b>Amylin/Lilly</b> —Strong Byetta monotherapy data	
• <b>Vivus</b> —Pipeline overview at Research and Development Day	
• <b>Lilly</b> —Analyst meeting reinforces commitment to diabetes	
• <b>BMS/AZ</b> —Intent on Saxagliptin 2008 filing	
• <b>Orexigen</b> —Pipeline overview provided at analyst/investor “state of mind” day:	
• <b>Amylin</b> —Exciting pipeline reviewed at R&D day; bullish LAR superiority trials planned	
• <b>Sirtris</b> —Three new SIRT1 activators described in article in <i>Nature</i>	
• <b>Oramed</b> —Completion of Phase 1 Animal Studies	
• <b>MannKind</b> —Another TI insulin phase 3 trial, emphasis on differentiation	
• <b>Metabasis</b> —Second-generation FBPase inhibitor in phase 2 after CS-917 failure	
• <b>Arena</b> —All pivotal phase 3 trials for lorcaserin underway	
• <b>Alkermes</b> —Bullish on once-weekly exenatide and AIR insulin	
• <b>DexCom</b> —Continuing progress on all fronts	
• <b>Medco</b> —Medco holds analyst dayLargest internet pharmacy expects 10% growth in '08	
• <b>Merck</b> —Big win at Prix Galien	
• <b>Tethys</b> —Developing a diabetes risk test	
• <b>AtheroGenics</b> —Phase 3 clinical trial of AGI-1067 fully enrolled; skepticism persists	
4. Medical Students and Diabetes: Staying Away in Droves .....	19
5. Editorial: Why Medical Student Aren’t Pursuing Diabetes .....	24
6. Interview with FDA Insider Dr. Mary Parks .....	26
7. In the News: New Type 2 Treatment Algorithm EASD & ADA – and Talking to Dr. David Nathan about these Changes .....	31
8. Conference Notes: Global Diabetes Summit .....	35
9. Literature Review: Activators of SIRT1 for the Treatment of T2DM .....	38
10. Literature Review: US Prevalence of Chronic Kidney Disease .....	40
11. Diabetes Comings and Goings .....	41
12. Close Concerns Market Index and Final Thoughts .....	42

## 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 [closeconcerns.typepad.com/close\\_concerns\\_weblog/](http://closeconcerns.typepad.com/close_concerns_weblog/)

- **December 17:** Combination therapy: the future of obesity drugs?
- **December 14:** Avandia in the news again
- **December 11:** Solid Third Quarter 2007 Performance for J&J
- **December 5:** SIRT1 - A new and exciting diabetes drug class

Besides writing our own blog, we also write a blog for Revolution Health called "Up Close and Personal" on life with diabetes. You can find it at [www.revolutionhealth.com/blogs/kellyclose](http://www.revolutionhealth.com/blogs/kellyclose)

- **December 13:** ICES ices Avandia
- **December 5:** Byetta vs Exenatide once weekly
- **November 21:** Being Thankful
- **November 20:** MIC-1: An on-off switch for hunger?

## Videos

Below is our favorite YouTube video in diabetes this month – we made this during WDD:

- "World Diabetes Day: Coit Tower"  
[http://www.youtube.com/watch?v=bVI\\_BuOkPNk](http://www.youtube.com/watch?v=bVI_BuOkPNk)

## Coming soon in DCU...

We'll have our review of the Diabetes Technology conference in our January issue, with our take on Dr. Richard Kahn's surprising and disappointing talk on the value of technology in particular. In the first half of the year, ADA Postgrad, ENDO, and ADA will all take place in our fair city by the Bay ... and as always, the JP Morgan conference takes place in Union Square early January. 2008 promises to be a most exciting year for diabetes technology and therapeutics and we look to cover it as closely as possible - incredible conferences, intriguing clinical literature, and much on the product front, including JDRF trial results on CGM in the late part of the year (for us, this is among the most highly awaited data in diabetes, full stop) and multiple drug FDA submissions promised, including Bidel's Viaject, BMS/AZ saxagliptin, Merck's taranabant, Mannkind's TI, and Novo Nordisk's Liraglutide. Ambitious, all, but potentially game-changing.

## 1. Quotable Quotes in Diabetes

*Tolerability then becomes, for lack of a better term, more of something that affects the marketability of the product. [High tolerability] doesn't necessarily mean that a drug is safe. Tolerability and safety are two different things.*

—Dr. Mary Parks, clarifying the difference between safety and efficacy of a drug. Our interview with Dr. Parks is on page 26.

*We discussed whether we should eliminate the TZDs from the algorithm, but the consensus was that the data were not conclusive enough to remove them completely. However, the caveats that we provide are strong enough that I think most physicians will be cautious in using them.*

—Dr. Nathan, discussing why TZDs remained on the ADA/EASD recommended treatment algorithm for type 2 diabetes in spite of growing safety concerns about the drug class. Our interview with Dr. Nathan is printed on page 32

*“...Moreover, blood sugar levels vacillate wildly because of stress, anxiety, or mood changes. They fluctuate when your mother-in-law visits or when the Red Sox are playing the Yankees, when you're on a job interview or a date or a bumpy plane ride, when your favorite department store has a huge sale or when you're drawing to an inside straight. In other words, life changes your blood sugar.”*

—James S. Hirsch, in an article about reimbursement for continuous glucose monitoring entitled “In Search of Reimbursement: A CGM Odyssey,” published in our latest issue of our patient newsletter *diaTribe*.

*“This therapy is NOT smoke and mirrors! It can and will work as we learn how to best use it.”*

—Dr. Irl Hirsch, speaking at the Global Diabetes Summit about the bright future of continuous glucose monitoring (CGM). Dr. Hirsch predicts that CGM will become the “standard of care” for the treatment of type 1 diabetes within the next 5-10 years.

*“The ADA is under pressure to put exenatide [Byetta] and DPP-4 inhibitors [Januvia] on the recommended ADA algorithm. They [industry] would like to have them there. Arguably, one could look at [Januvia and Byetta] as the new and improved sulfonylurea... But until we have long-term safety, the ADA is relatively unlikely to elevate them onto the algorithm.”*

—Dr. John Buse discussing why the ADA has not added Byetta and DPP-4 inhibitors to the ADA recommended treatment algorithm.

*“This epidemic will be in the 21st century what HIV/AIDS was in the 20th century. Some say that everything is fine today, but this is an illusion.”*

—Dr. Pierre Lefebvre, Immediate Past President of the International Diabetes Federation, speaking at the Global Diabetes Summit in Columbus, OH.

*“Relatively little rigorous evidence is available about whether the benefits of more expensive therapies warrant their additional costs.”*

—Drs. Peter R. Orszag and Philip Ellis, in an article arguing for more targeting of therapy toward patients who benefit the most and the need to generate more information about the relative effectiveness of medical treatments. The original article was published in the November 8 issue of *New England Journal of Medicine (NEJM)*.

*“If you don't give insulin, it's very difficult to measure insulin resistance accurately.”*

—Dr. Richard Bergman, underscoring that the glucose clamp remains the gold standard for measuring insulin resistance and that the HOMA method of measuring insulin resistance is frequently misused and is only useful for patients with normal beta cell function.

*“It is unclear how Medicare will generalize the principle of refusal to pay for poor-quality care beyond this initial and largely symbolic effort.”*

—Dr. Meredith B. Rosenthal, in an article discussing the Centers for Medicare and Medicaid Services’ (CMS) new rule in which it will cease paying hospitals for care made necessary by ‘preventable complications.’ The article, entitled “Nonpayment for Performance? Medicare’s New Reimbursement Rule,” appears in the October 18 issue of *New England Journal of Medicine (NEJM)*.

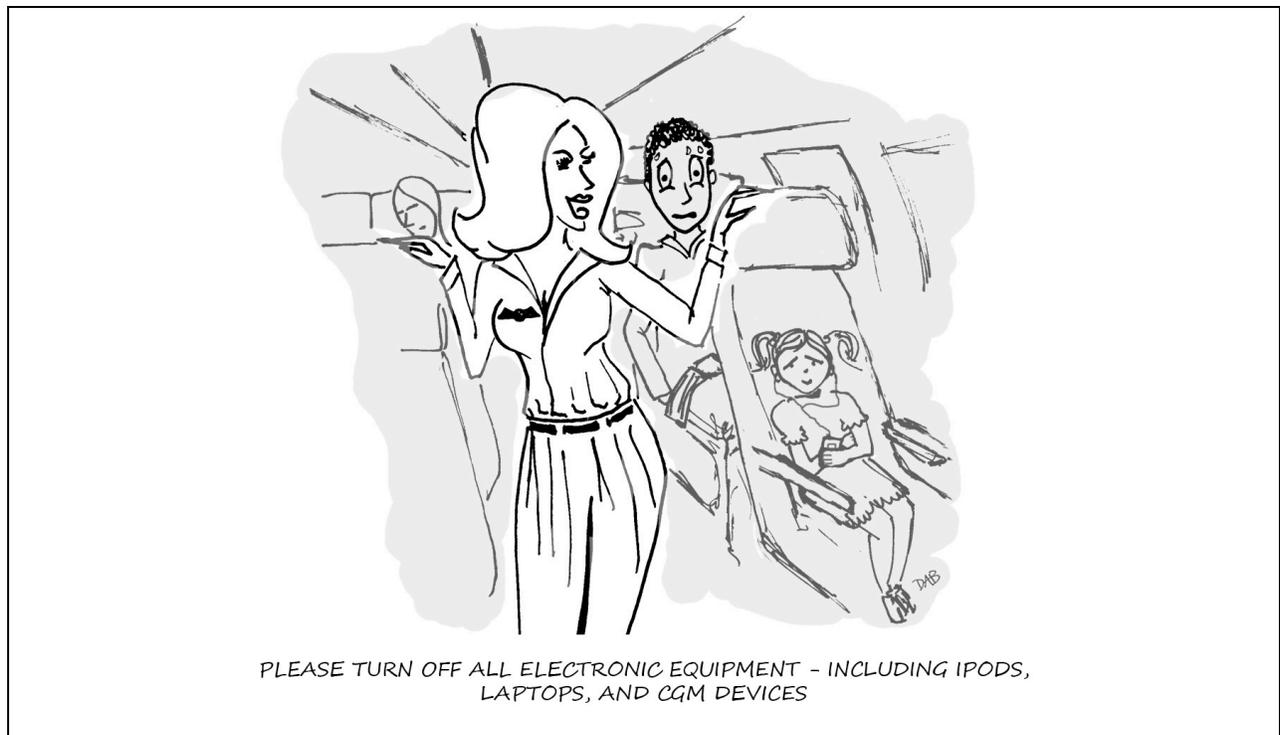
*“Survey data suggest that the prevalence of [chronic kidney disease] in the United States is high and has increased between 1988-1994 and 1999-2004, from 10% to 13%, while awareness of kidney disease among the general public remains very low.”*

—Dr. Joseph Coresh and colleagues in an article about chronic kidney disease entitled “Prevalence of Chronic Kidney Disease in the United States,” published in the November 7 issue of *JAMA*. The article is reviewed in this issue of *Diabetes Close Up*.

*“Physicians may believe that their patients are not at risk for chronic kidney disease if their blood glucose, lipids and/or blood pressure are controlled. This is simply not true. Chronic kidney disease is an insidious consequence of these diseases and can progress quickly without routine monitoring. ”*

--- Herman Hurwitz, MD, FCAP, senior medical director, Quest Diagnostics Incorporated.

## 2. diaTribe FingerSticks



-by Daniel A. Belkin

### 3. DCU Company Watch

- **J&J—New LifeScan Leadership / Exclusive rights to Cyberonic’s vagus nerve stimulation technology:** LifeScan has new leadership again - as reported last month, Don Casey is such a powerhouse that he was promoted *already* to a new position - Worldwide Chairman, Comprehensive Care, a group that encompasses, in addition to J&J’s Diabetes Franchise (LifeScan and Animas), Cordis (J&J’s cardiovascular franchise), J&J Vision Care, and Ortho-Clinical Diagnostics. The former Medical Devices and Diagnostics was split into Comprehensive Care and Surgical Care. Meanwhile, Michel Paul, Worldwide President of DePuy Mitek has been tapped to lead LifeScan and Animas, effective January 2. Paul has had an impressive career at J&J to date, including a stint running the bariatric franchise at Ethicon-Endo Surgery (now Bariatric Edge), which we assume means he brings a strong understanding of obesity needs in particular. We understand he is very well-liked and that he has a strong record in sales and product development in particular. Following Don Casey is going to be a very tough act to follow (20% growth, J&J Diabetes Institutes, UltraMini), but lucky for Paul, he’ll be reporting to Casey, and we believe Casey’s influence should be very long-lasting. To boot, he has one of the best teams in diabetes technology history – we’ll be excited to watch progress.

And, J&J certainly seems committed to a broader strategy in the metabolic arena! More news on this front was that on December 18, 2008, J&J’s Ethicon Endo-Surgery acquired exclusive rights from Cyberonics to patents and patent applications pertaining to vagus nerve stimulation (VNS) for the treatment of obesity, diabetes and hypertension, in overweight patients. Cyberonics will receive \$9.5 million plus royalties on commercial sales of products covered by the subject patents. J&J’s purchase further underscores its deeper commitments in the diabetes and obesity arenas. As a reminder, the vagus nerve connects the brain with many organs in the abdomen and plays a role in stomach emptying and other aspects of digestion. Cyberonics has been developing medical devices that provide VNS to treat depression and epilepsy. Recent evidence suggests that the vagus nerve may also be a target for weight loss – by blocking the vagus nerve, hunger signals from the stomach are reduced and gastric emptying is slowed. Blocking the vagus nerve may be a less invasive alternative weight loss procedure to gastric bypass surgery; although it remains largely untested and preliminary evidence suggests that it is less effective overall than other forms of bariatric surgery – less effective perhaps but better safety perceptions are certainly important in this arena. Cyberonic’s VNS technology may give Ethicon a jump-start in developing vagus nerve blocking technology for the treatment of obesity. Other companies are competing in this area as well. Only last month, a development stage medical device company called Enteromedics that is developing a treatment that blocks signals to the vagus nerve using high frequency, low energy, electrical impulses completed its IPO. Enteromedics plans to submit the PMA in mid-2009, for commercialization in early 2010 – for more on prospects see our November Company Watch. Ethicon has not announced its explicit plans regarding vagus nerve treatments but we imagine with Don Casey overseeing the group, time is not a-wasting.

- **Novartis—Galvus moves forward in the EU but higher h-a-s-s-l-e expected compared to Januvia:** On December 17, Galvus received a positive opinion from European Union’s Committee for Medicinal Products for Human Use after the committee made changes to prescribing recommendations due to liver safety concerns. Galvus has been recommended for use only with a sulfonylurea at a 50 mg once-daily dose and with metformin or a thiazolidinedione at a 50 mg twice-daily dose. The 100 mg one-daily dose will not be available due to concerns about liver damage, a clear negative. Although there were no head to head comparisons of Galvus and Januvia, we’ve heard that the 100 mg dose of Galvus was likely more efficacious than the highest available dose of Januvia – now, the two drugs are likely to have similar efficacy. More negative

for Novartis in our view, patients on Galvus must have liver screening conducted at the start of treatment, every three months after starting therapy for the first year, and then on occasion after the first year of therapy – this definitely increases the “hassle factor” involved with the drug and would be considered a major marketing negative.

On balance, we don't perceive this news as a big negative for Merck, since Novartis still won't re-submit Galvus in the US until 2009 and even in the best case (which this isn't), we believe DPP-4 inhibitors will be difficult to market in EU due to the (to generalize wildly) preference for cheap, proven drugs. Still, it is progress for Novartis that it should be able to obtain some commercial experience with Galvus in the not too distant future. These dosing changes open the path to formal regulatory approval in Europe, and Galvus should become available to patients in Europe in the first half of 2008. We continue to think that DPP-4 inhibitors will continue their success in the US if no safety flags emerge – development of strong long-term data will be key and we believe Merck is hard at work on this front.

