

DIABETES CLOSE UP

Diabetes Close Up
September 2005, No. 51
DCU on pre-EASD, mid-MMA, and post-FDA

The Shorter Version

From the Editor:

Coming to you from _stunning_ Athens! EASD begins in earnest on Monday (today) and if you aren't here, we wanted to urge you to tune into www.proactive-results.com later today at 10:00 am EST to hear the results of this historical PROspective pioglitazone Clinical Trial In macrovascular Events (PROactive) trial – the biggest deal in Athens! In the past, as many readers know, traditional type 2 drugs haven't improved macrovascular outcomes (almost but not quite in UKPDS) – today, we will hear whether Actos bestows a cardioprotective health benefit on high risk type 2 patients. It's the excitement here – a real outcomes trial to demonstrate whether Actos reduces total mortality and macrovascular morbidity in this high-risk, high-need group. The study has 91% power to detect a 20% reduction in the primary endpoint – to get to this level of power, we understand at least 760 primary endpoint events were needed – and they did get there, for better or for worse. We believe it'll be a positive study, and the side effect profile is what we'll be looking at in particular. Whether we can “extend” the study results to the class or whether they apply to Actos stands as a critical question.

The other big trial we'll be watching for is Medtronic's GuardControl study, where patients had the power to see 24/7 continuous glucose levels – we believe a study like this has serious potential to reduce outcomes like severe hypoglycemia and we'll hope for this outcome (as it were).

It's a crazy busy week – our schedule for EASD is on our website by our newsletters – www.closeconcerns.com - and you can check our blog (same, www.closeconcerns.com) nightly for our most valuable lessons learned.

–by Kelly L. Close

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The Longer Version

1. EASD: Focus on PROactive, GuardControl, Abbott's Navigator, and Rimonabant.

- **PROactive** – The conference has begun! Our schedule is on our website, as noted – we'll be back with a full report next month, along with our AADE review. Biggest news likely to come from this trial – stay tuned.
- **Guardcontrol** – So ISPAD took place in Krakow, Poland from August 31 to September 2. *Diabetes Close Up* was represented by Paris-based Jean-Philippe Gaetan who covered everything from patient empowerment to insulin sensitizer use in kids to problems behind obesity. Our larger report for the company will come next issue but in the meantime, we can say that the Medtronic results make us very eager to see the full Guardcontrol data. 'A1C isn't everything' was definitely a message working its way through the conference – Medtronic management adeptly pointed out that A1c misses glycemic instability, nocturnal hypoglycemia, postprandial hyperglycemia, and glucose patterns/excursions.
- **Navigator** – There were a slew of great symposia, but Abbott's at the sexy Metropolitan Hotel took the cake. Dr. David Klonoff showed the history of continuous monitoring, Jen Block, CDE at Stanford, showed prospective vs retrospective CGM "clinical application and utility," followed by Abbott's Geoff McGarraugh, a leader on the chemistry side, discussing real time continuous technology, closed out by Dr. Andreas Pfeiffer on the outlook toward the future. This was all followed by cocktails on the roof, where everyone continued to remark on how great Jen's numbers looked! On the positive side for Navigator, we learned that Navigator is intended now for *five-day* wear rather than three-day wear (with only four calibrations – hours, 1, 10, 12, and 72); on the flip side, we also learned that the device will be blinded the first ten hours in order to improve the technology among all users. On balance, we view the change as positive as it will help support all the scores. In the best moment of the evening, the very poised Ms. Block shared her glycemic patterns with us – half a week with Navigator off, and half a week with it on – the line in the end looked incredible and we could just feel her delight - in fact, we were feeling it too, in shared anticipation for what looks to be quite the technology.
- **Rimonabant**: So besides PROactive, the other word of the game here is Rimonabant, or Acomplia. The Rimonabant sanofi-sponsored symposium was packed, with perhaps 1500 people filling a room equipped with five large screens, audience-polling equipment, and mass quantities of well-dressed sanofi personnel. The big draw focused squarely on attention on the big drug. The polling devices revealed that the crowd was truly international—almost half from Western Europe, with significant representation from Eastern Europe, Africa, and Southeast Asia, and few from North America. A welcome by Chairman Matt Riddle included two major talking points: 1) the great variability in the presentation and care of diabetes, both between different countries and between different ethnicities in the U.S., and 2) the need for earlier, more widespread use of insulin therapy in type 2 diabetes. Polling the audience, Prof. Riddle showed that most there (79%) thought less than 40% patients in their area of the world were achieving an HbA1c of less than 7 (they're right). Likewise, 46% of the audience said that 20-40% of patients in their region already had complications at the time of diagnosis with type 2 diabetes. Right, again. The first speaker Prof. Paul Zimmet of Australia put the polling devices to a more subversive use, asking the controversial question: do you believe in the metabolic syndrome? In defiance of the recent EASD/ADA rejection of this diagnostic category, a stunning 88% of the audience responded positively. *This affirmed one of the major messages of the day, which was that metabolic syndrome is a valid and important disease condition.* One presenter attacked this question with such force that a nearby physician described him as "evangelical." Almost as shocking, the second major theme of the day was abdominal fat—shocking not perhaps in concept, but more in presentation, as we saw multiple photos of obese abdomens. Dr. Robert Ross drove home the point that clinicians should be measuring waist circumference, not merely BMI or body weight. This measure of abdominal obesity serves as a surrogate measure for visceral fat, which corresponds to risk level for mortality and CVD, and it also can change with exercise when weight may not. With respect to treatment, Ross spoke to the benefits of a healthy lifestyle...
- **Rimonabant, Part 2**: Closing out this section, Prof. Luc Van Gaal of Belgium presented results from rimonabant trials, positioning it as an all-powerful drug: affecting the hypothalamus, adipose tissue, muscle, liver, and GI tract, rimonabant is believed to decrease food intake and lipogenesis while increasing glucose uptake, adiponectin, and satiety signals. Results from the four concluded RIO studies have shown a reduction in waist circumference and weight, with 39% of women on 20mg of rimonabant losing >10% of their body weight throughout the 2-year trial, compared with 12% on placebo. Rimonabant was also shown to dramatically cut the incidence of the controversial metabolic syndrome—from 42% to 21.5% in the

