DIABETESCLOSEUP

Safety first ... October 2007 • No. 73

From the Editor

Hello, everyone! What an issue, with Pfizer dropping inhaled, earnings, safety buzz, EASD, the Cleveland Clinic's obesity meeting, our new column "Diabetes Comings and Goings" ... we know 47 pages is a little over the top, but our goal is to keep you on top of the diabetes world.

We did the JDRF walk Saturday in gorgeous Crissy Field in San Francisco*! It was a beautiful day and our team was happy and together, and I was so grateful to have everyone there. Talk about lucky. We were the last ones to leave and I still tore myself away – nothing like that view nor that feeling of community. I'll mention that we have* ***not*** *yet achieved our goal of raising $5,000 – I thought we would, but fundraising has been slower than usual, though we're grateful for every cent. If 90 of you could help with $35 each (or 45 with $70, or anyone with a big budget with $3,150, you get the idea) we and JDRF would so happy. Thank you for considering it – we would love nothing more than to exceed our goal, so if you can help us, please click here. As many of you know, JDRF is doing exceptional things to make life better for people with diabetes, and we are especially excited about the research on the continuous monitor and on complications. JDRF has enlisted some of the best minds in the world – we're proud that many are even nearby at Stanford. We want the funding to continue. I have gone from resenting my CGM to loving it. I feel safer and so lucky that I can afford it. There's much work on access to do as we're very far from wide acceptance – JDRF is helping lead the charge and I feel recently more certain that day will come. Until then, I feel a little bit more equipped every day to handle this scourge.*

Safety first – the message of the moment. *That's our bottom line for our interview this issue with Dr. Steven Nissen, so check that out on page 20. We're grateful for his candor. He is smart, persuasive, and very controversial, and yes, he does like to grandstand. But I have to say, I believe he puts patient safety first. That's good enough for me.*

Speaking of safety first, what's the deal with the FDA? *If millions of diabetic patients are doing so poorly – and they are – doesn't a drug's risk-benefit trade off matter? This comes to mind in light of several recent FDA decisions. We understand the importance of the pancreatitis label update for Amylin: it isn't new information, we know the rates are declining, and it's hard to get very worried at this stage about 30 cases in over 700,000 people on the drug. The label update for Merck's Januvia (post-marketing reports of hypersensitivity reactions and exfoliative skin condition, including Stevens Johnson syndrome) had new information in it. Good for FDA for spreading the word even if there is no causality there at this moment.*

But what about the FDA's non-approval of Symlin for type 2 patients on basal insulin*? We are surprised and disappointed by the decision, since there is nothing in the data that suggests this combination is unsafe. When cost-benefit starts to be compromised, we feel like the FDA has ceased to care about patients in the way that we count on.*

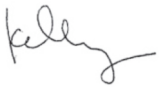
Think about insulin*. If you're a patient, you know it's a difficult drug to use that can seem unsafe. It has a very narrow therapeutic range– but it exists because it saves lives. It would be nice to have alternatives to this given that the public healthcare system in the US doesn't compensate doctors and nurses to train people appropriately. The FDA's non-approvable letter for Symlin is counter-intuitive. Is*

Symlin dangerous for type 2 patients on Lantus and Levemir? No. How many patients have A1cs not at goal that haven't been able to go on mealtime insulin? Hundreds of thousands is probably an underestimate. We wish more people could go on mealtime insulin, and we feel that when our healthcare system changes its focus to sufficiently reimburse providers for chronic care, more will go on insulin successfully. What is the reason this alternative – Symlin – isn't available? The FDA didn't say. We have a call into Mary Parks, who runs diabetes at the agency, and we'll let you know what she says (if anything).