- **Merck—Januvia filed in Japan:** On December 12, Merck's Japanese partner, Ono Pharmaceuticals, announced that it had filed for approval to sell sitagliptin (marketed as Januvia in the US) Japan. Merck intends to market the sitagliptin through its Japanese unit Banyu Pharmaceutical. According to the World Health Organization, there are nearly seven million people with diabetes in Japan, about one third the size of the US market.
- **Biodel—Ambitious agenda for VIAject in 2008:** During the Biodel 4Q earnings call on December 11, CEO Dr. Solomon Steiner highlighted the company's achievements this year, including a successful IPO that raised ~\$80 million, acquiring patent protection for the company's two leading drug candidates (VIAject and VIAtab), and phase 2 clinical data for VIAject presented at EASD. In the phase 2 clinical study, we were impressed to see that VIAject had a more rapid kinetic profile than insulin lispro (Humalog, Lilly), albeit in a small number of patients, which resulted in greater reductions in post-prandial glucose and reduced hypoglycemia. In the study, 13% of patients using VIAject experienced hypoglycemia, compared with 26% of patients using lispro and 27% of patients using human insulin. We do have some concerns about the design of the study (we attended this presentation at EASD); notably, the carbohydrate dose was unusually large (120 g), and the timing of the insulin administration (both lispro and Viaject) was immediately prior to the meal, which is not as suggested – though we do believe that is how insulin is typically used, so perhaps this does resemble a more “real-world” study. Indeed, Dr. Steiner contended during his presentation that most patients take their rapid acting insulin immediately prior to eating, and differences in time-to-onset in the study are large enough to account for discrepancies in time of administration prior to eating – an argument with which it's hard to find fault.

Biodel has an ambitious agenda for 2008. Dr. Soloman maintained that the company would finalize enrollment of the two VIAject phase 3 studies for type 1 and type 2 patients (n=400 each), complete pharmacokinetic and pharmacodynamic studies, present pivotal phase 3 data, file an NDA by calendar year end 2008, and finalize a commercial strategy. We believe it will require a very a busy year to reach this goal, but there is definitely significant interest in seeing these data. FDA would only require non-inferiority to regular insulin for approval, we believe, but we assume there is a very good chance to show superiority. Faster insulin would result in fewer “swings” for patients and could have very positive implications for work on the artificial pancreas and closed loop systems, depending on how much faster the insulin is and how the overall profiles look. Net losses for the quarter were \$8.4 million, up from \$3.9 in the comparable period last year, due to increased R&D spending. Biodel has cash equivalents of about \$80 million, or 9-10 quarters at the current burn rate.

**Merck—Talking up taranabant, with ambitious plans to file in 2008:** At the Merck 2007 Annual Business Briefing on December 11, Dr. Peter S. Kim, President of Merck Research Laboratories, spoke about Merck's CB1 receptor antagonist, taranabant. Notably, Merck anticipates filing an NDA for taranabant in 2008, which was earlier than we had anticipated given all the anxiety (so to speak) surrounding Sanofi's similar CB1 receptor antagonist, rimonabant. Merck showed new data on taranabant and reviewed some data we had reported on from NAASO. In phase 2, taranabant was generally well tolerated and caused ~4% weight loss for the 2 mg treatment group, and ~5% weight loss for the 6 mg treatment group. This was large trial (n=533) and we look forward to seeing safety, efficacy, and tolerability results in phase 3. Dr. Kim said that the taranabant phase 3 clinical trial will include doses up to 2 mg but no higher due to the lack of efficacy improvement above 2 mg in phase 2 – we assume there were efficacy/ safety tradeoffs here. In our view, taranabant's possible association with depression, as indicated by its association with “depressed mood/symptoms” in phase 2, remains a major concern. The issue of depression is one of the factors that has kept rimonabant from being approved in the US, and it is likely that depression is a mechanistic effect of CB1 antagonism.

Dr. Kim also spoke about the differences between rimonabant and taranabant. He said that the safety profiles of the drugs are “substantially” different, as indicated by the preclinical data. In contrast to rimonabant, taranabant had greater than a 100-fold safety margin for neurological effects such as convulsions and seizures in non-human primates. The FDA has concluded, according to Merck, that rimonabant differs from others in the class by its narrow therapeutic index. Notably, the taranabant phase 3 clinical program will include patients with depression who are on one anti-depressant – no doubt this is because Sanofi didn't do this and it was probably a drawback for them at their advisory board meeting as they didn't have the experience in this group. Dr. Kim said that Merck hopes to gain clinical experience in treating this patient population with taranabant.

Kenneth Frazier, Executive Vice President and President of Global Human Health, also spoke at the meeting and reviewed the “unprecedented execution” of the Januvia/Janumet franchise. Despite being the first drug in the DPP-4 inhibitor class to be approved, Januvia discovery and development occurred in only 3.8 years, compared to an industry average of 7.1 years. As another point of reference, the other DPP-4 inhibitor that had been characterized as a leader prior to recent safety issues, Novartis's Galvus, began development at a similar point as Januvia, and approval is unlikely in the US before 2009. Januvia has been approved in 64 countries and gained reimbursed in 14. In the US, Januvia is now covered by most managed care plans, representing over 200 million covered lives. There have been approximately three million prescriptions of Januvia since the drug's initial launch. As in previous briefings, Mr. Frazier called attention to the absence of cannibalization of Januvia sales from the introduction of Janumet, the combination Januvia/metformin pill. Although Janumet holds only ~0.6% of the oral diabetes and GLP-1 market, the Januvia franchise (Januvia + Janumet) now represents over 4% of the oral diabetes and GLP-1 market. Mr. Frazier mentioned that the next stage of the development program for the Januvia/Janumet franchise will include 15 more studies to begin in 2008, adding to the 49 studies that have already been completed or are underway. The studies will be geared towards obtaining additional long-term data, new uses, and potential combination and new formulations of Januvia/Janumet.

- **Novo Nordisk—Positive LEAD3 data released and filing expectation moves up a bit:** On December 11, Novo Nordisk announced the results of the highly anticipated LEAD3 (Liraglutide Effect and Action in Diabetes) trial and held a conference call to discuss the results. The data were very positive from our perspective in completing the clinical package to be sent to

FDA and EU regulatory authorities. From an 8.2% baseline, A1c dropped over 1 point on average; in patients not previously on therapy that had a baseline of 8.5%, A1c dropped an impressive 1.5% (patients most out of control can improve more easily). Over 50% of patients on liraglutide reached an A1c of 7% and ~35% reached an A1c of 6.5%. For drug-naïve patients, over 60% reached an A1c of 7%. Novo Nordisk confirmed it will submit this in 2Q08, slightly earlier than had previously been planned (mid-08 had been the earlier goal). Although nausea was higher than in other LEAD trials, over 95% of the patients were no longer experiencing nausea after three months on therapy – we believe titration has become more nuanced and patients are more successful with it over time. Weight loss noted as a 3-4 kg difference between liraglutide and the SFU used as an active comparator (glimepiride, an SFU that is known for less weight gain than other SFUs). Versus baseline, the weight loss was likely in the range of 2 kg, similar to AMIGO trials, though that is not the right comparison because that was at six months, and weight loss hadn't reached a plateau.

From a regulatory and marketing and payor perspective, these data should be viewed quite favorably. While SFUs are cheap, they can be difficult for patients to use as they cause hypoglycemia and weight gain. Novo Nordisk has now tested liraglutide in a very broad population and appears likely to present to both FDA and the EU regulatory authorities a very full clinical package, including studies with those on metformin, SFUs, TZDs, insulin, etc. It also has tested liraglutide in monotherapy, as well as in patients using two, three, or more oral drugs, or insulin. Novo Nordisk stressed that it now has all the data required to submit for FDA and EU approval and that all steps in the product supply chain are complete. A range of phase 3b studies are in the works, including a six-month head-to-head versus Byetta. This study has now been enrolled and the results will be announced around the time of product launch, presumably in the first half of 2009 if all proceeds on track. Upon launch, liraglutide is expected to be available in a pre-filled pen with a 32-gauge needle.

- **Amylin/Lilly—Strong Byetta monotherapy data:** On December 6th, Amylin and Lilly released impressive monotherapy data for Byetta that should win the company a monotherapy indication – and fast! In the monotherapy trial, A1c reduction was 0.9% for those on the regular dose (10 mg) of Byetta, very strong in our view given the 7.9% baseline. It is hard to compare this monotherapy trial to Novo Nordisk's, in which the population had an 8.5% starting A1c. The Byetta patients were likely recently diagnosed, and it would be important in our view to watch durability in this group, which likely has stronger beta cell function than other patients who take the drug as an add-on therapy later in disease progression. From a public health perspective, getting people on earlier, more aggressive therapy could be a real positive as durability may be even more impressive than those who take it later. For those on the lower dose (5 mg) of Byetta, A1c reduction was 0.7% - subanalysis not given but our guess is their baseline was even lower. Impressively, 60% of patients on Byetta monotherapy got to 7% A1c or less. We thought the most notable news about Byetta monotherapy was the very positive side effect profile, notably very little nausea: only 3-13% of patients in this study experienced nausea, compared to ~40% in the AMIGO trials and ~20% in the recently released once-weekly exenatide results. We believe this is because there was less "noise" from other compounds that also cause nausea - we imagine if once-weekly exenatide is also given to those recently diagnosed, the nausea rate could look even better. Although it is common to hear praise about metformin as a cheap, great, safe drug, we believe the tolerability issues, chiefly nausea, do deter adherence, which really isn't discussed - likely this contributes to the 60%-plus patients not reaching glycemic targets.

The Byetta monotherapy indication should be submitted in the next several months. We would anticipate a late 2008 approval considering Amylin and Lilly already have an approvable letter,

and this is striking monotherapy data. The approval could potentially come even before that depending on how fast the filing can happen. We would term the filing a milestone when it happens as we believe a monotherapy indication could be quite meaningful commercially. Our model notes nearly 900,000 new type 2 patients in 2007 alone in the US, and we believe by 2010 the annual increase in newly diagnosed type 2s will be over 1 million. We also believe there is an emerging trend toward starting a therapy, monitoring it, and if it isn't working, moving to another therapy faster. All this bodes well for Byetta. We also believe millions of patients in the US alone on single-agent therapy have tolerability issues (hypoglycemia with sulfonylureas, gastrointestinal issues with metformin) who would be promising monotherapy candidates for Byetta.

- **Vivus—Pipeline overview at Research and Development Day:** On December 6, Vivus held an R&D Day in New York City to showcase the development and rationale for Qnexa, currently in phase 3 testing. Peter Tam, senior vice president of product and corporate development at Vivus, put forward that Qnexa's components – topiramate (generic Topamax) plus phentermine – provide synergistic weight loss and cancel out adverse effects (for example, topiramate is a depressant and phentermine is a stimulant). In our view, Qnexa is a model of the overall direction that the obesity market is moving toward: lower dose combination therapies. As obesity expert Dr. Louis Aronne explained in his presentation at the meeting, combination therapies that tackle counter-regulatory responses offer the potential to overcome the ~7% weight plateau that is observed with currently approved drugs.

Dr. F Xavier Pi-Sunyer, a highly regarded obesity expert from St. Luke's at Columbia University, discussed the Qnexa phase 3 clinical program, specifically the one-year EQUIP (OB-302) and CONQUER (OB-303) trials. These studies are designed to generate risk/benefit data on Qnexa for the treatment of obesity and related co-morbidities, in support of product approval, formulary acceptance, and reimbursement. The company plans to enroll EQUIP with 1,250 obese subjects without metabolic co-morbidities, and CONQUER with 2,500 overweight and obese subjects with metabolic co-morbidities. A third six-month study, EQUATE (OB-301), initiated on December 7, will evaluate the safety and efficacy of Qnexa vs. topiramate, phentermine, and placebo monotherapy in 700 obese patients with co-morbidities.

Although Vivus' approach is very rational, we also believe the competitive landscape has become tougher for obesity drugs in development. Other more efficacious and safer combination therapies are in development, such as Amylin's pramlintide +leptin combination therapy, which is in phase 2b. In phase 2, Qnexa caused ~10.4% weight loss, compared to ~12.7% for pramlintide + leptin. Assuming both finish phase 3 testing, that will be a better time to compare side effect profiles. Although Qnexa's monotherapy components are already approved drugs, their mode of action (CNS) is inherently risky and unexpected long-term risks are possible. One important takeaway from the meeting was that Vivus is very focused on tackling type 2 diabetes with Qnexa. The drug does not specifically address hyperglycemia, but like other weight loss agents, it may indirectly improve glucose control by addressing the underlying issue of obesity. There is an ongoing study for Qnexa in type 2 diabetes that should be completed in 1H08, and Vivus has planned an extension study as well.

- **Lilly—Analyst meeting reinforces commitment to diabetes:** Lilly hosted an analyst meeting on December 6 that we felt strongly reinforced its commitment to diabetes, Byetta, and once-weekly exenatide, while de-emphasizing insulin (shock!). The attention and enthusiasm for Byetta and once-weekly exenatide was deeper than we had seen earlier or anticipated, and we view this as a positive for both Lilly and Amylin. Management seems to be very committed to moving once-weekly exenatide through the regulatory pathway as quickly as possible, though we did not really learn much on the likelihood that bioequivalency studies would be required by the

FDA. As noted at Amylin's R&D Day, Lilly and Amylin are already at work on several superiority trials for once-weekly exenatide that gives us confidence from a competitive perspective. This in turn increases our confidence in the prospect that analyst estimates will be moving up for 2010 and beyond for the compound. Lilly also confirmed that it is working with Amylin on once-weekly exenatide for obesity. (Can pre-diabetes be far behind? We hope not.)

Byetta's international launches should gain steam in 2008 with 60 countries to be added to the 21 to date – this compares to 64 international launches for Januvia – as a reminder, Lilly is responsible for all of Byetta's international launches. There have been several impressive reimbursement achievements abroad with Byetta: NICE in the UK is at the top of the list in our view. Germany has had good progress also, and we believe from recent discussions that Lilly has a re-energized presence there. Having the distinguished Dr. Robert Heine from the Netherlands leading development should help Lilly's progress substantially, and we believe his presence internally and externally will be a major positive for Lilly. Asia we note is slower - Byetta BID seems to be positioned there for 2011. A China launch would be hoped for in the coming years though Lilly wasn't specific here; still, its business there is expanding at a very healthy 28%, where we understand diabetes is driving growth (albeit from a relatively low base; Lilly hopes to have over \$500 million there in sales by 2015).

Lilly management said it was moving its internal GLP-1 program into phase 2 in the second half of next year. We are surprised it has taken this long although we didn't get the sense this was overly prioritized at Lilly. Management was still very upbeat about prospects for its inhaled AIR insulin. They should benefit from their immense knowledge and insight on insulin initiation challenges and by the cool Alkermes device, which is about 20% of the size of the first-generation Exubera device. They understand not only convenience in devices but also ease of use; dosing will be much easier as well. We believe these challenges were underestimated with the first generation of Exubera. Still, this is an uphill battle in our view.

- **BMS—Intent on Saxagliptin 2008 filing:** BMS held an analyst meeting in New York on December 6 in which it said it would file saxagliptin in 2008 – we think this is another ambitious plan for filing in 2008 (along with Merck, Bidel, Mannkind) but we clearly see why they'd like to be #2 to market in the US given Januvia's strength to date. Management was generally upbeat on the drug, but indicated the possible risks with saxagliptin pertaining to skin issues that all drugs in the DPP-4 inhibitor class seem now to have experienced in some form (either through Steven Johnson's Syndrome, monkey toxicity, etc.). We learned of several new studies that will be conducted, including: 1) a head-to-head saxa/metformin versus Januvia/metformin (that's also bold in our view); 2) a renal impairment study; and 3) an add-on combo with insulin study. While BMS and partner AZ would have their work cut out for them battling Merck, they look like they could be second to market; Novartis's Galvus looks to be stuck until 2009, when a resubmission may occur. BMS' SGLT-2 inhibitor was also discussed - dapaglifozin. This compound was referred to as "first in class," and management sounded enthusiastic about it - more so than with saxagliptin, possibly because competition isn't as tough as yet. Dapaglifozin works by preventing the re-absorption of glucose in the kidney, and therefore promotes the excretion of glucose in urine. Management repeatedly referenced potential for weight loss though this needs more study. We are very interested to see potential synergy with other diabetes agents since, as management pointed out, this isn't an insulin sensitizer or a secretagogue.
- **Orexigen—Pipeline overview provided at analyst/investor “state of mind” day:** On December 5, Orexigen Therapeutics held its first analyst/investor day in New York City. No new clinical data were presented at the meeting as this was more a pipeline discussion. Dr. Eduardo Dunayevich, Chief Medical Officer of Orexigen, provided a clinical overview of the company's two

products under development: Contrave, a combination of the generic drugs bupropion and naltrexone; and Empatic, a combination of the generic drugs bupropion and zonisamide. Contrave has completed phase 2 and is entering phase 3. Empatic is currently in phase 2b. Neither drug needed phase 1 testing because they comprise components that have already been approved - clearly a positive for commercial progress. Contrave's phase 3 program will require 1,500 patients exposed to the drug for over one year.