group on 20mg of rimonabant ($p < 0.001$). Concerns about tolerance remain, with the primary side effects psychiatric (depression), gastrointestinal, and related to the nervous system. This appears especially important given exclusion criteria (strong) – many at ADA said merely ‘*oh they’re messed up on CNS anyway*’ – exaggeration at best, we believe. The crowd seemed to respond well to the presentation, although strangely there were no questions asked during the “rimonabant Q&A.”

- **Rimonabant, Part 2:** Dr. Julio Rosenstock described his protocol for using the treat-to-target method in type 2 patients, again highlighting the need for more aggressive therapy here. He noted that HbA1c is “too high,” insulin given is “too little” and “too late.” He suggested that insulin should be started when the HbA1c is above 7.0% despite maximum dosage oral medication. In keeping with the tone of the day, Dr. Rosenstock noted that he was hopeful that insulin glargine plus rimonabant might prove an excellent therapeutic combination.

--by Leah Edwards, Katelyn Gamson, and Kelly L. Close

2. **Diabetes Care Alert! “The Burden of Mortality Attributable to Diabetes” Roglic G, et al. Diabetes Care September 2005. 28(9): 2130-2135.**

Statistics based on death certificates characteristically underestimate the global number of deaths due to diabetes, as people with diabetes usually die of cardiovascular disease or kidney disease rather than causes uniquely linked to diabetes itself, such as DKA or hypoglycemia. The authors of this article sought to provide a more accurate estimate of the number of deaths attributable to diabetes in the year 2000.

In order to estimate the global burden of diabetes mortality, the researchers used the software program, DisMod II, which was developed for the Global Burden of Disease 2000 study. This program is often used by the WHO for disease estimates. The authors modeled the relationships between incidence, prevalence, and disease-specific mortality. They used estimates for prevalence and number of people with diabetes from a WHO study published in 2004 (Wild S, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27: 1047-1053, 2004).