All we're asking the FDA is to give drugs a chance and to have some really good reasons why if it says no. *Non-approval is a really strong phrase. Does it make sense to limit innovation, to limit patient choice? No. It doesn't.*

In closing, the news that Pfizer was shuttling the inhaled insulin business was an indication that even a pharmaceutical giant *– with all the money in the world – doesn't really understand the diabetes market. Our take was that many things went wrong, but most of all, they didn't look at it from a consumer perspective. It was disappointing, from our perspective… Another potential alternative, gone.*

Sincerely,



Kelly L. Close

Major Headlines

In This Issue

Blogwatch

Blogwatch - See below for blogs since our last monthly newsletter. You can see any update online at http://www.closeconcerns.com/ as well as subscribe to the RSS blog feed.

- **October 18:** Pfizer's approach to Exubera - what's wrong with this picture?
- **October 5:** Come walk with us! JDRF Walk, October 20 in San Francisco...
- **October 5:** Obesity in America: Over-eating or under-exercising or ....?
- **October 5:** American dichotomies: Red states, Blue states... What's next? Fat States, Lean states?
- **September 28:** A Big Effort For Diabetes In The Big Apple
- **September 26:** Byetta on TV ...
- **September 26:** Good news for a select few type 1s...
- **September 21:** EASD wrap up: It's all about insulin
- **September 21:** Lilly's winning tagline, "We take diabetes personally"
- **September 18:** EASD Day #1 - Very busy time as diabetes hits Amsterdam...

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

- **October 1:** Symlin pen approved by FDA, hurrah! ~ Symlin with basal unapprovable? unbelievable ...
- **September 27:** New Byetta TV ad - check it out ~
- **September 26:** JDRF Promise To Remember Me Campaign
- **September 25:** cupcakes, donuts and salad bars...
- **September 21:** EASD continues ~ diabetes vaccine?
- **September 19:** New guidelines set for post-meal glucose at European meeting
- **September 13:** Fabulous new Ad Council campaign jolts us to reality... and action!

Videos

Below are our favorite videos in diabetes this month:

- Great DTC is here with new Byetta advertisement
  http://www.youtube.com/watch?v=UccrcOlv55Iaasdf
- The value of diabetes educators
  www.youtube.com/watch?v=cXQQ4zuivDo
- AADE takeaways
  http://www.youtube.com/watch?v=6cZNL7XUluw
- "Take control of your A1c" - a very cool backwards diabetes commercial
  http://www.youtube.com/watch?v=C86QmRVk_7k

Coming Soon in DCU...

Some terrific conferences are in the works over the next couple of weeks, with the Diabetes Technology conference here in the Bay Area on October 25-27, the Canadian Diabetes Meeting in Vancouver on October 24-27, and NAASO in New Orleans right now (through October 24). In the next couple of issues we'll feature some insights from these meetings as well as our interview with AADE educator of the year Teresa Volpone.

1. Quotable Quotes in Diabetes

"The problem with reversing obesity is that in the short term, nothing feels better than eating ice cream while watching TV; the negative consequences are all long-term."

—Gary Foster, PhD, on the challenge of weight loss.

"I sit here very humbled and very concerned that we're not going to find an easy solution [to obesity]. The body's underlying biology is so effective. The whole reason we've evolved to have memory is to help us find food… There won't be a magic bullet."

—Former FDA Commissioner Dr. David Kessler, speaking at the Cleveland Clinic Obesity Summit on the challenge of reversing trends in obesity.

"The one thing we know about reinforcing stimuli is that the way you view the product is critical."

—Dr. Kessler arguing that in order to fight obesity, we need to change the perception of large portions from "value" to "disgusting" much in the way the perception of cigarette smoking in the US was changed from "glamorous" to "gross."

"Something is going on with obesity, and it ain't just eating at McDonalds."

—Dr. Richard Atkinson, arguing recently that the obesity epidemic around the world is caused by a virus.

"Decades of multidisciplinary research have transformed science fiction into scientific possibility!"

—Dr. Philippe Halban, speaking at EASD about the pace and direction of scientific research on beta cell regeneration.