Management underscored that Contrave's and Empatic's components have synergistic modes of action. In phase 2, Contrave produced from 6.6% to 10% weight loss, compared to only 2% for bupropion and 1% for naltrexone separately. It was necessary to demonstrate synergy in phase 2, but now that synergy has been demonstrated there will be no monotherapy arm in the phase 3 trial – this is another positive, since that would have made enrollment more difficult. In the optimal dose (referred to as NB32), there was a 16% discontinuation rate due to adverse events. The most commonly reported adverse event was nausea - a well-known side effect of naltrexone. The phase 2 trial contained an immediate release formulation of naltrexone, and using a sustained release form should produce better results and better intellectual property protection.

An overarching theme of the presentation was that obesity is a disease of the mind rather than metabolism. Management underscored that while many obesity researchers focus on how the body's fuel and fat levels control appetite, habits and desires often override metabolic need. By affecting dopamine and other neurotransmitters, Orexigen's drugs target movement, motivation, reward, and well-being (i.e., the addictive properties of food). Highly regarded obesity expert (and former NAASO president) Dr. Louis Aronne spoke at the event about the future of obesity treatment. He called for better understanding of metabolic and counter-regulatory systems in order to develop more targeted therapies. He expects that in the future, more treatments will be developed to affect specific central and peripheral targets and greater efficacy will be achieved with rational combination medical and surgical therapies. Dr. Aronne cited Orexigen's drugs as examples of rational combination therapies that work synergistically. Notably, he also spoke enthusiastically about the results from Amylin's exciting pramlintide + leptin combination trial – we doubt this was scripted but was interesting to hear.

- **Amylin—Exciting pipeline reviewed at R&D day:** On November 28, Amylin held its second annual R&D day in New York. Dr. Orville Kolterman reviewed the currently marketed and later-stage products in Amylin's diabetes program, including Byetta, Symlin, and exenatide once-weekly (curiously, management did not refer once to exenatide once-weekly as LAR – we assume there is a goal to emphasize the dosing frequency). Dr. Kolterman expressed optimism that a monotherapy indication for Byetta is on its way pending a successful trial that will be presented before the end of the year (see above!). Prior to seeing the data, we thought that if the A1c drop for monotherapy approached 1%, that would be a relatively impressive result for both recently diagnosed patients and “diet and exercise” patients who were consistently failing lifestyle therapy but had difficulty with other therapies such as metformin (40% had GI issues in ADOPT), SFUs (hypoglycemia is a common problem as is weight gain as is secondary failure – it doesn't work very long), and TZDs (weight gain, edema, bone fractures, CHF concerns, and MI concerns).

It was very interesting to learn more from Dr. Kolterman about the once-weekly exenatide/Byetta trial. After a 30-week treatment period, more than 75% of subjects reached the ADA target A1c of 7%, and approximately half reached an A1c of 6.5%. The average starting A1c was approximately 8.5%. In the renowned Treat To Target study, only about 57% of subjects reached an A1c target of 7% using Lantus insulin; the starting A1c in this trial was not significantly different at 8.6%. In the exenatide once-weekly study, even patients with a starting A1c of 9% did very well, with a notable 66% reaching an A1c of 7% and one third reaching a target A1c of 6.5%. We found this especially

remarkable since we would have assumed that patients with an A1c of over 9% had little beta cell function and would not be the best candidates for Byetta. In fact, it seems these might be among the best candidates for LAR, perhaps because at least one reason for their extremely poor A1c's is resistance to insulin – either by them or their doctors.

The most exciting element of the day was hearing plans for superiority trials for once-weekly exenatide – this is a comprehensive plan where the drug will be tested vs. DPP-4 inhibitors and TZDS, Lantus, and metformin. We believe the metformin study may support the EU filing. These will be multi-hundred-person trials of ~six months (we don't know whether some may be longer, have open-label elements, etc.) Although it wasn't discussed at the meeting, we see the prospects for once-weekly exenatide for pre-diabetes and Byetta for treating diabetes in the hospital as very significant. Given the public health crisis associated with pre-diabetes (54 mm Americans) and the tremendous evidence showing the need for tighter glycemic control in the hospital, we think these areas should be explored at length, and we would see government funding as appropriate. We discussed with a highly regarded doctor the potential for diabetes “remission” for those in the hospital in particular and the potential for people to “un-do” their pre-diabetes (those recently diagnosed with lots of beta cell function could do this). Very exciting.

Later at the meeting, Dr. Baron reviewed Amylin's middle-stage product pipeline. He spent most of his time discussing strong results from Amylin's phase 2 study of pramlintide + leptin. Although leptin is ineffective in monotherapy because of leptin resistance, pramlintide is a leptin sensitizer. In Amylin's phase 2 study, pramlintide + leptin combination therapy achieved 12.7% weight loss – a result Dr. Baron characterized (appropriately in our view) as “unprecedented.” Overall, 89% of patients on the combination therapy achieved greater than 5% weight loss, 56% lost 10% or more, and 28% of patients lost 15% of weight or more. Strikingly to us, patients continued to lose weight through the end of the study, and it is not clear that 12.7% weight loss is the floor – we doubt it is, given the apparently downward sloping curve. Another highlight was Dr. Baron's remark that the target product presentation for pramlintide + leptin is a twice-daily injectable in a single disposable pen.

As the last speaker, Dr. Michael Hanley spoke about Amylin's process of drug discovery, which begins with the discovery of novel peptides. The company has greatly expanded its ability to find peptides and screen them for commercial potential. Amylin has been “overwhelmed” by the peptides it has discovered. In order to preserve its key commitment to diabetes and obesity, while at the same time creating the most possible value out of its peptide library, Amylin has pursued alliances into new therapeutic areas. This includes an alliance with BioSeek (inflammation), Xenome (peptide libraries), Kelaroo (computational sciences), and Psylin (CNS). After attending the excellent meeting, we believe we will see real breakthroughs in the high-need areas of diabetes and obesity. Based on the data, we feel highly confident that their once-weekly exenatide (submission still planned “by mid-09” though further information on that front makes us believe there is a good chance it will be before then) and pram-leptin obesity combination (phase 2b) will enable breakthrough therapies.

- **Sirtris—Three new SIRT1 activators described in article in *Nature*:** On November 29, Sirtris researchers published an article in the journal *Nature* showing that three novel SIRT1 activators - SRT1720, SRT1460, and SRT2183 - may enhance insulin sensitivity without contributing to weight gain or increasing the risk of hypoglycemia. The most potent of these compounds, SRT1720, was shown to be similar in efficacy to rosiglitazone (Avandia). This suggests that the other two compounds (as well as the company's lead compound, SRT501, a proprietary formulation of resveratrol) are less effective than Avandia. On December 13 at the RBC Capital Markets Healthcare Conference, Sirtris also presented data showing that one of its

new chemical entities is equally or more effective at controlling blood glucose than Merck's Januvia. Since all these molecules activate only SIRT1, the study strongly supports the notion that SIRT1 is an important target for increasing insulin sensitivity and that SIRT1 activators will likely become an important drug class. Upcoming trials in 2008 will establish whether the safety and efficacy observed in these animal models can be extended to patients with type 2 diabetes. Our full review of the article is on page 38. Later, Sirtris announced that the National Institute of Aging (NIA) has selected one of Sirtris's SIRT1 activators for an Interventions Testing Program, to study the effect of SIRT1 activation on aging. The company would not disclose which SIRT1 activator had been selected. However, we suspect given the timing of the announcement that it is one of the company's new chemical entities. The announcement is indicative of the close relationship Sirtris has maintained with the academic community. Furthermore, the announcement may be viewed as a positive suggestion of the way Sirtris's drug candidates are perceived by leading aging researchers within the NIA.

Management also presented at the Lazard Healthcare Conference on November 29, where it explained that Sirtris' strategy is to develop drug candidates that target the sirtuin family of enzymes with the goal of producing the same benefits that can be achieved with calorie-restricted diets, for the treatment of metabolic and mitochondrial diseases. The presentation focused on Sirtuin's lead drug candidate, SRT501, which reduced glucose and insulin levels with a "very benign side-effect/adverse event" profile in preclinical models. It is currently being tested for type 2 diabetes in several phase 1 and one phase 2 trial; results from a once-per-day dosing study are expected in "a few months" and from a twice-per-day dosing study early next year. Sirtris hopes to partner SRT501 sometime during phase 2 development. Management noted that SIRT1 activation produces even larger benefits in combination with metformin. Management pointed to the other six members of the sirtuin family (SIRT2-7) as additional potential targets for the development of drugs to treat "disease of aging." Sirtris currently has a cash balance of \$127M.

- **Oramed—Completion of Phase 1 Animal Studies:** On November 15, Oramed reported that it had completed animal studies for its oral insulin capsule as part of phase 1b clinical trials. This follows the successful completion of a Phase 1A clinical trial of oral insulin gel capsules in eight healthy volunteers earlier this year. That study was intended only to assess safety and tolerability as well as the absorption properties of Oramed's oral insulin product. Oramed, which is based in Israel, expects to complete formal phase 1 clinical testing by mid-2008. Oramed is not the only company pursuing oral insulin – Emisphere and others have candidates as well. Although an oral insulin delivery route would certainly be patient-friendly, it remains to be seen whether it is clinically and commercially viable. We remain very skeptical.
- **MannKind—Another TI insulin phase 3 trial, emphasis on differentiation:** MannKind has initiated a fifth phase 3b clinical trial to further differentiate TI insulin, an inhaled insulin product, from currently available rapid acting analogues at the time of launch. The trial is on top of the four clinical trials underway for TI's new drug application (NDA): 1) 009, a pivotal Phase 3 study comparing the efficacy of mealtime use of TI to mealtime use of rapid-acting subcutaneous insulin in a population of approximately 500 patients with type 1 diabetes for a 12-month period. The trial began enrolling in the first quarter of 2006.; 2) 102, a pivotal phase 3 study comparing the efficacy of mealtime use of TI to the twice-daily use of premixed insulin in a population of approximately 500 patients with type 2 diabetes for a 12-month period. The trial began enrolling patients in the first quarter of 2006.; 3) 103, a phase 3 study intended for label expansion comparing the efficacy of TI alone and in combination with metformin in 420 patients with type 2 diabetes previously not at goal with metformin and sulfonylurea. This trial began enrolling in the

second quarter of 2006. 4) 030, a two-year pivotal phase 3 safety study testing pulmonary function in patients who are treated with TI insulin as compared to oral or injectable therapies.

The new trial, number 117, will compare TI to Humalog in type 1s. Insulin glargine (Lantus) will be used as a basal insulin in both treatment arms. An important difference between 117 and the other trials is that 117 has very aggressive goals – both treatment arms will be titrated to fasting glucose levels <110 mg/dL. The 117 trial appears to be designed to highlight TI's rapid onset of action and short duration of action. In the time since Pfizer's discontinuation of Exubera, MannKind's management has been eager to differentiate TI from Exubera. Management has previously argued that unlike Exubera, TI insulin will offer clinical advantages because it has a kinetic profile that mimics the body's physiological response to glucose, and it has pointed out that TI is absorbed instantly and peaks in only 12-14 minutes – faster than the current generation of rapid-acting analogues. We understand that if TI's time profile is as rapid as management has previously described, the 117 trial will show less hypoglycemia in the TI arm relative to Humalog. The 117 trial may also call attention to differences in weight profiles between TI insulin and Humalog. MannKind reports that it has planned other clinical trials to highlight TI's clinical advantages, although it has not yet released details about these trials. We look forward to reporting on the results of the 117 clinical trial and other TI clinical trials.

At the Piper Jaffray Healthcare Conference on November 27, management said that last trial for TI will be completed in early December (2007) and the company plans to file the NDA roughly one year afterwards. The target population will be type 1 and early type 2 patients; the marketing focus seems to be on the ability to achieve normal meal-time excursions with minimal risk of hypoglycemia due to the rapid kinetics of the drug (peak in 12-14 minutes). Management emphasized that TI is “nothing like Exubera,” which was a “very expensive way to inconveniently deliver insulin.” As well, TI has no effect on the lungs; Mannkind will have data on ~3,500 patients by filing and plans to have capacity for 2 million patients as well as educational programs for endos. Also in the pipeline are two inhaled Technosphere formulations of GLP-1 (phase 1a results for MKC253 were released in early November); management mentioned lack of nausea, vomiting, and sweating in phase 1 trials, as well as significant bioavailability. Management said it is not looking for a development partnership but would be interested in co-promotion/marketing; it has a cash position of \$454M after its recent self-managed secondary financing round, led by Al Mann, Fido, and Legg Mason.

- **Metabasis—Second-generation FBPase inhibitor in phase 2 after CS-917 failure:** Management explained at the Lazard Healthcare Conference on November 28 that MBO7803, Metabasis' second-generation FBPase inhibitor, is currently in phase 2a trials. As a reminder, FBPase is a key enzyme in the liver gluconeogenesis pathway. Inhibiting it should reduce overall levels of blood glucose. Management noted that this mechanism acts independently of insulin and thus is a prospect for both monotherapy and combination therapy. However, Metabasis' first-generation molecule, CS-917, licensed to Daiichi Sankyo, failed to show efficacy in a three-month phase 2 study. The phase 2a trial for MBO7803 is a 100-patient 28-day trial with results expected in 2Q08. Management said that it will look for partnerships at the “appropriate time” – we assume that companies will be cautious about the FBPase inhibitor class after CS-917's failure. Other drugs in Metabasis' core pipeline include MBO7811, an orally active TRBeta agonist for hyperlipidemia in phase 1b trials, which the company expects to be usable in combination with statins. Phase 2a trials should begin at the end of 2008 if the current study goes well. The company is also working on a preclinical glucagon agonist and a preclinical AMPK activator for diabetes; the latter is in partnership with Merck. Metabasis currently has \$51M in cash.