Roglic, et al. found that the global excess mortality attributable to diabetes in the year 2000 was approximately 2.9 million deaths. This estimated global excess mortality is equivalent to 5.2% of world all-cause mortality in 2000. The poorest African countries, along with Cambodia, Laos, Myanmar, and Vietnam had the lowest percentage of excess deaths (2.4%), while the Middle East (9% in Arabian Peninsula) and North America (8.5% in the Region of the Americas) had the highest percentages of excess deaths due to diabetes. The percentage of excess deaths peaked at age 50-54 years in countries with a high prevalence of diabetes in younger age-groups, such as Southeast Asia Region (SEAR D), Arabian Peninsula, Eastern Mediterranean Region (EMR B), and Western Pacific Region (WPR B3). In contrast, the percentage of excess deaths due to diabetes peaked in the age range of 55-59 years in the rest of the world. 75% of all deaths in individuals with diabetes younger than 35 years were attributable to diabetes. 59% of deaths in people with diabetes aged 35-64 years were attributable to diabetes, and 29% of all deaths in people with diabetes aged over 64 years were attributable to the disease.

The 2.9 million estimate is three times higher than estimates presented in international reports based predominantly on death certificates. Additionally, this estimate is similar to the number of deaths reported for HIV/AIDS in the year 2000. Women represented a greater proportion of deaths attributable to diabetes than men (1.5 million vs. 1.4 million), which the authors explain is due to females’ lower background mortality levels.

Although diabetes is often seen as a disease of mostly affluent countries, the data from this study suggest that, in most developing countries, almost one in ten deaths in working individuals aged 35-64 years can be attributed to diabetes. While the estimated global mortality attributable to diabetes in this study is much higher than the estimates that are commonly presented, the authors report that it is still likely an underestimate, since it is based upon the WHO prevalence of diabetes, which studies have shown is itself an underestimate. The diabetes-attributable mortality found in this study moves diabetes from the eighth to the fifth place in cause of death ranking. The preceding four causes are communicable diseases, cardiovascular disease, cancer, and injuries. The number of deaths related to hyperglycemia would be even higher if impaired glucose tolerance as a cause of mortality were taken into account. This study is the first to present the global estimates of mortality attributable to diabetes.