"Type 3 diabetics – the non-diabetic partners of diabetics – always think they know it all."

—Dr. Steve Edelman, discussing the challenges of a relationship between people with and without diabetes at a recent TCOYD meeting.

"Well-controlled diabetes is the leading cause of nothing."

—Dr. Bill Polonsky underscoring that diabetes is, as he put it, "not a death sentence."

"…if you will excuse the pun, the DREAM trial was a nightmare. There was a drug, rosiglitazone, which reduced the incidence of new-onset diabetes by 60 or 70%. But all of the cardiovascular events were going in the wrong direction."

—Dr. Steven Nissen, discussing the series of events leading to his famous NEJM meta-analysis on the cardiovascular risks of Avandia (see our full interview with Dr. Nissen on page20).

"Endocrinologists have… spent their entire lives believing that the most important thing about treating diabetes is to reduce hemoglobin A1c, so they've had a very glucose-centric view, and I simply don't agree. I believe that the reason you want to lower HbA1c is to reduce the complications of diabetes… This singular focus on blood sugar… has led to a misunderstanding of what it is that we're trying to accomplish when we give these drugs. With a PPAR like rosiglitazone that causes myocardial infarctions, fractures, macular edema, and heart failure – I don't really care if it lowers blood sugar. It's not of benefit to patients."

—From our interview with Dr. Nissen.

"Do you know that when you put a black box warning on a drug that its sales are rarely affected at all? If the FDA had quietly relabeled rosiglitazone, people would have continued to be exposed to the drug.

The reason that it's a good thing that the media jumped all over this is that the drug is effectively not being used anymore."

—Dr. Nissen, justifying the media attention given to his meta-analysis on the safety of Avandia.

"Here's the most important principle, and it's one that no one wants to hear: the absence of evidence is not evidence of absence."

—Dr. Nissen, explaining that health care providers and patients must be wary of the safety of new drugs when little evidence is available.

"Unfortunately, in this current environment where the FDA is unwilling to act, and is really impotent in many ways, the only way we get action is to directly inform the public. I would argue that while it made life tough and did create some anxiety, it also meant that a lot of people that were being harmed by a drug got to talk to their physicians about it. A lot of physicians had the opportunity to change the therapy for their patients. Frankly, wide public discussion of the Avandia affair has led to much more good than harm."

—Dr. Nissen, arguing that his meta-analysis and the subsequent media firestorm were good in the long-run for patients.

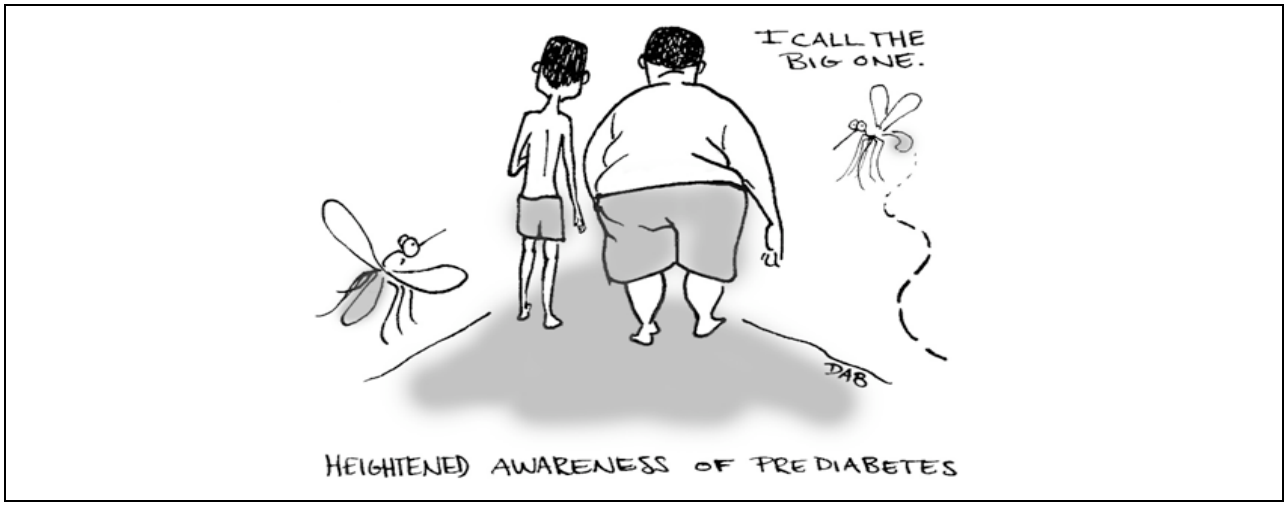
"To the extent that Exubera gets people to take insulin who otherwise wouldn't, I think it's a great thing."