- Arena—All pivotal phase 3 trials for lorcaserin underway:** Management discussed Arena’s five pipeline candidates at the Lazard Healthcare Conference on November 28 and promised to announce a sixth drug soon. Farthest in development is lorcaserin, a 5-HT<sub>2C</sub> serotonin receptor antagonist in phase 3 trials for obesity. The largest phase 3 trial, BLOOM, passed its six-month safety review for valvulopathy in September; the 12-month review is expected in March 2008. BLOOM is a two-year, 3,100-patient trial testing a 20 mg daily dose of lorcaserin vs. placebo. Arena announced the initiation of two additional one-year phase 3 trials on December 13; BLOSSOM and BLOOM-DM will evaluate 10 mg and 20 mg doses of lorcaserin vs. placebo in ~3,750 patients; the latter trial will look specifically at patients with type 2 diabetes. Interestingly, while echocardiograms (to monitor for valvulopathy) will still be done on patients in these two trials, FDA-defined valvulopathy is no longer an exclusion criterion for enrollment as it was with the BLOOM trial. At the Lazard conference, management emphasized that the valvulopathy problems encountered with the fenfluramines, which targeted both the 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> serotonin receptors, were associated with 5-HT<sub>2B</sub> antagonism and are not seen with lorcaserin. So far, the clinical trial data seem to confirm this. The most common adverse effects with lorcaserin are headache and nausea. Arena will file lorcaserin with the three phase 3 trials and plans to launch in 2010; it expects to partner the drug sometime after the next safety review but before the NDA. Arena has partnered with Ortho-McNeil (JNJ) to develop drugs for type 2 diabetes; their leading candidate is APD668, currently in phase 1 studies. The molecule targets the glucose-dependent insulinotropic receptor (GDIR) to stimulate glucose-dependent insulin production. Metabasis has received \$43 million so far from the partnership and is eligible to receive \$295 million in milestones plus double-digit royalties.
- Alkermes—Bullish on once-weekly exenatide and AIR insulin:** Management gave a quick update on Alkermes’ product pipeline at the Lazard Healthcare Conference on November 28. Among the products discussed included once-weekly exenatide; management noted that Amylin is now planning market-position studies for the product, which it characterized as the “most exciting thing next to the Red Sox winning.” As a reminder, in the phase 3 trial, three out of four patients reached A1c <7% and there was 30% less nausea than with twice-daily Byetta. Management said that Alkermes’ role now is to transfer the manufacturing technology to Amylin. Regarding AIR insulin, management said that the secret to success is “better data, better product, and better partner” and remarked that patients in clinical studies don’t want to give the device back. Unlike Exubera, AIR insulin will be dosed in insulin units (IUs). A few ongoing studies were highlighted: Lilly is conducting concordance studies to look at differences in glucose control between patients on pulmonary and non-pulmonary insulin; these are patients who are on oral medications, Byetta, etc. AIR insulin is also being tested against Lantus; this will be an interesting result to look at, as it focuses on the insulin-naïve population as potential users. Management characterized Lilly as a “terrific partner.” Alkermes is manufacturing the insulin capsules for the device and will receive 10%+ royalty and manufacturing benefits from Lilly in what management called one of its “more favorable licensing agreements.”
- DexCom—Continuing progress on all fronts:** Management gave an update at the Piper Jaffray Healthcare Conference on November 27. The presentation began with a review of the demographics and costs of diabetes, after which management emphasized that hypoglycemia is the main limiting factor on tight control. Management highlighted that the second-generation sensor is approved for seven-day use and has the smallest needle and wearable pod on the market – user reviews continue to be strikingly better than with the STS first generation – clearly much learning was put into fast action. DexCom received approval in mid-November for calibration with any FDA-approved meter; the new instrument should be available at the end of Q1 and the company plans to upgrade users by the end of Q2. This is an excellent example of DexCom’s talent

for moving through FDA deftly using smaller steps. Users who don't currently use LifeScan meters for all blood glucose monitoring (probably at least half) are eager to carry around fewer items to make the continuous monitoring work – this is also a prime example of the company reducing hassle for patients. Easier for providers too – the newer calibration will also be easier to teach as it is fewer steps). Commercially, DexCom will continue to target the largest practices while expanding its product line. The pivotal trial for its third-generation sensor has been completed and it plans to file shortly – this newest iteration is designed for better accuracy, will have a 75% smaller sensor (enabling smaller gauge, another positive), and will be easier to manufacture. On the reimbursement front, new codes will be effective January 1 and DexCom hopes to have contracts early in 2008. Management mentioned that 28% of hospitals have adopted tight glycemic controls and 17% more are in the process of doing so; we do think that the inpatient application of CGM is an extremely important market and are interested in the progress of DexCom's in-hospital monitoring program.

- **Medco—Largest internet pharmacy expects 10% growth in 2008:** On its analyst day on November 10, Medco discussed its current business (of most interest to the diabetes world is that it is the largest internet pharmacy and a leading specialty pharmacy) and made several references to its purchase of Polymedica, through which it added another million to its three million base of mail order pharmacy clients with diabetes. This is quite an asset, in business parlance terms, especially considering the >96% retention rate. Medco served 23.5 million mail order prescriptions in 3Q07 with expected 10% growth in 2008. Management referenced its Fairfield, OH, facility, which only handles people with diabetes, as an increasing focus. According to its metrics, only 7% of patients with diabetes adequately manage their blood sugar – we aren't sure if that is their population specifically (which would be damning); we more commonly use the NHANES statistic that only ~35% of patients with diabetes have A1c <7%. Interestingly, the company appears to divide its patients into categories of "well", "acute", "chronic", and "complex" in order to streamline customer service. We would love to know how its diabetes patients fall into these buckets; personally, we don't like the idea that someone can't be both "well" and "chronic" although we recognize that that likely isn't the case for a majority (or even a big minority) of its patients. Another interesting statistic: 49% of Medco members utilize 96% of funds spent on drugs – we were actually surprised it wasn't even more tilted. Management also pointed out that proven research can take 40-plus years to enter into practice. The depressing example cited was that retinal exams were recommended for people with diabetes in the 1980's but fewer than 40% receive them today despite proven evidence of benefit.
- **Merck —Big win at Prix Galien:** At Prix Galien's inaugural event in the United States, Merck's type 2 diabetes drug Januvia was named 2007's Best Pharmaceutical Agent, while its Human Papillomavirus vaccine Gardasil was named Best Biotechnology Product. The Prix Galien award is one of the highest honors for pharmaceutical research and development. Former Merck CEO P. Roy Vagelos also had a share in the acclaim, picking up the prestigious Pro Bono Humanum Award for his campaign to eliminate river blindness. Januvia's honors come at a great time for Merck, as the Januvia franchise continues to expand in the wake of Avandia's troubles, and Novartis' Galvus looks to be stalled at the FDA through 2009-2010.
- **Tethys—Developing a diabetes risk test:** Tethys Bioscience is developing a test that uses protein biomarkers to evaluate a person's risk of developing diabetes within five years. Whereas current predictive diabetes tests are inconvenient as well as inaccurate, Tethys believes that its test will be simple and will allow clinicians to intervene to delay or prevent diabetes in the most at-risk patient groups. To identify biomarkers independent of classical diabetic risk factors such as obesity, Tethys screened more than 90 serum biomarkers associated with key mechanisms of

type 2 diabetes disease development. The samples were obtained from a banked longitudinal outcomes study called the Botnia Study.

Tethys presented the results of a nested case-control study utilizing samples from the Botnia Study at the ADA and EASD conferences earlier this year. In the study, baseline samples from approximately 150 subjects who later developed type 2 diabetes were matched by glucose status with baseline samples from approximately 300 subjects who did not later develop the disease. The researchers found that serum biomarker patterns, described by a “Tethys Diabetes Risk Score (DRS),” could distinguish individuals who developed diabetes in less than five years (N=88; “early converters”) from those who developed diabetes after five years but before 17 years (N=60; “late converters”) as well as those who did not develop diabetes (N=239; “non-converters”).

The effectiveness of the Tethys DRS was confirmed in a five-year population-based longitudinal outcome study of progression to type 2 diabetes among nearly 7,000 subjects in the Netherlands, called Inter99. In the Inter99 study, patients with a high Tethys DRS had a 25% chance of developing diabetes in five years, compared to only a 1-2% chance for patients in the lower Tethys DRS group. The data suggest that the Tethys DRS can differentiate individuals who will be early-, late-, and non-converters with greater accuracy than traditional clinical risk markers or fasting plasma glucose. Whereas genetic assays can show at best a 30% increased risk of developing diabetes, the Tethys test shows approximately a 400% increased risk of developing diabetes in patients with high Tethys DRS.

Tethys investigators are in the process of translating the multi-protein biomarker research tool to the commercial platform assay. The company’s product development efforts have been guided by health economic analyses. Tethys management believes that, given the cost savings if the test is used to guide appropriate intervention leading to prevention of diabetes and its complications, reimbursement will eventually be obtained. Tethys Bioscience executives Mickey Urdea and Michael Richey told us in an interview that the company plans to charge in the vicinity of \$250 for the biomarker test, though the company would not later confirm this number. Regardless of the eventual pricing, reimbursement will clearly be a focus of the company’s efforts moving forward. As prevention is largely in the hands of primary care, Tethys plans to pursue partnerships with pharmaceutical companies to help educate that large, key audience. One obstacle we foresee regarding FDA approval is the lack of ethnic diversity in the Botnia and Inter99 trials. Management stated that it is currently pursuing additional studies to answer the question of ethnic diversity. Tethys looks to submit the test for FDA approval, for an early 2009 launch. Although Tethys is not a household name, the company is starting to turn some heads. At the Global Diabetes Summit in Cleveland, Ohio (see page 35), Dr. Richard Bergman gave a talk about in vivo integrated assessment of insulin secretion in which he also discussed the need for more accurate diabetes prediction tests and mentioned Tethys’ approach. Dr. Bergman also revealed that he is a key advisor for the company – that is a major coup for Tethys in our view.

- **AtheroGenics—Phase 3 clinical trial of AGI-1067 fully enrolled, skepticism persists:** On December 18<sup>th</sup>, AtheroGenics announced that it has completed enrollment of its phase 3 clinical trial of AGI-1067, an anti-inflammatory drug in development for the treatment of type 2 diabetes. The phase 3 trial, called Novel Anti-Diabetic Agent Evaluation Study (ANDES), enrolled about 1000 type 2s in approximately 150 sites in the US, South Africa, India and Eastern Europe. The company plans to report an interim analysis of the study in 2Q08 and deliver the final results in the second half of 2008. AGI-1067 was first developed by AtheroGenics in partnership with AstraZeneca as an anti-atherosclerotic agent. In phases 1 and 2, the drug was well tolerated and showed some positive effects on plaque volume; however, the drug proved to be ineffective at preventing cardiovascular events in its pivotal phase 3 trial (called ARISE). AstraZeneca

subsequently cancelled its partnership with AtheroGenics. However, in the ARISE trial, AGI-1067 showed some statistically significant improvements in glycemic control and AtheroGenics is now trying to pursue AGI-1067 as a treatment for type 2 diabetes. Recently, AtheroGenics suffered yet another setback when it discovered that the higher dose of AGI-1067 is associated with liver toxicity. It has dropped the highest dose of the drug, and will randomize patients to receive only a 75 mg or 150 mg of AGI-1067 (or placebo) in the ANDES trial. We look forward to seeing the results of the ANDES trial, but in the meantime we remain skeptical of the efficacy and concerned about the safety of AGI-1067. AtheroGenics is trading at approximately \$0.40 a share, down from an all-time high of \$35 a share in late 2004.

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

#### 4. Medical Students and Diabetes: Staying Away in Droves

*America's shortage of endocrinologists is compromising care for diabetic patients. Fewer than 3,000 endocrinologists are currently practicing in the U.S. – while 3,000 more patients in the U.S. are diagnosed with diabetes each day. Many established endocrinologists are retiring, leaving for industry, focusing on research, or working in areas outside of diabetes. So why aren't more medical students choosing to specialize in a field – diabetes care – that will clearly be in huge demand for years to come?*

*Between April and August of 2007, we conducted a survey to test our hypothesis that medical students are disinclined to pursue diabetes and, if true, to determine why they are uninterested and to find out what can be done to reverse the trend. We surveyed 524 students, representing all four years of medical school, with a small bias toward first year (first: 39%; second: 23%; third: 12%; fourth: 26%). They attend a variety of schools, though highly competitive institutions are represented somewhat disproportionately. (All schools represented are listed at bottom of this story.) Many of the respondents were from the University of California San Francisco (26%) or from Harvard (17%), while 15% attended Columbia.*

*The survey confirmed that medical students are staying away from diabetes in droves. Only seven students (1.3%) expressed an interest in endocrinology, and only three of those students were interested in diabetes care. Only immunology (1.1%) and rheumatology (0.7%) generated less enthusiasm.*

*Asked to identify two factors that were deterring them from specializing in diabetes care, many students cited the challenges of inadequate compensation as well as modifying patient behavior. Specifically, 46% said changing patient behavior was too difficult while 37.9% identified the lack of procedures (which we see as a proxy for compensation); 20.8% said overall compensation was too low, and 14.1% said reimbursement was insufficient for the time required to care for diabetic patients.*

##### **HERE IS A MORE DETAILED BREAKDOWN OF THE RESULTS**

- **Overall most medical students reported having had some exposure to diabetes during medical school.** Just under 27% said they had not yet had any exposure to diabetes in medical school, though this number may reflect largely first year students. Nearly 36% of respondents reported having had “a little” exposure to diabetes, while 30.6% said they had “some” and 6.9% said they had “a lot.”
- **The majority of students surveyed would like to enter a medical or surgical specialty.** More than three quarters of respondents (76.1%) said they wanted to be specialists rather than generalists.
- **Despite the low interest in diabetes, a substantial number of students (32.4%) appear to be interested in treating chronic disease.** Interest in treating acute disease was

higher (42.1%); slightly more than a fifth of respondents were interested in treating generally healthy patients (21.1%), who were defined in the survey as patients likely to be seen by dermatologists, orthopedists, pediatricians, and obstetricians. Not surprisingly, only a small number of students (4.4%) were interested in professions that did not involve direct patient care (e.g., radiology).

- **Many students expressed an interest in outpatient medicine (40.2%);** however, the majority of respondents were primarily interested in practicing in a hospital-based setting or acute-care setting (59.8%).
- **As expected, when students were asked about the type of medicine they were interested in, the most popular choice was internal medicine (28.3%).** A substantial number of students were interested in a surgical subspecialty (16.9%) and roughly one in ten (10.8%) expressed an interest in pediatrics. Only 6.3% were interested in family practice or primary care, with still fewer interested in general surgery (5.7%), obstetrics and gynecology (4.9%) and psychiatry (4.0%). Almost a fifth (17.8%) of those students interested in entering internal medicine or pediatrics were unsure of which subspecialty to pursue. This result is not surprising given that few of the respondents would have had significant exposure to specific subspecialties.
- **Of those students who identified a subspecialty of interest (N = 281), cardiology was the most popular (14.6%).** This was closely followed by infectious disease medicine (12.5%) and oncology (11.0%).
- **Most other subspecialties were considerably less popular.** Fourteen respondents (5.0%) expressed an interest in gastroenterology, nine (3.2%) were interested in geriatrics, seven (2.5%) in hematology, seven (2.5%) in sports medicine, six (2.1%) in nephrology, and six (2.1%) in pulmonology.
- **We asked respondents to rank certain attributes of a specialty in terms of importance in choosing that specialty, from 1 to 6, with 6 the most important:**
  - **Intellectual satisfaction** scored highest, with an average of **5.1**
  - **Work-life balance** (hours, call frequency) scored **4.7**
  - **Scope** (specific or broad skills) scored **4.4**
  - **Type of patient interaction** (long term, short term, etc.) scored **4.4**
  - **Location** (or location possibilities) scored **4.4**
  - **Personal inspiration** (a mentor, role model, experience) scored **4.2**
  - **Patient population** scored **4.2**
  - **Working** (or not working) **with hands** scored **4.1**
  - **Severity of conditions** treated scored **3.9**
  - **Typical outcomes** (usually get better, usually don't, etc.) scored **3.9**
  - **Team style** (big team, little team, solo) scored **3.8**
  - **Compensation** scored **3.8**
  - **Length of training** scored **3.6**
- **When choosing a specialty, the vast majority of medical students are concerned primarily with the intellectual satisfaction of the work.** Nearly half (45.6%) of respondents ranked intellectual satisfaction as 6 with 81.6% ranking it as 5 or greater; this compares to only 3.8% who ranked intellectual satisfaction as a 1 or 2. Compensation was ranked as a 5 or 6 by only 31.3% of respondents (with fewer than 10% ranking it a 6), and nearly a fifth

(17.6%) ranked it at a 2 or lower. Similarly, length of training was a major concern (5 or 6) for less than a third (26.5%) of students.