--by Katelyn Gamson

3. Asking Bob Knorr Ten Questions on the MMA

- **Thank you SO much for being with us to discuss the multiple black boxes surrounding reimbursement, Bob! Tell us, what are the biggest issues around reimbursement right this second?** *The implementation of the Medicare Modernization Act (MMA) will continue to dominate the headlines for the foreseeable future. Although the Rx Drug benefit has received most of the attention, there are also several critically important initiatives within the MMA that are particularly important to reimbursement for new medical device technologies. These initiatives include such seemingly diverse initiatives as Medication Therapy Management (MTM), Chronic Care Improvement (CCI), Expanded Screening for Diabetes, and Competitive Bidding for certain product categories. Underlying these initiatives is CMS' attempt to apply private sector principles such as risk sharing and pay-for-performance to public health. In passing the MMA Congress has indicated a willingness to expand benefits for individuals in exchange for free market efficiencies such as competitive bidding. The thing that I find most intriguing is the value that CMS places on information as opposed to traditional tangible products. For example, CMS has relegated marginally differentiated products (such as traditional glucose meters) to commodity status while paying a premium for diabetes management programs under the CCI.*
- **Okay back up please! Let's say – just pretending! - I don't know anything about the MMA and in fact I just learned this excellent abbreviation. Where would I go - what would I do?** *Okay, well you can find the full text at <http://www.cms.hhs.gov/medicarereform/MMAactFullText.pdf> for starters ... (Ed. note - this link is a little scary because it literally is the entire act and the government seems very bureaucratic and this isn't that easy to navigate – of course that's why you should read on!)*
- **Hmm, well, that link has a lot of legalese, weird italics pieces to it. What does this mean for, say, management teams or investors in new medical technologies?** *Strategy for new medical technologies should be especially focused on in evaluating the reimbursement structure into which their technology will fit. This has become even more important in my view as the MMA is changing the fundamental reimbursement structure of certain categories, particularly those products that support chronic disease states.*
- **So interesting – so on that note, if you were a manufacturer, what would be keeping you up at night?** *Actually, many of the changes included in the MMA should not be a surprise to any major manufacturer. CMS signaled its intention to introduce many of these private sector initiatives over four years ago with several key demonstration projects, such as diabetes management and congestive heart failure. Now is the time for established manufacturers to focus their efforts on integrating their products into MTM and CCI programs. Companies that fail to do this may find themselves on the outside as a commodity-like supplier to more innovative service/information companies that are emerging to capitalize on these new Medicare structures. New ventures in particular need to ensure that they really understand the new business model that will be defining the environment in which they will be competing in the next two to three years. It's no longer simply about smaller, faster, more accurate, etc. Companies with products that treat chronic diseases really need to reassess how their product fits within the new Medicare reimbursement structure.*
- **Mmmm. This sounds worrying. Well, more broadly, how should changes in reimbursement impact the diabetes market? What are the specifics on what's happening on the reimbursement front as far as blood glucose strips are concerned, for example?** *The MMA should impact the diabetes market by expanding the overall market and reallocating dollars into preventive care for the undiagnosed and most costly sub-segments of the market. The new wide-reaching screening benefit that went into effect in January, 2005 has the potential to bring millions of new individuals into the market. Medicare is intent on defraying the cost of new prevention benefits through competitive bidding on more mature products such as blood glucose supplies.*
- **You have noted that the Medicare competitive bidding starts in 2007 – what are the dynamics of this situation and how much deeper are price cuts likely to go? Have there been any recent changes here?** *In tracking Secretary McClellan's comments on the subject of innovation it is clear that he is interested in redirecting Medicare dollars away from nominally innovative product categories into preventive care*

programs. In projecting the potential impact of competitive bidding I think that generic drugs provide a good surrogate. Competitive bidding involving highly profitable product categories with multiple second tier suppliers are likely to see the same sort of price erosion (in the 60-70% range) that branded drugs see when they go off-patent. Reimbursement cuts in excess of 20% were planned for 2005. These reductions are projected to be even deeper when competitive bidding is fully implemented in 2007. (Ed. Note – we think it’s dangerous for the government to call anything to do with diabetes monitoring non-novel – we sure as heck would be upset if we had to start using some generic brand who positions itself to be as good as the major brands when they aren’t even close! In our view, industry puts the margin from these products to fabulous use. Sixty to seventy percent!?!)

- **Well, I’m taking a deep gulp – I had no idea changes could be this far reaching. What implications are there for the broader market?** *Private payers should benefit from lower price points revealed through competitive bidding and also from more aggressive pricing from companies with excess capacity resulting from losing Medicare bids. I think that it would be naïve for DME manufacturers to assume that can prevent erosion in certain categories by using the pharmaceutical industry’s argument that it will kill innovation. CMS has already made the decision that certain product categories are good enough in their current state and there is no reason to expect that the private sector will not follow. (Ed. Note – see above. We asked Bob what chance there was for diabetes to be opted out and it sounded like he thought slim to none ...)*
- **On another diabetes med tech front - are pumps going to see similar pricing pressure?** *I see pumps differently for several reasons. First, there is still room for further, meaningful innovation in the pump segment. Secondly, pumps currently only marginally penetrated the Medicare population. Finally, there are not multiple private label manufacturers capable of aggressively bidding down prices..*
- **Is there any positive news from the pre-diabetes front on screening?** *Beginning in January, 2005 Medicare began covering diabetes screening for “at risk” patients up to twice per year. The “at risk” definitions are fairly broad and consistent with ADA and AACE guidelines. The benefit is intended to support early intervention efforts and avoid the costs of a diabetes epidemic. This was an important part of former HHS Secretary Tommy Thompson’s plan of attack in his “war on diabetes.” I have been directly involved in several initiatives with the AMA, CMS and Congress over the past 18 months that bode well for diabetes screening and longer-term glucose control. I expect there will be positive news on both fronts before the end of this year.*
- **My time is up, you say?! Please tell us a bit about your company and how we can reach you.** *Tapestry Medical Inc. (TMI) has two separate but related lines of business. Our principle business is providing specialized distribution for niche products. In the past year we have become the leading provider of Home PT/INR Monitoring products and related services through our exclusive relationship with Roche Diagnostics. This business involves integrating their market-leading CoaguChek® product into TMI’s own branded service offering. We are in the process of taking on several other unrelated product lines that require similar infrastructure that most start-up companies do not have and/or larger companies simply cannot justify. Our infrastructure includes a network of over 200 nurse educators who provide face-to-face training in all 50 states and all the systems and procedures needed to be a distributor of prescription products. Our secondary business is a small strategic consulting division comprised of a network of experienced, independent business professionals each of whom has over ten years of medical device/diagnostics experience. We specialize in developing reimbursement-related business strategies and integrating them into a larger sales and marketing plan. It is a very “hands on” approach. The skill sets of TMI Associates include reimbursement strategy, market analysis/business modeling, financial planning, scientific/technical writing, and professional relations and advocacy.*