—Dr. John Buse, discussing Pfizer's inhaled insulin product, Exubera, in the journal Diabetes, Obesity, CVD ("DOC").

"It is concerning that few children using CSII [continuous subcutaneous insulin infusion], the best insulin delivery system currently available, reached their A1c goal."

—McVean, J. et al. in an article entitled "Factors Correlating With Improved A1c in Children Using Continuous Subcutaneous Insulin Infusion," published in the October 2007 issue of Diabetes Care, lamenting that only 38% of the patients in their study of children using pump therapy reached the ADA's A1c treatment goals. (Ed. note – we imagine the percentage who reach goal who are not on CSII is more lamentable.)

2. diaTribe FingerSticks



-by Daniel A. Belkin

3. DCU Company Watch

- **Novo Nordisk wins approval for Levemir in Japan:** On October 21, Novo Nordisk announced it had won approval for Levemir in Japan. This is another win for the Novo Nordisk franchise and gives it important ammunition against Lantus, which has been approved in Japan since late 2003. Though this might seem very late approval for Levemir, au contraire – Lantus gained approval in Japan three and a half years after its approval in the US in 2000, so relatively speaking, the two and a bit years it took for Novo Nordisk was relatively fast! We're trying to learn more right now about insulin use in Japan and admit we don't even know the market size there – we do know same as stateside, not enough people are at goal. We do think Novo Nordisk marketing on the importance of getting to glycemic targets will help the entire industry.

- **Merck—New indications and new warnings for Januvia as sales reach $204 million:** On October 22, Merck announced its 3Q07 results, and its strong result of $204 million in sales for the Januvia franchise – this follows quarters of $42 million, $87 million, and $168 million. Although the sequential growth curve was a little less steep this quarter, exceeding $200 million in a quarter is certainly an impressive milestone and Merck does seem on course to reach $700 million in its first year out. For context, that compares to $86 million for Lantus in its first full year out and $431 million for Byetta - injectables are different in our view because of the training involved. 2008 will be Lantus' eighth full year on the market, and exceeding $3 billion in revenue shouldn't be difficult at all – and this drug has lots of room to grow, just as we believe GLP-1 does. (We understand there's only one analyst model with Byetta/LAR revenues exceeding $5 billion at peak – if the peptide revolution is all we think it will be, this estimate will one day look low.) So back on Merck - this is Merck's third full quarter with Januvia, which is now approved in 58 countries and available in 33 – this has been remarkable execution for a drug launch. Expanded indications may also help drive growth for the Januvia franchise, although being approved for monotherapy right off the bat was really the big news, late last year. Nonetheless, Merck did announce on October 17, that it gained approval for Januvia as initial dual therapy with metformin and as add-ons with SFUs. This is a win for its franchise to have add-on use with SFUs - although we believe Januvia is more likely to be used as a replacement for rather than an add-on to SFUs. A bigger deal is the initial dual therapy – even if Janumet was already approved, dual initial therapy will undoubtedly become a trend, and since most plans likely require metformin first anyway, we consider this a win. So, too, is Merck's success with reimbursement - they said on their earnings call that Januvia is on tier 2 for 200 million in the US and that Janumet is on tier 2 for 179 million. We are impressed that the reimbursement has come this far this fast.