- **All categories assessed played some role in decision making for a substantial number of students.** No category was ranked as a 1 or 2 by more than a quarter of the respondents, and only length of training (8.7%) and compensation (5.5%) were ranked as a 1 by more than 5% of the respondents.
- **Despite the small number of students planning to enter endocrinology, many students (25.7%) reported having considered a career in diabetes care.** This fraction is comparable to those who had considered other more popular subspecialties such as dermatology (28.9%), orthopedic surgery (31.0%), and cardiology (58.2%).
- **When asked to check the two most important factors that would attract them to the field of diabetes, the most common factors cited were the social importance (48.8%) and the pandemic status of the disease (33.4%).** A complete breakdown of the results is presented below.
  - 48.8% said social importance
  - 33.4% said pandemic status
  - 24.6% said unique challenges to treat
  - 24.4% said good work-life balance
  - 21.6% said recent scientific advances in the area
  - 18.2% said interested in treating people with chronic disease
  - 17.3% said personal inspiration (a family member, friend, or I have diabetes)
  - 12.6% said recent advances that make a difference in how well I can deliver care
  - 12.0% said not enough people doing it
  - 4.3% said other
- **In a parallel question, students were asked to check the two most important factors that would deter from the field of diabetes.** The difficulties associated with changing patient behavior (46.0%) and a lack of interest in endocrinology (42.2%) were the most common responses. A complete breakdown of the results is presented below.
  - 46% said it's too difficult to change or impact patient behavior
  - 42.2% said they're not interested in endocrinology
  - 37.9% said lack of procedures
  - 20.8% said overall compensation is too low
  - 16.3% said scientific advances in the area are lacking or not as exciting as in other specialties
  - 14.1% said reimbursement is too low for the time it takes to help patients
  - 10.7% said poor lifestyle
  - 9.6% said other.

## DISCUSSION

- **Although many respondents reported having considered a career in diabetes care, only 3 of the surveyed students reported an intention to become an endocrinologist specializing in diabetes.** Given the enormous disease burden of diabetes in the U.S., these numbers are alarmingly small. Equally if not more troublesome, less than a quarter (23.9%) of

respondents were interested in careers in general practice. Since primary care physicians treat the majority of patients with diabetes, the lack of interest in general care is certainly troublesome.

- **The numbers reveal more when broken down by public and private schools.** Only 18.1% of students from the top private school, Harvard, planned on becoming generalists, while 34.9% of students from the top public school, UCSF, intended to become generalists. Of all respondents who attended a private school, 17.6% expressed an intention to become generalists, while 34.1% of respondents who attended a public school expressed the intention to become generalists. We would like to explore this further; we assume that loan size is a reasonable hypothesis for part of the difference.
- **Many respondents cited the social importance of diabetes care (48.8%) and the pandemic status (33.4%) as reasons to enter the field of diabetes.** This result suggests that students are not shying away from diabetes because they are unaware of the importance and/or treacherous state of the discipline. Rather, students are avoiding diabetes medicine because of a host of lifestyle concerns, which tend to tip them toward other fields with better reimbursement.
- **What we hypothesize is happening here** (though we don't yet have evidence) is that diabetes care is losing out to other fields that are both as socially important as diabetes and equally or nearly equally intellectually satisfying. If intellectual satisfaction and social importance are not major differentiating factors, other concerns grow to play a more significant role—notice that cardiology is ranked very highly by students in our survey. Heart disease is more prevalent than diabetes (though diabetes contributes significantly to the CVD disease burden) and is extremely difficult to treat and manage; the physiology is interesting and the reimbursements are fantastic. Note that our medical school advisors say, “Even oncology reimburses better than diabetes care, and the lifestyle is substantially more manageable than for cardio!”
- **Our guess is that students who want to treat a very important disease that is intellectually interesting are choosing cardiology or oncology rather than diabetes care because of financial concerns.** Even if their primary interest were diabetes medicine, this preference is unlikely to be able to outweigh concerns about their quality of life as a diabetes doctor. Consequently, diabetes medicine will have to compete directly with cardiology and oncology to attract aspiring physicians.
- **A significant number of students cited financial and lifestyle obstacles among the top two barriers limiting them from considering careers treating diabetes.** Students were asked to choose as many obstacles as applied from a preset list; 20.8% of students said that the overall compensation was too low, and 14.1% said reimbursements were not adequate for the time involved in caring for patients with diabetes. In addition many students cited poor lifestyle (10.7%) and lack of procedures (37.9%) as significant barriers. Procedures are often popular precisely because they are well reimbursed, though this should be directly assessed in further studies. Overall, 55.3% of respondents chose at least one of the four financially- or lifestyle-related factors as a reason for avoiding a career in diabetes treatment.
- **Students' frustration in changing patient behavior dovetails with concerns about reimbursement.** Since changing patient behavior is so time consuming – and changing patient behavior often lies at the core of diabetic care – students recognize that treating diabetic patients with current reimbursement levels is no way to get rich. The economics of diabetic care are made even more difficult for medical students who begin their careers with enormous med-school loans, a burden that is only intensified if additional training is needed for a specialty. This is also an area where changes in technology could have a dramatic effect on the perception of the

diabetes field within the medical community. Devices such as closed loop pumps and sensors that could be installed and monitored by diabetes doctors would provide the specialty with a potentially reimbursable procedure that could immediately and substantially improve a patient's quality of life. The introduction of more effective drugs to treat, or even cure diabetes and obesity may not lead to better reimbursement for diabetes doctors, but such therapies may nevertheless sufficiently reduce the frustration of managing diabetes to attract more doctors to the field.

- **In many ways, factors motivating medical student – idealism and intellectual curiosity limited by financial considerations** – capture the underlying problems of our health care system, particularly in the treatment of diabetes. And with med students avoiding diabetes as a specialty, this survey reinforces that the problem is going to get worse before it gets better.
- **In the meantime, we might ask how students' perception of the diabetes field would change were doctors better reimbursed for taking adequate time with their patients.** Although this might increase short-term costs for medical care, interventions that reduce the number of diabetes-related complications could ultimately lead to substantial health care savings in our view.

### **Schools Surveyed:**

In descending order of the number of respondents, students attended the following schools: UCSF, Harvard Medical School, Columbia, Emory, Loma Linda University, Stanford, Cornell, Johns Hopkins University, John A Burns School of Medicine, Philadelphia College of Osteopathic Medicine, University of Arkansas for Medical Sciences, Albert Einstein College of Medicine, Mt. Sinai, Brown, New Jersey Medical School – UMDNJ, Northwestern, Nova Southeastern University, University of Massachusetts, University of Pennsylvania, UST, Albany Medical College, Boston University, Botsford Hospital, George Washington University, Indiana School of Medicine, Meharry Medical College, Michigan State University, Morristown Hospital, NYMC, Robert Wood Johnson, University of Rochester, Rosalind Franklin University of Medical Sciences, Southern Illinois University, St. George's University, SUNY Upstate, Thomas Jefferson University, UCI, UCLA – DGSOM, University of Chicago, University of Colorado Health Sciences Center, University of Illinois (Peoria), University of Michigan, University of Pittsburgh, University of Texas, Western University of Health Sciences, WSU Boonshoft, and Yale.

### **Questions for Further Consideration**

*We are seeking funding to cover the costs of expanding this research – specifically, we would like to broaden our questions and survey audience, as well as increase the number of physician interviews. Below are some of the questions we'd like to ask:*

- **Intellectual satisfaction ranked more highly than any other characteristic when we surveyed students on the relative importance of a range of factors to their career goals.** Does the lack of interest in diabetes reflect a feeling that diabetes care is not intellectually challenging? Could this rather reflect a combination of additional “lifestyle” factors outweighing the intellectual component? Would the intellectual component of diabetes care be more apparent with some of the time pressure removed? Our strong view is that intellectual satisfaction is unlikely to override difficulties associated with reimbursement, overall low salary, and significant time constraints, all factors that can leave doctors feeling underappreciated and overworked, so if those barriers were reduced, there may be much higher interest in the field.
- **Difficulty in changing patient behavior was cited as a major obstacle in preventing students from considering careers in diabetes care.** How much does the lack of interest

in diabetes medicine reflect a general desire to avoid frustrating and often disappointing patient encounters? How much would this perception change with increased compensation? How much would this perception change with better therapy? Is it easier to struggle along with patients when the doctor is being reimbursed for the added time? We think the answer to this last question is probably “yes.” We are also not sure of the extent to which students’ education on better therapies lags behind the real world (both endocrinologists as well as patients).

- **Do perceptions of diabetes care change as students progress through medical school?** Does further experience with diabetes recommend for or against endocrinology as a discipline? Our current study did not have large enough numbers to perform adequate subgroup analyses. A larger study focusing on 3<sup>rd</sup> and 4<sup>th</sup> year medical students could provide information about trends in the perception of diabetes throughout a medical education.
- **How much attention is being paid to diabetes in the basic science portion of medical school?** The time spent exploring the complexity of diabetes may strongly influence students’ perception of the intellectual component of diabetes management.
- **Our study was limited in the number of schools surveyed** (a third of the students came from UCSF and Harvard alone). Are the trends we observed representative of the country at large? Are there important trends within particular geographic areas, or at specific schools?
- **How do practicing endocrinologists rate the challenges and rewards of their specialty?** Is the field what they expected when they first chose to pursue a career in endocrinology? Do they recommend the subspecialty to medical students? Do they recommend medical school when they talk with college students who have an interest in science? Are they concerned about the epidemic of diabetes, and the number of qualified doctors being trained to treat this epidemic?

—by Michael Dougan, James S. Hirsch, and Kelly Close

## 5. Editorial: Why Medical Student Aren’t Pursuing Diabetes

*This is the first in a series of editorials for DCU written by healthcare professionals and other leaders in the diabetes arena. Michael Dougan is currently a fifth year MD PhD student at Harvard Medical School. He has a longstanding interest in chronic inflammation and diseases of aging.*

Over the past generation, type 2 diabetes has grown from a relatively rare disease into a global epidemic. Despite the alarming rise in the number of Americans living with diabetes, few medical students are interested in diabetes medicine. With endocrinologists specializing in diabetes already in short supply, this lack of interest portends a serious shortage of qualified diabetes doctors in the near future.

The reasons underlying the lack of interest in diabetes medicine are multi-factorial, but relate to intrinsic characteristics of the diabetes patient population, as well as difficulties with reimbursement and perceived (and often real) limitations in current therapy.

In our survey of 524 medical students, intellectual satisfaction was the most highly ranked factor contributing to the choice of medical specialization. Students are keenly aware of the diabetes epidemic; a large number of students (49%) cited an interest in diabetes precisely because of the enormous societal burden of the disease. At first glance, these findings might suggest that diabetes medicine is likely unpopular because of a general lack of intellectual interest on the part of most students.

Nascent interest in endocrinology may be overridden by lifestyle factors (both economic and otherwise) that make disciplines like cardiology and oncology more attractive. Intellectual interest may be the single

most important factor in choosing a specialty, but that interest will be weighed against substantial differences in pay which exists among various medical specialties (with endocrinology regrettably near the lower end). Financial concerns are particularly acute for students at private medical schools who exit school with an average debt of \$150k and an annual salary of less than 50k for the first 3 to 7 years of their medical careers.

Inherent difficulties in treating diabetes reduces the intellectual satisfaction of diabetes care: the lack of interest in diabetes in part reflects a desire to diagnose and develop an efficacious treatment plan. Type 2 diabetes is a complex disease with an uncertain etiology. For the majority of patients, no curative therapies are available, and treatment plans are often cumbersome and difficult for the doctor to monitor and the patient to follow. Diabetes medicine has no equivalent of the coronary artery bypass graft, artery stent, or valve replacement all of which dramatically and rapidly improve cardiovascular health. Even in cancer medicine, curative therapy is more readily available, even if short-term outcomes are typically worse.

Diabetes is strongly linked to obesity, and the perception of this link plays a central role in the perception of diabetes as a whole. Many doctors view obesity in a light similar to smoking—a medical problem that is largely under the control of the patient, its persistence, in part, a sign of personal failing or laziness. This is not so much a lack of awareness of the complexity of obesity, as it is an expression of frustration at medical science's impotence in the face of this epidemic.

Diet and exercise should “cure” obesity and many cases of diabetes. The fact that behavioral modification is so rarely successful is frustrating to patients and doctors alike. This frustration only mounts when doctors are pressed for time, and poorly reimbursed for obesity-directed interventions. Under these circumstances, the personal financial sacrifice made by doctors who choose to treat diabetes and obesity seems daunting; it can be tempting to blame the patient for failing to meet that sacrifice with sufficient “effort.” For medical students, foreknowledge of this constant frustration is likely a significant factor limiting interest in diabetes medicine.

Despite substantial progress in diabetes medicine over the last decade, even our best current therapies are inadequate. Insulin injections can effectively lower plasma glucose, but carry a serious risk of hypoglycemia, and require significant monitoring by patients. All of our oral medications have unwanted side effects and are unable to restore normal beta-cell function. Newer treatments like incretin mimetics still require injections, and although they can decrease body weight and may even confer a small beta-cell protective (or even regenerative) effect, they are far from being able to reverse most established disease.

Attracting more doctors to the field of diabetes care will require substantial changes to the reimbursement structure. If doctors were reimbursed more fairly for taking the time to try behavioral modifications, changing patient behavior may seem less futile, and outcomes may actually improve. Although performance based pay is not popular among most doctors, tying measures of success to the amount of time doctors can be reimbursed for may make such a reimbursement structure more economically feasible. Such a system would also provide further incentives for successful behavioral interventions. The risk of such an incentive based system is that it could lead doctors to “dump” patients who are “underperforming”; this risk is probably most likely in punitive systems where base pay is decreased when doctors fail to meet specific measures. By tying performance to the length of patient encounters, rather than directly to pay, “dumping” should be less pervasive.

Improvements in diabetes medicine have the potential to transform the perception of the field among medical students. If more efficacious (perhaps even curative?) therapies were available, diabetes care would become less frustrating as we relied less on behavioral modification strategies. Technologies like closed-loop insulin pumps and sensors could provide an intervention that would immediately and significantly improve diabetes management. If endocrinologists were responsible for the installation and

monitoring of these pumps, this could also provide a billable procedure, one of the many factors cited by medical students as playing an important role in their choice of specialty.

The findings of our student survey suggest that the lack of interest in diabetes care has less to do with awareness of the epidemic (on the contrary this was cited as a positive reason for entering the field) than it does with a concern over the lifestyle of diabetes doctors. Patients with diabetes are so difficult to manage that progressive deterioration is common; this leads to persistent frustration which can sap the intellectual rewards from diabetes treatment. This frustration can often color the perception of diabetes patients, leading to a prejudice that further steers medical students towards other specialties. With these factors compounded by a less than competitive reimbursement structure, the lack of interest in diabetes medicine is not especially surprising. This should be a substantial concern for the country as a whole, given the enormous growth in diabetes prevalence and the significant implications for public health. Changes in reimbursement practices as well as improves in diabetes treatments have the potential not only to improve the quality of diabetes care, but also to increase interest in the field as a whole.

## 6. Interview with FDA Insider Dr. Mary Parks

*Employees at the Food and Drug Administration might very well feel under siege. A report made public last month, written by three members of the FDA Science Board, concluded that the FDA's dearth of resources and poor organization have prevented the agency from keeping up with scientific advances, which in turn has put American lives at risk. The challenge in diabetes seems that much greater because so many new drugs are under development and seeking FDA approval – and patients, needless to say, are in need of better therapies, at least based on the percentage that are in good glycemic control. Recently, we were able to speak with Dr. Mary Parks, current director of the FDA's Division of Metabolism and Endocrine Products (and the top person overseeing diabetes drug submissions) at some length about drug development in diabetes.*

*Dr. Parks understands pressures of the FDA well as she has been a medical officer at the FDA since 1998. From 2000-2006, before becoming division director, she was the medical team leader for the lipid-altering drugs group within the Division of Metabolism and Endocrinology Products. Upon Dr. David Orloff's departure from FDA (he had been in the top diabetes drug spot for five years), she was promoted to this spot. Before joining the FDA, she was an adjunct professor in the Division of Endocrinology and Metabolism at Georgetown University Medical Center, where she also trained for her internship, residency, and fellowship. In a wide-ranging interview, Dr. Parks sheds some light on the process of writing the diabetes and obesity draft guidances, the effects of the Avandia controversy on the FDA's handling of drug approvals, the selection of external advisory panel members, and what she thinks patients should do now who are failing their therapy.*

Kelly Close: Thanks for joining us. Can you give any commentary as to when the diabetes draft guidance will be produced?

Dr. Mary Parks: We are coming close to publishing the diabetes guidance for public comment. I can't tell you when it's going to happen, but probably at the end of this year or early 2008.