Readers can reach Robert J. Knorr, MBA, M.Sc. at rknorr@tapestrymedical.com.

This is the second in a series of interviews of note to be published by DCU – our first was published in April, a discussion John Eng, powerhouse inventor of exenatide – now known as Amylin’s Byetta. That interview can be found here <http://www.closeconcerns.com/dcu/47%20Diabetes%20Close%20Up.pdf>. If you have suggestions for future interviews, please write Kelly at kclose@closeconcerns.com. Thanks very much!

--by Kelly L. Close

4. FDA on Inhaled Insulin:

Before a packed room at the Holiday Inn in Silver Spring, Maryland, the Endocrinologic and Metabolic Drugs Advisory Committee met September 9 to discuss approval for Pfizer's inhaled insulin drug Exubera. The drug was summarily recommended for approval for type 1 and type 2 patients with diabetes after a wide-ranging discussion focused more squarely on questions related to safety than efficacy, in our view. Some points of interest from the day:

- **A benign opening!** Rather than open the discussion with admonitions about the importance of safety, Dr. David Orloff opened the discussion more benignly, and we felt that there was almost the assumption of approval, despite the major questions still at hand. We were also surprised that there wasn't more lobbying for oversight or surveillance. While some would say that oversight/surveillance is a routine post-approval requirement, so such lobbying would have been redundant, we would have at least expected more discussion on it. It is true that the company had already submitted its post-approval surveillance plan, and apparently that was enough. As we learned from one of our top advisors recently, often companies do submit such plans ahead of time, often in an effort to use a strong surveillance package to try to soften any rough edges that the product in question may have. From our view, we would've liked more discussion of enforcement about the plan, to give us more comfort that the wrong patients (smokers, those with asthma, COPD, kids, etc.) won't take it. But, but, we get ahead of ourselves, don't we! On to what ultimately happened!
- **Recommendation to approve Exubera in type 1 and 2 diabetes:** Ultimately, despite extensive discussions about safety of Exubera, the panel voted 7-2 in favor of approval for both type 1 diabetes as well as type 2 diabetes. Additionally, the panel voted 7-2 that there was *enough* clinical trial evidence that Exubera could be effectively applied to an "intensive" glycemic control regimen and that the efficacy of Exubera had been adequately assessed in patients with type 2 diabetes. Interestingly, the dissenting votes in each case were different. For many type 1s, we actually do doubt that there is a way that Exubera could be effectively applied to an intensive glycemic control regimen – that's because specificity of dosing will be sub par for many type 1s. Ask any type 1 what is the smallest dose of insulin they take, and they won't say 'three units,' which as we understand it, is the smallest dose one can take because one pellet is the equivalent of three units. Although we don't have hard data to back it up, we think reduction of glycemic instability is becoming more and more common among type 1 patients – that means avoiding post-prandial spikes (yay, Symlin) and when the spikes to emerge, to blunt them immediately. With inhaled, the smallest "bolus" as well as the smallest "correction" will be three units. It's fine that that is what it is, but for anyone to say that use of Exubera *only, combined with Lantus*, for an intensively managed patient is as good as being able to take half a unit of insulin with a syringe (17% as much) or one tenth a unit with a pump (3% as much) is ... okay, we're going out on a limb here, but we think that is wrong! Just because this is wrong doesn't necessarily mean this shouldn't be approved for type 1 – we agree it is right to have more options. And actually, we might say that because some percentage of PWD (patients with diabetes) don't correct because they don't like shots – well so may be for some, control could be improved. We would not probably view those patients as so intensively managed to start, however. Semantics? To some extent, maybe! We'll climb down, now ...
- **It didn't make sense!** So moving on, while we weren't necessarily surprised by the approvability of inhaled insulin, we were surprised that the recommendations for approval came so quickly - "Yes! Yes! Yes, with caution! Yes! No. Yes! ..." – particularly because there were so many questions on safety and inconsistent bioavailability throughout the day. (This inconsistent bioavailability is an interesting one – it doesn't sound good and then again, how consistent is the response to insulin that any of us (any of us PWD we mean) have re: any insulin we take any day of the week? Who knows! There are always reasons we can think of for why our blood glucose isn't what it quote unquote should be – oh-the-exercise-I-did-slash-was-going-to-do-oh-insulin-sensitivity-varies-by-time-of-day-oh-a-cheeseburger-has-more-fat-content-than-a-hamburger, etc. We do think though that inconsistent bioavailability is ultimately more worrisome than inconsistent regular response to insulin, due to the absence of precise dosing one currently enjoys if one takes insulin by syringe or pen or better yet by pump.)
- **Big picture!** However, we know how badly doctors want patients to improve, and to recommend *rejection* of a therapy without hard evidence to back it up wasn't going to happen. Ultimately we're happy that patients have another option to try, given outcomes are so poor, although we'll hope that the safety front is examined very carefully – we believe it will be, since another Rezulin isn't something anyone wants to have happen, least of all Pfizer. One thing we do know – restrictions and recommendations are generally