Kelly: Terrific! Can you comment on what it has been like putting this document together?

Dr. Parks: I think that, really, all guidances for drug development really require a lot of review research. Not only in what we already have in hand, but also reviewing the literature. I know that for the diabetes guidance, we began three or four years ago to call in experts in the area. This isn't done in a vacuum. We really call on stake holders from academia, industry, and patient

consumers. I believe there was a session at a workshop where consumers could weigh in; certainly during the period for public comment, anyone can comment.

Kelly: Right.

Dr. Parks: There are a lot of people with a lot of vested interest in this, including personal interests. We certainly hope that these diseases, type 1 and type 2 diabetes, will be cured. There is a lot of evidence for type 2 prevention, but it is difficult for a lot of patients to adhere to strict lifestyle modifications. You also have to weigh in all of the risks of therapy. It's a difficult risk/benefit calculus to make.

Kelly: Would you say that the recent Avandia controversy has changed the way you think about risk/benefit?

Dr. Parks: Personally, I don't think Avandia has changed things for me. This predated Avandia. I've been in this position for two years. For better or for worse, all the public hears is Avandia and they think it's the controversial matters that change the way we operate. I think when you talk about prevention of chronic diseases, you always have to weigh in: 1) What are we preventing? 2) What is the effectiveness of the drugs? 3) What are the risks? This has been on the minds of reviewers long before Avandia.

Kelly: With the obesity draft guidance, people were eagerly awaiting some of the hard numbers- how long the trials had to be, things like this. Were you surprised by any of the reactions to the draft guidance? I know there hadn't been a new obesity guidance in about 10 years.

Dr. Parks: My deputy, Eric Coleman, is the person to talk to. He's really the key author of that guidance and has been responding to public comment. Most of the responses were not surprising to us, and there are only a few items to refine before finalizing it. This is really kudos to the authors of the draft guidance.

*Editor's note: We reached Dr. Colman, who commented "The response to the obesity guidance has been mixed, as expected, given that Industry has provided the greatest amount of feedback. The pre-diabetes question is not something the obesity group has discussed or entertained."*

Kelly: Will the final obesity guidance be in 2008?

Dr. Parks: I hope so! If you work on something for so long, you really want to get it out there and start using it as the groundwork for drug development.

Kelly: Another thing we wanted to ask about is, given that diabetes has so many demands on the FDA, how severely is the diabetes community being affected in terms of product approval and product safety?

Dr. Parks: That's a hard question for me to answer. I don't have enough facts or data to answer that question. I'm going to defer, if that's ok.

Kelly: On a scientific level, can you talk about which new mechanisms for diabetes you find the most interesting?

Dr. Parks: There are so many new targets and mechanisms for the treatment of type 2 diabetes. This is very promising. As I mentioned before, for really a good half of the century, we were only talking about the replacement of insulin or increased insulin production. But in the past 10-15 years, the scientific community has gained a much better understanding of the mechanisms of type 2 diabetes. As you get older, your insulin resistance increases, even in the type 1 population. With the science really showing there are other areas to target, it is still a very promising field for drug development and for patients. As we have seen, even with all the good

therapies out there, many patients require multiple treatments, and no size fits all. It depends not only on their perspective, but also their comorbidities. Physicians need to look at every drug that is available and select what is best. The FDA will not blankly go out and endorse one drug, or one mechanism. Some people respond better to one than another.

Kelly: You've mentioned tolerability and safety. Metformin is a drug that works very well, and is very safe, but a lot of people can't really stay on it. How do you feel about this?

Dr. Parks: Absolutely, I think that's another reason for us to not start to rest on our laurels and say, we have this therapy, and that's all we need. You really capture there that while it's effective for many patients, it's something that many patients are not willing to take. They are willing to try something else, even if it means using a product that's more modest in efficacy. GI intolerance is a big problem. Tolerability then becomes, for lack of a better term, more of something that affects the marketability of the product. That doesn't necessarily mean that a drug is safe. Tolerability and safety are two different things. We'll see this with many other drugs. Niacin is a very effective drug. But a lot of patients can't tolerate the flushing. People stop therapies for a lot of reasons that we can't control.

Kelly: We recently conducted a survey of about 500 medical school students, and we found that very few students are interested in getting into diabetes. There were a variety of reasons for this. We're asking doctors to take on a lot, and they're not so well reimbursed. We wonder if one of the reasons why Januvia has been very successful is because it is very well tolerated, and this makes it easier for doctors to prescribe.

Dr. Parks: I don't think I can comment. It's a shame that we're losing a lot of good people in the base specialties such as endocrinology. That's not something we, as an agency, can really fix.

Kelly: Right, of course. This is another question about physicians. It seems complicated how you work out the panels for drug approval. Screening out conflicts of interest seems to prevent many experts from appearing on the panel. Looking to the muraglitazar meeting, there was not a whole lot of concern from doctors on the panel. But Dr. Nissen came in and really studied the data...

Dr. Parks: I have to correct that, but finish your question.

Kelly: Can you talk about how the panels are selected?

Dr. Parks: I don't know how I can comment on the muraglitazar panel. But I do need to correct something you said. Dr. Nissen seems to have touted that it was his *JAMA* publication that stopped the FDA from approving muraglitazar. That was not the case. It's not unusual for the agency not to follow the recommendation of the advisory committee. In fact, internally, that was going to be the case. Dr. Nissen's publication happened right before the final FDA decision was announced. His review was actually based on Dr. Golden's review. Its unfortunate our reviews are not available to the public. The final recommendations are not going to be available. If you look at what she provided to the committee, she already had a lot of concern as well.

Kelly: So were the panel members just unfamiliar with the data? Did they not understand it? Did they not have enough time? This is surprising. I know it's not that frequent that the FDA doesn't follow the committee.

Dr. Parks: If I say anything, it would be speculative. Our members are very impressed with the recent advisory committees for rimonabant and Avandia. They read those packages very carefully. We let them be independent. Folks need to appreciate that they get packets, and they don't have it for the full 10 months that we have it. As much as we try to deliver all of the information, that's a lot of information to deliver in 8 hours. That's why one of the members once underscored it's

very hard. She was a consumer rep, and she said they were forced to make a draconian decision on Avandia. It's a difficult position, because they're weighing out costs and benefits in a small period of time with limited materials. When the agency makes a different decision, we're looking at the totality of the data that we've looked at much longer.

Kelly: How do you choose who's on the panel? For example, how would you decide to have a psychologist or a cardiologist? Are they really screened out if they have been involved in the development, or do they just disclose conflicts of interest?

Dr. Parks: You know, there's a process for this that goes beyond the review division. We put forth some names, and there are some conflicts of interest that are, let's say, inexcusable, for lack of a better term. We can't grant a waiver if they've been involved as a consultant for the drug, as you can imagine. Connections to competing products may also be inexcusable. There's really a lengthy screening process. Another office in the agency does this. Since it's very difficult to bring people on board now, the reviewing division tries to cast a large net to get experts on the panel.

Kelly: Wow, do people refuse to be on the panel?

Dr. Parks: Well, the advisory committee consists of a number of standing members. At every point of time, there are people of different specialties in the committee.

Kelly: Do people ever say they don't want to be standing members?

Dr. Parks: Yes, yes I have. A lot of them don't have the time to fill out all of the paper work. It's a long, laborious screening process.

Kelly: Switching gears a bit, any insights into the DPP-4 inhibitor class or incretin class more broadly - safety concerns? Can you comment on Galvus - is the filing still alive? Can you discuss other drugs like Takeda's alogliptin?

Dr. Parks: No comment.

Kelly: An R&D leader at a pharmaceutical company recently told us that in his opinion any new drug to treat diabetes does not stand a chance of approval at the FDA. We can't imagine this is true but it would be great if you could discuss how the agency is balancing the risk/benefit ratios.

Dr. Parks: No comment.

Kelly: Is the FDA moving towards approving only a single drug in any class as opposed to allowing physicians to choose between multiple drugs in a class?

Dr. Parks: No.

Kelly: Will the FDA take into consideration pricing as part of approval? I know that this isn't your mandate, but we've heard that EMEA might start reviewing reimbursement issues as part of the approval process because they don't want to keep approving drugs that governments won't pay for. We would love any commentary on this.

Dr. Parks: From Randy Lutter: FDA administers the FDCA, which directs us to approve products if the benefits outweigh the risks. But this condition is unrelated to how the products are priced. So pricing of products is outside our consideration.

Kelly: Can you discuss the Symmlin non-approval? Is the FDA concerned that only 29% of patients with diabetes take insulin while 60% or more are out of control in terms of their A1c?

Dr. Parks: No comment.

Kelly: Do you urge companies to consider using continuous monitoring to determine what glucose changes take place besides A1c?

Dr. Parks: There hasn't been a situation in which continuous monitoring has been necessary unless there is a particular device under investigation that is trying to mimic endogenous insulin secretion. Short answer is no, not typical of studies in CDER.

Kelly: Is there a chance A1c will not be the only endpoint in diabetes or is that destined to remain the gold standard?

Dr. Parks: Currently, HbA1c is NOT the only endpoint. While it is the primary endpoint currently required for evaluating efficacy, there are other measures of efficacy and, just as importantly, safety, that must be weighed in the risk-benefit decision.

Kelly: What are the foremost concerns in running your part of the FDA?

Dr. Parks: Resources.

Kelly: Right. I'm curious if you can talk a little bit more about this. Diabetes is exploding, with thousands diagnosed each day, endocrinologists leaving the field, and 2/3 of patients out of control. I can't imagine the pressure you're experiencing. I'd like to hear a little bit more about resources.

Dr. Parks: I think that individuals within and outside the agency recognize the need for greater resources – personnel, and also the infrastructure to allow us to do the work. It's heartening that I have people in the agency who are aware of the difficulties that the review division has in making day-to-day decisions. This is not a new problem, and it's considered at every renegotiation. We have to provide up-to-date information on our workload, and how we're able to complete it. There's a lot of data collection so that resources can be increased.

Kelly: When was the last time that resources were increased at the agency?

Dr. Parks: I can't say there's a specific diabetes resource. Resources are given to the whole organization, and the workloads of the individual divisions determine resources. As you can imagine, my division's workload is pretty high.

Jim Hirsch: Ultimately the agency is funded by Congress and the president. Do you believe they appreciate the problems the agency has in terms of diabetes?

Dr. Parks: Well, you might want to ask them that question.

Jim: But you understand the challenges better than they do. What do you think?

Dr. Parks: I rarely interact with them, so I'm basing this off what I read and my impressions. I am rather disappointed with how our, hmmm, well. Whenever there's any sort of hearing on an FDA hearing, there's always two sides to the story, or three sides. Lawmakers are not very balanced at looking at all of the reviews and the data before taking a side. They could do a better job of carefully looking through materials before making a statement.

Jim: But, well, my question has more to do with resources required for a field that is exploding with new patients and new drugs. Is the FDA able to handle those challenges? Does the government recognize those pressures? I know you're reluctant to get into that. But what can we, as a community, what can we do?

Dr. Parks: I think you're asking a much broader question. They're dealing with a budget with a war oversea, education, subsidies; you really need to sit down and look at the federal budget. I really can't answer that question.

Jim: Are you in a position to advocate for diabetes?

Dr. Parks: Within the agency, yes. To Congress, no.

Jim: Who at the agency is in a position to advocate for diabetes?

Dr. Parks: The commissioner, or the secretary of HHS. We also have a consumer group that tackles various diseases and interests.

Kelly: I think we would be interested in that. But the follow-up question: is this job harder than you thought? How have the past two years been in your position?

Dr. Parks: I have been a lot busier than I thought I would be, but I'm not disheartened. The people in our division are just very, very dedicated. I don't see that the challenges, such as Avandia, should make us not continue. We continue to learn and grow, and we shouldn't give up.

Kelly: What do you most love about your job?

Dr. Parks: The dedicated people with whom I work who continue to commit tireless hours to improve public health.

Kelly: What are prospects like for patients with diabetes in the next five years? 10 years?

Dr. Parks: Diabetics have more options today than they did 10 years ago. Back then they had three drug classes to choose from. Two caused weight gain and hypoglycemia including one that requires injections (insulin) and one that has now become the favorite of most diabetologists. Unfortunately, one drug is not enough for most patients. With the many different drugs available to patients and physicians today, different options for differing needs can be considered before starting insulin. More choices do require careful understanding of the risks/benefits of each drug and marrying the right drug to the right patient. And, of course, we should never stop trying to improve our lifestyle and dietary habits. The benefits of those interventions go beyond glycemic control.

Kelly: What can industry do to improve patient care?

Dr. Parks: It's always a balance between advertising, marketing, and education. It should be fair and balanced so that physicians know what's best for patients.

Kelly: Thank you so much for your time.

Dr. Parks: Thank you.

## **7. In the News: New Type 2 Treatment Algorithm EASD & ADA – and Talking to Dr. David Nathan about these Changes**

*The ADA and EASD have produced an update to the algorithm on type 2 diabetes treatment, originally published in 2006. The purpose of the update was twofold – 1) to reflect recent concerns regarding the safety of the TZDs, especially Avandia, and 2) to recognize the approval of Januvia –which wasn't that meaningful since new drugs aren't allowed to be part of the algorithm until long-term data are amassed. The algorithm was said to be published simultaneously in the journals Diabetes Care and Diabetologia but as of press time, it is not yet out in Diabetes Care. We hadn't anticipated a meaningful change in physician behavior stemming from the new document although after speaking with Dr. David Nathan, one of the authors of the new algorithm, our sense is there is more negativity on the TZD class that will be felt by PCPs. Our interview with Dr. Nathan is printed at the bottom of this review.*

- **The authors of the new algorithm are:** Drs. David Nathan, John Buse, Mayer Davidson, E. Ferrannini, Rury Holman, Bob Sherwin, and Bernie Zinman. Notably, Dr. Robert Heine was not listed as an author in spite of his work on the 2006 algorithm – we assume he could not be an author because he is now at Lilly and would present a conflict of interest (though many conflicts of interest are noted on the cover of the present paper).
- **The "maze" showing various options for patients is essentially unchanged** - it still begins with lifestyle and metformin, then goes to a branch with the choices of basal insulin, SFUs, or TZDs, followed by insulin intensification. The most "advanced" option is still intensive insulin treatment, metformin, and TZDs, although TZDs now have a "plus/minus" beside them to indicate this is an important choice whether to include.
- **Although the TZDs remain on the treatment algorithm, the TZD footnote has been changed.** Avandia is now noted as possibly being associated with more frequent MIs (heart attacks). The TZD category is decidedly more crowded in the "disadvantages" area as CHF and fractures have also been added. The footnote for TZDs now reads, "Associated with increased risk of fluid retention, congestive heart failure and fractures. Rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of myocardial infarction."
- **Byetta and Januvia are still not part of the algorithm;** they are noted in the "other" drugs category. At the World Diabetes Summit in Columbus, OH, on December 1, former ADA president Dr. John Buse spoke briefly about why the ADA has not added exenatide and DPP-4 inhibitors to its recommended treatment algorithm. He explained that the ADA is awaiting more long-term safety data for both classes of drugs before updating its chart, although like Dr. Nathan below, he didn't give a sense of how much data were needed. He said that both drugs will probably eventually appear parallel on the algorithm to sulfonylureas, and arguably one may view them as "the new and improved sulfonylureas." Given the current regulatory and safety climate, we aren't too surprised that Byetta and Januvia haven't yet been added, though in reality, given the uncertainties of TZDs and the dangers of insulin, we don't think a lot of harm would be done in adding them with the provision that the ADA and EASD were looking for longer-term data. We do anticipate at least GLP-1 will be added in the next update.
- **Byetta and Symlin still have "frequent GI problems" noted as a disadvantage** - metformin has "GI distress." We note that in ADOPT, 40% of patients experienced GI problems associated with metformin. This raises an interesting question: at what threshold does a drug move from having "GI side effects" to "frequent GI side effects"?
- **Overall, the update should have a negative effect on clinician TZD use.** The update does seem slightly negative for the TZD class of drug, though it is significant that the TZDs retain their position on the chart. It seems strange in our view that the "most intensively" managed patient on the algorithm should use basal and mealtime insulin and metformin and a TZD, though as noted that is "plus/minus" – a more negative slant than previously – given the safety concerns with TZDs, we will be interested to watch how much experience is needed before incretins, especially GLP-1 compounds, are added to the algorithm.

**We had several remaining questions about the new algorithm, which were answered by Dr. David Nathan, head of diabetes at Mass General in Boston and an extremely powerful figure in the diabetes arena. Our interview with him on the update follows.**

Kelly Close: Thanks for taking time to speak with us. Can you tell us, in your view, what the biggest difference is between the present algorithm and the previous version?

Dr. Nathan: The change isn't major, but it's very, very specific. The new version specifically addresses the use of rosiglitazone or pioglitazone in the algorithm. The TZDs were one of three second-step choices, and what we wanted to do was take the recent meta-analyses and the two new black-box warnings, one for TZDs in general and one specifically for rosiglitazone, into account. Based on the concern regarding safety issues, we wanted to urge physicians to be very cautious before they use TZDs, and before they use rosiglitazone in particular. The changes weren't meant to be a complete rewriting of the guidelines. The only other change we made was to acknowledge in one of the tables that the DPP-4 inhibitor sitagliptin (Januvia) had been approved.

Kelly: Right. Was it a possibility that the TZDs actually would be officially downgraded as an alternative?

Dr. Nathan: We discussed whether we should eliminate the TZDs from the algorithm, but the consensus was that the data were not conclusive enough to remove them completely. However, the caveats that we provide are strong enough that I think most physicians will be cautious in using them. The safety concerns regarding osteoporosis, fluid retention and CHF apply to both pioglitazone and rosiglitazone, while concern regarding increased risk for myocardial infarction applies only to rosiglitazone.

Kelly: Sorry, what I mean was, was there an option between removing it and using it as a cautious second-tier choice that was considered? I wondered, for example, if the group considered the use of TZDs as a final-tier choice only after metformin, sulfonylureas, and insulin.

Dr. Nathan: "Second tier" makes it sound as if it's a second choice. It's not. The algorithm suggests using the medications in an orderly fashion, and the TZDs are one of the three classes of medications- insulin and sulfonylureas are the other two-that should be considered if lifestyle intervention and metformin do not achieve the HbA1c target of less than 7%. Each of the interventions was recommended on the basis of its relative advantages and disadvantages. The advantages of insulin are that it's the most effective agent in lowering glycemia with extensive experience; however, it requires an injection and is associated with weight gain and hypoglycemia. Sulfonylureas are also quite effective in lowering glycemic levels and are inexpensive, but they also can cause hypoglycemia and weight gain. The TZDs are somewhat less powerful but don't cause hypoglycemia. On the negative side, TZDs are not only associated with fluid retention, which we knew about, but there is now more serious concern about congestive heart failure and osteoporosis. Moreover, the recent meta-analyses suggest additional risk for myocardial infarction associated with rosiglitazone, but not pioglitazone. Whether rosiglitazone causes excess cardiovascular events must still be considered an open question; however, the safety concerns that have been raised would suggest using other available agents. Of course, clinicians need to apply their clinical judgment and consider individual patient characteristics in applying the algorithm.

Kelly: One other thing we were wondering about was why fractures weren't mentioned as a disadvantage in the table for TZDs.

Dr. Nathan: We do discuss the increased risk for osteoporosis and fractures that has been recently linked to the TZDs. I think that the DREAM study was the first to look at osteoporosis in the context of a controlled clinical trial.

Kelly: Got it – sounds like there are some nuances between what's in the table, what's a footnote, etc. – we will be looking at that in more detail in the future and we appreciate that clarification. Another thing we want to ask you about was the fact that the "most intensively"

managed patient is on basal and mealtime insulin and metformin and a TZD, given the safety questions with TZDs.

Dr. Nathan: If patients don't respond to the first or second steps of the algorithm, they will usually require insulin therapy. In general, insulin therapy- added to metformin- can be initiated with basal dosing, for example with bedtime NPH or Lantus insulins. This was described in the original algorithm. Intensification of insulin therapy may require the addition of a second dose of NPH, or of rapid-acting insulin before one or more meals.

Kelly: Switching gears, then, we also wondered about incretins. We understand that they weren't made part of the algorithm and wondered how much long-term data would be needed before consideration?

Dr. Nathan: There's no specific metric to determine when we will consider adding new drugs to the algorithm. The consensus is based not only on effectiveness, but also on factors such as safety, experience, acceptability, and expense. There needs to be a consensus. We'll see what happens when we meet again, and whether the committee members think that there are enough data to forge a consensus and include any of the newer drugs in the algorithm.

Kelly: The group meets every two years?

Dr. Nathan: We're not on a specific time line. Our most recent meeting was prompted by the accumulating data and concern regarding the TZDs. I think we'll meet as often as the data merit.

Kelly: You mentioned efficacy and safety really driving the algorithm, and I wonder how does tolerability play in?

Dr. Nathan: Our evaluation of the available drugs did include consideration of tolerability. The first cut point was whether the drugs had passed the safety bar of approval by the FDA and its European counterpart. Beyond that, we recognized that just because a drug has been approved by the FDA doesn't mean there's zero risk. We also considered acceptance, which is different than tolerability, cost, interactions with other drugs, and the complexity of the regimen. We took into account the totality of issues that affect a patient taking a drug and/or a doctor prescribing it. Tolerability does play largely into it. Drugs that people don't tolerate, or won't tolerate for long, would be obviously a strike against that drug, whether it's safe, or effective, or not.

Kelly: We also wondered just in light of ADOPT and sulfonylureas' high secondary failure rate in this study, is "short duration" appropriate to describe sulfonylureas? And is there a high secondary failure rate, or if that short duration of action was also something that was considered a disadvantage? Also, you mentioned the potential beta cell burnout for sulfonylureas, and we wondered how that played into your views?

Dr. Nathan: I think there are accumulating data that sulfonylureas seem to work like gang-busters early on, but that beta-cell function may subsequently decline more rapidly than with some other medications. The longevity of effectiveness isn't well understood for many drugs, and especially the newer ones, so it is difficult to compare the medications on this count. One of our concerns is maintaining a range of therapeutic options for this chronic, progressive disease.

Kelly: Could you tell us what you thought about the GI side effects of the different classes? It seems like sometimes drugs were listed as having "GI side effects" or "frequent GI side effects."

Dr. Nathan: The GI side effects that you get with the GLPs, but not with the DPP-4s, are fairly frequent. GI side effects are even more common with the alpha glycosidase inhibitors. Metformin has GI side effects as well. Comparing the frequency of GI side effects among the different classes of drugs is problematic since there are no head-to-head studies.

Kelly: Could you talk about what you think the main take-away should be for doctors who treat patients with diabetes who are reading this, especially primary care doctors? Not just for the update, but also doctors who are reading the consensus statement for the first time.

Dr. Nathan: Type 2 diabetes is a chronic degenerative disease that results in progressive beta-cell failure and rising A1c's over time. We have previously treated it in a step-wise, "lente" fashion. A major thrust of the guideline is to treat people aggressively and to change the therapy when needed to reach a specific hemoglobin A1c target of less than 7%, which has been demonstrated to reduce long-term complications. If patients are not achieving an A1c level less than seven percent, then therapy needs to be changed, and usually on a fairly frequent basis. The second main takeaway is that physicians should initiate metformin, concurrent with the initiation of lifestyle intervention, at the time of diagnosis, assuming that there are no specific contraindications. The third takeaway is that there is a hierarchy of medications that one can use, and it's not a huge list. There are three medications that we're suggesting might be added to metformin.

Kelly: Just a follow-up on that, do you think that insulin might be used earlier and more aggressively as a result of the algorithm?

Dr. Nathan: Yes. We anticipate that insulin will be considered earlier, and used as necessary to achieve target glycemia. Obviously, the ability of the patients to "tolerate" any of the classes of anti-diabetic medications will influence the choice of medications within the algorithm.

Kelly: What about your own clinical process. Would you be willing to say if you support use of TZDs in your own practice?

Dr. Nathan: In our own practice, we have used TZDs relatively infrequently compared with other anti-diabetic medications. Historically, when we used a TZD it was more likely to be pioglitazone because of its relatively advantageous lipid effects compared with rosiglitazone. We have always been rather careful about the fluid retention.

Kelly: Thank you – this wraps up our questions on the ADA/EASD consensus update. Dr. Nathan, we really appreciate your time and insights very much.

Dr. Nathan: And thank you as well.

—by Mark Yarchoan and Kelly Close

## 8. Conference Notes: Global Diabetes Summit

November 30, 2007 – December 1, 2007 • Columbus, OH •

[http://medicalcenter.osu.edu/healthcareprofessionals/conferences/global\\_diabetes\\_summit/](http://medicalcenter.osu.edu/healthcareprofessionals/conferences/global_diabetes_summit/)

*The Global Diabetes Summit was one of the most exciting and best organized conferences of the year. Approximately 650 people from at least 14 countries attended the first day of the conference, filling the Hilton Hotel ballroom where it was held.*

- **The organizer of this conference was Dr. Kwame Osei of Ohio State University Medical Center.** He began organizing this conference over two years ago, arranging for many leading experts in diabetes to speak. This is the second diabetes meeting organized by Dr. Osei -

12 years ago he arranged a much smaller Global Diabetes Summit that was held in Ghana. Given the success of the present meeting, Dr. Osei now hopes to hold a Global Diabetes Summit every four years in Columbus, Ohio. The meeting's global orientation reflects Dr. Osei's belief that diabetes is a worldwide problem that must be tackled comprehensively. While this certainly isn't a new theme, many of the statistics provided were very provocative. Along the same lines, several speakers, including Dr. Osei, complained that the World Bank underfunds chronic non-communicable diseases such as diabetes. The World Bank and other organizations spend much more on HIV/AIDs than diabetes, even though diabetes is responsible for many more deaths worldwide. He also aims to have a variety of different topics presented, because he believes that a problem with other conferences is that attendees often attend only lectures in one particular area of focus.

- **Exhibitors included** Sanofi-Aventis, Abbott (Diabetes Care + Nutrition), Novo Nordisk, Merck, Lilly, Takeda, Pfizer, GSK, DexCom, Novartis, Amylin, Medtronic, Roche, J&J, and others.
- **Dr. John Buse spoke briefly about why the ADA has not added exenatide and DPP-4 inhibitors to the ADA recommended treatment algorithm.** He explained that the ADA is awaiting more long-term safety data for both classes of drugs before updating its chart. He said that both drugs will probably eventually appear parallel on the algorithm to sulfonylureas, and arguably one may view them as "the new and improved sulfonylureas." Given the current regulatory and safety climate, we aren't too surprised Byetta and Januvia haven't yet been added, though in reality, given the uncertainties of TZDs and the dangers of insulin, we don't think much harm would be done by adding them with the provision that the ADA and EASD were looking for longer-term data.
- **In a session on continuous glucose monitoring (CGM), Dr. Alan Marcus, Vice President and Global Director of Medical Affairs for Medtronic Diabetes, revealed that Medtronic Diabetes will release an enhanced sensor-augmented pump that shuts off insulin delivery in response to a low alarm if the patient fails to act.** This is the first of a series of important interim steps toward achieving a closed-loop system. Medtronic is actively moving in the direction of the closed-loop with the incremental addition of automatic features over the next several years. The company believes the future of diabetes management is an integrated insulin pump and CGM system, and continued improvements will be made in the way these devices gather data, talk to each other, respond, and ultimately automate. The sensor-augmented pump will be released in Europe only in 2008. Notably, this isn't being introduced in the US, we presume because it would take longer here to get through the regulatory system - ironic for a safety feature.
- **Based on communication with numerous independent experts, Dr. Barry Ginsberg estimated that closed-loop systems would become available at the earliest in 2013-2015.** Great progress has been made toward a closed-loop system, but numerous challenges remain. The current generation of continuous monitors has a mean inaccuracy of about 12%. The 95% confidence limits are  $\pm \sim 30\%$ , meaning that a blood glucose reading of 200 indicates that blood glucose has a 95% chance of being between 140 and 260. Frequent samples partially overcome this problem, as do slow corrections (more readings during correction period). For a closed-loop system, accuracy will need to increase to at least 99%. It will also be difficult to detect when a meal is eaten, and it will be impossible to tell how much or what is eaten. Patients will need to enter some information into the device. A final challenge is that insulin bioavailability varies (for regular insulin, action varies by  $\pm 35\%$  for 95% confidence interval) and duration of insulin action (i.e. insulin on board) changes. It will be necessary to know how much insulin is present to avoid overdosing.

- **During a workshop on continuous glucose monitoring (CGM), Dr. Irl Hirsch stressed that although CGM may improve care for many patients, not all patients are good candidates.** Along those lines, CGM may be a better tool for patients with lower HbA1c levels than for patients with higher HbA1c levels, for whom improvements can be achieved by other means. Dr. Hirsch ended his talk with the intriguing prediction that CGM will become the “standard of care” for the treatment of type 1 diabetes within the next 5-10 years.
- **We also greatly enjoyed Dr. Robert Rizza’s very technical lecture on the similarities between pre-diabetes and diabetes.** Dr. Rizza explained that both are associated with defects in insulin secretion, impaired hepatic (liver) and extra-hepatic insulin action, and reduced beta cell mass. Not all people with pre-diabetes share the same defects, however – in some patients, one of these defects will in a sense “drive” the others. For this reason, using directed therapies to correct specific metabolic defects in a given individual is more likely to be successful in treating or preventing diabetes than treating everybody the same regardless of the underlying cause of their hyperglycemia. He expressed a strong belief that more targeted therapy is going to be feasible with the numerous novel drugs that are in development.
- **Dr. David Harlan of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) discussed some of the limitations of islet transplantations.** In 2007, the best estimates of 20-year mortality for children and young adults with type 1 diabetes are around 3%, compared to about 1% for children and young adults who don't have type 1 diabetes. This amounts to a difference of about 2% or about 0.1% per year over a 20-year span. Therefore, new therapies must have a safety profile that will not elevate risk by more than 0.1% per year. Even patients with long-standing and poorly controlled type 1 diabetes have an annual risk of 1% or less.
- **There are many limitations to islet transplantation success.** One problem is islet numbers - there are about 6,000 pancreas donors per year in the US, and most islet transplant recipients require two donors. Therefore, about 1,500 patients (0.15% of type 1s in the US) could receive a transplant. The technique is also very expensive, costing about \$150,000 per transplantation. Yet another limitation is that a significant number of islet transplantation recipients develop renal insufficiency as a result of their islet transplant immunosuppression.
- **There is a long-standing debate about whether insulin resistance or beta cell failure is the cause of diabetes.** Dr. Richard Bergman explained that we now finally know that both are the cause and work together to cause diabetes. Many individuals have normal beta cells in the sense that they can compensate for insulin resistance with increased insulin production. This is often termed the metabolic syndrome. In other people, the ability to compensate for insulin resistance is limited. The ability to compensate for insulin resistance is very different in different ethnic groups – beta-cell compensation for insulin resistance is particularly limited in some Arabic and Asian populations. Given the importance of insulin resistance, it is necessary to accurately measure insulin resistance in many studies. A prominent focus of Dr. Bergman's talk was also to discredit surrogate measures of beta cell function and insulin resistance. He explained that the HOMA method of measuring insulin resistance is only useful for patients with normal beta cell function. The gold standard for measuring insulin resistance is the glucose clamp.
- **Dr. Frank Vinicor gave a very clear, extremely well organized, and highly provocative talk, sharing his experiences at the Centers for Disease Control (CDC) to discuss the challenges we face as individuals and as a society in fighting diabetes.** One problem is that the US does not pay enough attention to non-communicable chronic diseases such as diabetes. Dr. Vinicor also explained that several models have shown that the most

effective point of intervention is fighting obesity. Finally, Dr. Vinicor discussed the difficult questions we as a society must face in fighting the diabetes epidemic with limited resources. For example, we must choose whether to invest in drug discovery or drug availability. We must also choose whether to focus our diabetes prevention only in the US, or also abroad. He summed up his own talk by explaining that in a world with lots of people with diabetes and lots of new ways to help, “we also need to change lots of ways we used to think.”