quite difficult to enforce and we'll be watching to see how closely this is monitored – very, we expect, but how successfully is harder to say since it isn't up to the companies.

- **Importance of training highlighted again and again:** Throughout the day, panelists pointed out how important training of doctors, nurses, and patients would be – we second this, especially for patients who start at ground zero, carb counting! Interestingly, even the “no” votes weren't necessarily due to safety alone, but even here, training was emphasized (one panelist voted no because he doesn't believe training will take place). Yes, education was stressed by many doctors today, and we suspect Pfizer will need to invest extensively on this front – we also believe they are well prepared to do it, although we do question what overall drug profitability will be. They haven't set pricing yet, and we look forward to information on this front!
- **Medical need well articulated:** Another thing that really set the tone for the day was Dr. William Cefalu's cogent talk on medical need. He made it very clear that current therapies aren't doing the job and that more options are needed! At the end of the day, while there were some very real discussions about lung cancer – insulin is a known growth factor, after all. However, given that lung cancer would be a rare event, very large trials would be needed to understand whether there the risk of lung cancer is real – by contrast, much of the information focused on cough, and panelists probably just didn't feel that they could hold back on cough grounds!
- **Hypoglycemia not an issue to delay approval:** The panel said that the safety of Exubera and hypoglycemia had been adequately assessed in type 1 intensively managed patients as well as in type 2 patients. We were surprised about this since hypoglycemia is typically such a hot button. –important to realize, we suppose, that there are no apparent difference in hypoglycemia.
- **Next, the panel also conveyed its belief that there was sufficient evidence** to assess pulmonary safety in patients without underlying disease.
- **By contrast, the panel voted that it did not have enough data to assess pulmonary safety of Exubera in patients with underlying lung disease.** We would've been shocked had this been negative. This vote was 5-4 and we were actually more surprised that *anyone* said they had enough evidence on this front. Bottom line, we think that it is probably very difficult to generalize about lung health of such a varied population and that probably drove the yes votes. In particular, there was major concern expressed about people with viral upper respiratory infection, asthma, COPD, and smoking. The panel had fewer worries about clinical concerns and recommendations on titrating and going back and forth between inhaled and sub-cu insulin.
- **Our overall take was while the panel wasn't absolutely enthusiastic about Exubera, mostly due to lingering questions about safety** (some of which can't be answered for years), it still felt **squarely that it did not have enough evidence to hold the drug from the market.**
- **We also feel that the FDA and the doctors** on the panel feel a growing pressure to try to create more options for patients with diabetes because current options are clearly not working – as was pointed out multiple times, over two thirds of patients with diabetes are not at goal and the FDA/panel may just see things getting worse not better. They may feel paving the way for another option will provide good incentive for patients to become more engaged in their health – or at least that if they keep the option from the market, they are doing patients a disservice.
- **Given the success of simplicity to date, we believe the panel also may have felt, even sub-consciously responsible to help bring more options to patients, particularly “simple” options.** As a reminder, Lantus, which achieved over \$1.0 billion in sales in 2004 (just three years after the US product launch), has been a very big hit with patients. In reality, we feel Exubera will not be as simple as is expected, because patients will still have to be taught how to use it, how to check their glucose scores, how to count carbs for a meal (many) and dose insulin properly, etc. That said, we look forward to seeing some action reports!
- **Challenges remain:** We believe that many challenges face Pfizer as it scales up for commercialization. We would expect a positive approval decision by the end of October and then we would look for next challenges to be associated with pricing, reimbursement, coverage, uptake, and profitability. As noted, we don't necessarily think that the drug is as simple as it appears and this will prompt problems for PCPs, who have very limited patient time as it is.
- **Other musings/items of note/speculation:**
 - Panel members asked to see a sample of the Exubera device and the sponsor, Pfizer, didn't have one! *What?!* This struck us as very odd.
 - Many complained that the size of the device is too big – while we agree about the need for miniaturization, we also feel that it's a first generation device and size won't hurt too much at this

stage since it's first in class. Alkermes and Mannkind both have much sleeker devices – we would expect Pfizer/Nektar is probably very closer to filing one of its own as well, especially given its recent purchase of Aerogen technology.

- What will pricing be? We would look for at least 3x the cost of Lantus but likely lower than 5x the price, based on profitability needs combined with not limiting demand. That said, premium pricing – at all – is going to be very tough to justify. Europeans just look and shake their heads when discussing inhaled insulin – it won't be taking off here.
- There was extensive discussion of variability among patients and the impact of inhaled insulin – why so variable, everyone asked? We reckon there's probably substantial variability with patients taking traditional insulin analogs – we just rarely hear about it!
- There will be a lot of people contraindicated from use, including *all* smokers, *all* people with asthma, *anyone* with COPD, etc. One can use Exubera if one is an “ex-smoker” – how does one define ex-smoker? Five years without a drag? Six months? And then what is people surrounded by passive smoke are contraindicated? How is that defined? Before I met sweet John I used to have lots of drama and trauma in my life, which including dating lots of smokers (not simultaneously) – I bet if I were to take a poll, six months wouldn't equal ex! What would you say?! Then again, I don't need to take a poll since I'm here in Europe – I just have to walk around the Peace and Friendship stadium and ask anyone who has lighted up – almost everyone today, 11 am.
- How much hassle is hassle factor? There was quite a bit of focus on device related questions—reliability, cleaning and care of the device, etc. We'll have to see how this goes.
- Pfizer has studied this drug for ~ 10 years and has established non-inferiority with regard to HbA1c vs an active comparator (though certainly not a particularly aggressive regimen). Aside from cough, which appears to be a ‘nuisance’ side effect there is a small decrease in FEV1, which is not progressive—the etiology of which is not understood. Bioavailability is highly variable (more so than for SC which is also quite variable) and is altered by upper respiratory infection, smoking, COPD and asthma. Nonetheless with good compliance intra-individual results are reasonably reproducible and patients should certainly be able to learn to titrate dosage to meet their needs.
- **Look for approval as early as the end of October, a pricing decision shortly thereafter, and then the education should reach full throttle!** We'll be staying tuned and watching for implications on the drug and device front!