- **Dr. Alain Baron of Amylin Pharmaceuticals provided a somewhat basic overview of incretins and the efficacy of Byetta** – we knew this would be the case since it was a CME and many people still had little access to education on incretins. He highlighted evidence that Byetta improves beta-cell function and explained that incretins have a role both during and between post-prandial periods; he called diabetes a GLP-1 deficient state, which we thought was interesting – it’s all a big question the extent to which we are moving toward a GLP-1 centric treatment regime. At the end of his presentation, Dr. Baron reviewed exenatide once-weekly clinical data – this part of his presentation was an abridged and simplified version of the Amylin R&D day in New York. It is also worth noting that like the presenters at Amylin’s R&D day, he referred to exenatide LAR only as “exenatide once-weekly,” stressing the frequency element.
- **There was an ongoing debate at the meeting about the value of “the metabolic syndrome.”** Dr. David Kelly raised several concerns about the advent of the syndrome, namely: 1) there is considerable doubt about its value as a CVD risk marker, 2) some of the parameters and set points need to be adjusted for ethnic data sets, and 3) the criteria are somewhat arbitrary and are not derived from prospective clinical trials. Dr. Robert Eckel countered that the purpose of the metabolic syndrome is misinterpreted. It was not designed to be a global risk predictor; instead, it was designed to facilitate lifestyle intervention and it serves this purpose very well. The metabolic syndrome is a term that patients can understand and act upon when “diagnosed.”

—by Mark Yarchoan and Kelly Close

## 9. Literature Review: Activators of SIRT1 for the Treatment of T2DM

*In the November 29th issue of Nature, Dr. Jill Milne and colleagues report on a series of animal studies that evaluated the therapeutic potential of a novel SIRT1 agonist (SRT1720, Sirtris Pharmaceuticals) as a treatment for type 2 diabetes. In all three animal models, SRT1720 lowered plasma glucose and enhanced insulin sensitivity without contributing to weight gain or increasing the risk of hypoglycemia. SRT1720 was quite potent and, when compared to rosiglitazone (Avandia, GlaxoSmithKline), both agents had similar efficacy at lowering plasma glucose. As SRT1720 is the most potent of Sirtris’s molecules in development, in our view this suggests that SRT1460 and SRT2183 (as well the company’s lead compound- SRT501, a proprietary formulation of the naturally occurring compound resveratrol, now in phase 2) may be less potent than rosiglitazone. In our view, Sirtris’s SIRT1 activators are promising because of their purportedly high tolerability and positive side effect profile, but only time will tell whether they live up to their promise – big promises for now. Although the mechanism linking SIRT1 to type 2 diabetes is not entirely understood, based on these animal models SIRT1 agonists are promising candidates for novel diabetes therapeutics. That said, these are the early days of SIRT1 research. Upcoming trials in 2008 by Sirtris Pharmaceuticals will establish whether the safety and efficacy observed in these animal models can be extended to patients with type 2 diabetes.*

- **SIRT1 is a member of the sirtuin family of NAD<sup>+</sup>-dependent de-acetylases.** SIRT1 functions by removing modifying acetyl groups from other proteins, inducing changes in protein function; however, few direct targets of SIRT1 activity have been identified.

- **The sirtuin family has been implicated in progressive diseases including diabetes.** SIRT1 appears to be important in the mechanism linking calorie-restriction to increased longevity in animal models. SIRT1 is weakly activated by resveratrol, a compound found naturally in red wine; resveratrol has been used successfully to extend lifespan and ameliorate type 2 diabetes in several animal models. In a 2003 publication in *Nature*, several synthetic small molecule activators of SIRT1 were identified. Treatment of both yeast and flies with these compounds led to increased longevity.
- **In this report, three synthetic activators of SIRT1 (SRT1460, SRT1720, and SRT2183) were further characterized** and tested for their ability to ameliorate disease in three animal models of type 2 diabetes. Each of these agonists was identified using a screen for compounds that enhanced the enzymatic function of human SIRT1.
- **SRT1720, the most potent of the three SIRT1 agonists, increases SIRT1 enzymatic activity up to 700% at low micromolar concentrations.** Each of the other two agonists acts at similarly low concentrations, and can enhance enzymatic activity by 300% to 400%.
- **SRT1720 binds to a region of SIRT1 that overlaps with both the resveratrol and SRT1460 binding sites.** This finding suggests the potential for an endogenous activator of SIRT1. None of the compounds bind to either the NAD<sup>+</sup> binding site or the protein binding enzymatic site.
- **SRT1720 was tested in three animal models of obesity-associated type 2 diabetes for its ability to lower plasma glucose and enhance insulin sensitivity.** Two mouse models were used: the diet induced obesity model (DIO) and the leptin deficiency model. In addition, the efficacy of SRT1720 was also examined in Zucker fa/fa rats (a widely used rat model of genetic obesity).
- **In all three models, SRT1720 treatment led to a decrease in both plasma glucose and circulating insulin.** Insulin sensitivity was also improved in all three models. In the DIO model, the efficacy of SRT1720 at lowering plasma glucose was comparable to that of rosiglitazone (Avandia, GlaxoSmithKline). Rosiglitazone was not tested in either of the other models. The implications of this are that most likely SRT1460 and SSRT2183 (and SRT501-resveratrol, now in phase 2) are less potent than rosiglitazone. However, it is not clear how directly molecular potency is reflected in efficacy, and the lower potency of these molecules may be compensated by high tolerability and an encouraging side effect profile.
- **SRT1720 treatment did not produce significant changes in body weight.** Although the mechanism by which SIRT1 enhances insulin sensitivity is not clear, the effect does not appear to depend on improvements in body weight. From a commercial perspective, it is a negative that no weight loss was found, though a modest positive that there was no weight gain.
- **In the DIO mouse model, animals fed on low calorie food did not experience a change in plasma glucose during SRT1720 treatment.** This result suggests that hypoglycemia is not a substantial risk associated with this class of agents – definitely a strong advantage. In our view, Sirtris is hoping that SIRT1 activators are going to thrive on tolerability (much the way Januvia has) and a broad spectrum of positive metabolic effects down the line.
- **Although these studies are clearly preliminary, SIRT1 agonists may have significant potential as novel therapeutics for type 2 diabetes** if we see in human trials what has been suggested in these animal models. All three of the animal models used in this study have played important roles in the identification of other classes of diabetes therapeutics. SRT1720 is quite

efficacious (comparable to rosiglitazone in some studies) and appears to have minimal side effects in the systems evaluated – assuming more side effects don't emerge, which is certainly possible. SRT1720 was initially identified through its ability to activate human SIRT1, suggesting that this compound could have efficacy in humans. This possibility will be directly tested by Sirtris Pharmaceuticals in upcoming human trials in 2008.

- **This work was supported by Sirtris Pharmaceuticals.** The final author on the paper, Dr. Christoph Westphal, is CEO of Sirtris.

—by Michael Dougan and Mark Yarchoan

## 10. Literature Review: US Prevalence of Chronic Kidney Disease

*In the November 7 issue of the Journal of the American Medical Association (JAMA), Dr. Joseph Coresh and colleagues present data from the National Health and Nutrition Examination Surveys (NHANES) 1988-1994 and 1999-2004, showing that the prevalence of chronic kidney disease (CKD) has increased from 10% to 13% in the US between 1988-1994 and 1999-2004. In spite of the high incidence of CKD, awareness of CKD in the US remains very low, and a majority of people with CKD are unaware of their condition. This calls attention to the failure of CKD screening in the US; according to Quest Diagnostics, approximately 60 percent of patients with diabetes and CKD, and 52 percent of patients with diabetes, hypertension, and CKD did not receive a urine test to check for albumin from 2005-2006 even though yearly screening for CKD is recommended for high-risk patients. This is just one more example of how our system is better set up for acute rather than chronic care – to the detriment of diabetic patients in particular.*

- **DCU spoke with Dr. Herman Hurwitz, senior medical director of Quest Diagnostics Incorporated, who underscored that increased awareness and utilization of a readily available inexpensive test will be key in reducing the prevalence of CKD.** He share with DCU: “...Physicians may believe that their patients are not at risk for chronic kidney disease if their blood glucose, lipids and/or blood pressure are controlled. This is simply not true,” adding, “Chronic kidney disease is an insidious consequence of these diseases and can progress quickly without routine monitoring. Patients at increased risk for chronic kidney disease should be screened for microalbuminuria at least annually, while those with confirmed microalbuminuria may require even more frequent monitoring depending on their response to treatment. Yet, our data suggests that at-risk chronic kidney disease patients are not being monitored as recommended by established guidelines. In this case, the medical community has a tool that, if used well, has the potential to truly make a difference and save lives.”
- **In the present study, Dr. Joseph Coresh and colleagues estimate the prevalence of chronic kidney disease (CKD)<sup>1</sup> in the US** using data from the National Health and Nutrition Examination Surveys (NHANES), a national representative sample of over 13,000 US adults<sup>2</sup>. By comparing the prevalence of CKD from NHANES 1999-2004 and NHANES 1988-1994, the authors examine trends in CKD stages and severity.

---

<sup>1</sup> CKD stages were classified on a four point scale, in accordance with the National Kidney Foundation guidelines. Briefly, stage 1 is defined as albuminuria (the presence of excessive protein in the urine) + glomerular filtration rate (GFR), (fluid filtered by the kidney) of > 90 mL/min/1.73 m<sup>2</sup>; stage 2 is albuminuria + GFR of 60-90 mL/min/1.73 m<sup>2</sup>; stage 3 is albuminuria + GFR > 30-59 mL/min/1.73 m<sup>2</sup>; and stage 4 is defined albuminuria + GFR of 15-29 mL/min/1.73 m<sup>2</sup>.

<sup>2</sup> NHANES is conducted by the National Center of Health Statistics and includes a laboratory assessment of albuminuria and serum creatine secretion, two accurate measures of CKD, thereby providing a rigorous measure of CKD prevalence in the US.

- **The authors found that the prevalence of all stages of CKD increased significantly from NHANES 1988-1994 to 1999-2004.** Overall prevalence of CKD increased from 10% to ~13 % (or about 20 million adults in the US). This included an increase in stage 1 CKD from 1.7% to 1.8%; stage 2 from 2.7% to 3.2%; stage 3 from 5.4% to 7.7%; and stage 4 from 0.21 to 0.35%. This trend is consistent with the large increase in the number of patients with kidney failure treated by dialysis and transplantation in the US. Incredibly, this number has increased from ~210,000 in 1991 to ~470,000 in 2004.
- **The increased CKD prevalence is largely explained by increased prevalence of CKD risk factors** – obesity, diabetes, hypertension, and to a much smaller extent the aging of the US population. When the prevalence of CKD in 1988-1994 was age-adjusted to the 1999-2004 age structure, CKD rates increased from 10% to 10.3% - still far less than the 1999-2004 prevalence rate of ~13%. The increased prevalence of diabetes, hypertension, and obesity completely explained the overall increase in CKD rates (as marked by increased prevalence of albuminuria), but they do not account for the increase in CKD severity, as marked by decreased glomerular filtration rate (GFR), which essentially describes how well blood is filtering in the kidneys.
- **In spite of already high and increasing CKD prevalence, awareness of kidney disease in the US remains very low.** Only approximately 12% of men and 6% of women with stage 3 CKD reported being aware of having weak or failing kidneys. Even with stage 4 CKD, over half of subjects were unaware of their condition. According to a report by Quest Diagnostics a majority of people with CKD risk factors such as diabetes and/or high blood pressure do not receive CKD testing. The report shows that 60% of patients with diabetes and CKD, and 52% of patients with diabetes, hypertension, and CKD did not receive a urine test to check for albumin from 2005-2006.
- **The findings demonstrate a failure to implement regular CKD screening.** Guidelines set forth by the National Kidney Foundation, American Diabetes Association, and other organizations recommend an annual urine test to check for albumin among patients with diabetes, hypertension, cardiovascular disease, and/or other risk factors for CKD. Early detection of CKD even when no symptoms are present is important because it can prompt an early intervention, slowing disease progression to chronic kidney failure. According to Quest Diagnostics, the number of deaths from CKD in the US has increased by over 50% over the past 16 years.
- **Dr. Joseph Coresh and colleagues highlight that increasing prevalence of CKD, combined with a failure to test for and treat CKD, leads to increased complications** and a higher rate of chronic kidney failure, requiring treatment with dialysis or kidney transplantation. It is well documented that individuals with CKD have increased risk of cardiovascular disease mortality. Therefore, the alarmingly high rate of CKD and low rate of CKD awareness calls attention to the need for greater albumin testing and CKD public health planning.

—by Mark Yarchoan

## 11. Diabetes Comings and Goings

- **Michel Paul** will become Company Group Chairman, Diabetes Franchise, at J&J, effective January 2; previously, he led DePuy Mitek at J&J. (See page 5.)
- **David Conn** joins Agamatrix as Chief Commercial Officer; he was previously COO at Pelikan Technologies.

- **Elisabeth Lindner** has joined Diamyd Medical as President and Chief Executive Officer. She has worked at Octapharma AB and Pharmacia Corporation.

Please e-mail your Diabetes Comings and Goings to [kelly.close@closeconcerns.com](mailto:kelly.close@closeconcerns.com).

## 12. Close Concerns Market Index and Final Thoughts

We don't have a formal "conference preview" this month, but we do hope to see some of you at JP Morgan's 26<sup>th</sup> Annual Healthcare Conference in San Francisco starting January 7. The event will bring together more than 300 companies and about 3,500 investors. In the past, the event has been a great opportunity to at least catch a glimpse of some of the great company execs in the industry. Although we're most excited about the various industry presentations, we're also looking forward to the keynote presentation, which will be delivered by best-selling author and *Washington Post* reporter Bob Woodward. Below are the companies in diabetes or obesity (or circling around it) for whose presentations we'll be fighting for seats:

- **Monday, January 7th:** Bayer, Roche, Abbott, Orexigen, Sirtris, Becton Dickinson, and Biogen.
- **Tuesday, January 8th:** Medtronic, MannKind, Home Diagnostics, Merck, Takeda, Insulet, Eli Lilly, Glaxosmithkline, Enteromedics, and Nektar.
- **Wednesday, January 9th:** Alkermes, Arena, and Vivus.

**In our table of diabetes stocks, biggest movers over the last months were SIRT, up 19%, and BIOD, down 20%.** Also moving in double digit land was PODD, up 10% - and up 70% since its IPO about seven months ago – now that's movement.

	20-Dec-07	20-Nov-07		3-Jan-07		20-Dec-06		IPO		Market Cap
<b>GSK</b>	48.21	50.73	-5%	53.81	-10%	51.93	-7%	-	-	147.06B
<b>NVO</b>	63.59	64.9	-2%	83.46	-24%	41.42	54%	-	-	44.85B
<b>AMLN</b>	39.06	38.38	2%	36.32	8%	38.3	2%	14	179%	5.14B
<b>MNKD</b>	7.95	8.18	-3%	16.16	-51%	17.7	-55%	14	-43%	987.98M
<b>PODD</b>	25.46	23.25	10%	-	-	-	-	15	70%	653.36M
<b>SIRT</b>	16.9	14.15	19%	-	-	-	-	10	69%	406.10M
<b>BIOD</b>	16.78	21.17	-21%	-	-	-	-	15	12%	387.89M
<b>OREX</b>	14.99	14.26	5%	-	-	-	-	12	25%	379.97M
<b>DXCM</b>	8.6	8.15	6%	9.88	-13%	10.73	-20%	12	-28%	264.28M
<b>HDIX</b>	7.87	7.94	-1%	10.61	-26%	11.1	-29%	12	-34%	140.87M

*Diabetes Close Up* is a newsletter distributed eleven times per year highlighting notable information and events related to the business of diabetes. Subscription information can be found on our website [www.closeconcerns.com](http://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. Companies that are current clients of Close Concerns' advisory arm include Abbott, Amylin, Bayer, Becton Dickinson, Insulet, Johnson & Johnson, Medtronic, Novo Nordisk, Roche and a number of private companies.