--by Kelly L. Close

5. Conference and dLife previews – NAASO, 49th Scientific Annual Meeting of the Japan Diabetes Society

- **TIVO dLife - some amazing segments upcoming!** Do you know about this TV show on CNBC that focuses on diabetes – the ad copy says ‘for people with diabetes, their families, and those at risk’ (that's pretty broad) – and we would add for those who want to learn more about the medium! Here's a bit about the excellent fall line up ~
 - September 25, 2005: Pregnancy and diabetes expert **Dr. Lois Jovanovic** talks about preconception, birth, and beyond ~ Dr. J. was our doctor last year prior to the birth of our sweet Coco (we had a weekly Monday afternoon conference call every week, ten minutes prior to which I have had emailed her my excel spreadsheet with my blood glucose numbers ~ if my standard deviations looked out of sync, boy did I better have some better planning at hand!) – wow, can we say is she *amazing*! Truly one of the most inspiring people in diabetes we've ever met! It has been an honor to know her ~ definitely check out this episode, we have heard it is incredible.
 - October 2, 2005: **Dr. James Gavin** of the National Diabetes Education Program and **Dr. Leonore Coleman** are two docs featured – both are very focused and quite dynamic. Tune into this one too!
 - October 9, 2005: A diabetic neuropathy overview is given on this episode by **Dr. Aaron Vinik**, who knows more than absolutely anyone full stop on the subject - plus, Mother Love visits a podiatrist (you cannot resist her – try!).
 - October 16, 2005: Cardiologist **Dr. Sheldon Gottlieb** gives tips on minimizing risk factors for heart disease and Parade magazine editor Fran Carpentier will be on discussing juggling career and family with type 1 diabetes – I can't wait for this one! Also “tips for eating out without losing control” – well I don't need any more tips on this front since I started Symlin - I had 15 pieces of sushi last Wednesday at Ebisu at SFO (one of the best Sushi places *anywhere*, check it out ~)

including some amazing yellowtail and some fantastic unagi ...and I had 117, 80, and 94 at hours 1,2, and 3 post prandial – it doesn't get much better!

- October 23, 2005: CDE extraordinaire **Joy Pape** will be on, sharing her expertise on many aspects of diabetes, including travel in particular on this episode.
- October 30, 2005: founder of ChildrenWithDiabetes.com **Jeff Hitchcock** – ohmygosh any of you who know Jeff know how intense and brilliant and together he is – you must tune in to this one! I don't even know what the subject at hand was, but any time Jeff speaks, pearls topple out. Then, to boot, it is **Dr. Richard Rubin** and his son Stefan – we are SO lucky that behavioral expert Dr. Rubin is the next ADA President – we will expect to see much more on the behavioral front.
- November 6, 2005: The biggest myths and misconceptions about diabetes with **CDE Betty Brackenridge**; the kick-off of the BD Diabetes Makeover with Dr. Harvey Katzeff; and quick and easy low-carb wraps from Chef Chris Smith.
- **North American Association for the Study of Obesity** - www.naaso.org meets in Vancouver, British Columbia, October 15–19.
- **The Diabetes Technology Society** meeting takes place in our fair city by the bay (www.diabetestechology.org) November 10–12. Ross Jaffe, MD, of Versant Ventures and Kelly L. Close are co-organizing a morning on the “Business of Diabetes” – what should be some terrific discussions on glucose monitoring, insulin delivery, pharma, and stem cells ~! We hope to see you there ~
- **49th Scientific Annual Meeting of the Japan Diabetes Society** takes place in Japan, Tokyo May 25-27, 2006. <http://www2.convention.co.jp/jds49/english/greetings/index.html> We had the opportunity to met noted pediatrician and incoming IDF President Dr. Martin Silink in Athens – in Tokyo, he will present a comprehensive overview on the global impact of diabetes – combine that with the fact that Asia is, of course, where unbelievable growth in diabetes is taking place and we really need to understand the nuances of that better *and* the fact that special coverage will be given at this meeting to the development and regeneration of pancreatic beta cells and we're thinking this would be a pretty stirring meeting.

--by Kelly L. Close

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