  However successful it has been, we are more cautious on DPP-4 inhibitors due to recent safety issues. The big part of Merck's October 17 press release (though not the lead) was that the company also noted that the warning section of the label for Januvia has been expanded to include post-marketing reports of hypersensitivity reactions (anaphylaxis) and exfoliative skin condition including Stevens Johnson syndrome. SJS as it is known is not very calming – SJS is known to be a severe, idiosyncratic reaction, typically in response to various medications (antibiotic Bactrim is one), which are characterized by fever and lesions. As we understand it from a very smart doctor friend, patients are usually hospitalized and given very high dose steroids. He says the earlier it is caught, the better the outcome. The Januvia franchise has often been characterized in marketing literature as very safe, although there's not enough data to prove that yet – really it takes hundreds of thousands of patients on drugs for years to prove that. Some would say peptides are inherently safer and we will have history to bear that out – at any rate, Merck is certainly building a large database, though right now it has just 400 people having taken the drug more than two years. Some have argued that because the DPP-4 enzyme may be involved in many processes, DPP-4 inhibition is theoretically more dangerous

than administering GLP-1, the DPP-4 target hormone. To some extent, we think there has been some "crossover" in marketing literature with associating tolerability with safety - we have noticed this with more than one drug and certainly don't view it as a helpful trend. As noted below, Novartis management indicated on its October 18 conference call that it has not seen any incidence of Stevens Johnson syndrome with Galvus. The product has, on the other hand, been pushed back at FDA due to skin issues – coincidence? We imagine these skin issues hadn't come up before Janumet was approved during the second quarter. We can only ask questions at this point – how many cases of SJS were called in is unknown and of course as we understand it, there is no causality at this point. This is not the complication of choice – we did wonder what would have happened to Amylin stock had Byetta been associated with SJS!

- **Pfizer – Exubera, R.I.P.:** Pfizer announced on October 18 it would kill Exubera. The company will take a $2.8 billion pre-tax charge. We wish the company would have put as much investment into the product launch as it did the product – this will go down as one of the biggest product failures ever, and we're not that keen to have one of those in diabetes, given the lack of alternatives right now anyway. We've been cautious about how fast Exubera could grow given the lack of simplicity with the first generation and lack of safety data - some would always want to see 20-year safety data and from a patient perspective we understand that. This should probably put companies on notice that if the current generation isn't simple, it might just be best to wait until it is simple – at least while there is so much pressure on healthcare providers and so little reimbursement available for teaching. As well, patients *like* simple. Diabetes is complicated enough. It gets really depressing, actually, when drugs and devices don't work, and it's not exactly the same things as when your new GPS system doesn't work. We internalize this stuff as patients, we get impatient faster with diabetes treatments when they don't work as promised, we take it personally, and we aren't that tolerant. Anyway. We had been excited for future generations and hope to still see these – we had been counting on more long-term data, though, and now the clocks start ticking with all the other programs – Lilly/Alkermes and Mannkind and Novo Nordisk.

  It is worth noting that we don't think Pfizer handled the communication very well with Nektar. There was a press release from Nektar later that day saying it found out Pfizer's decision only with that morning's press release. Is that the best way to communicate with a partner? And it begs the question, had Pfizer involved Nektar a little more, maybe it would have been more successful? We also think Pfizer could have improved its press relations – for whatever reason, it refused our request to preview its direct-to-patient commericals earlier this year. We do hope new therapies continue to develop that have the potential to reduce the A1c. We don't need to contribute more to Monday-morning quarterbacking but will say that we hope more patient research is done next time so that the inherent difficulties of insulin are well understood. This, in the end, is why we think Pfizer pulled out – it didn't think it could surmount the problems associated with getting patients on insulin in the US healthcare system. So much for a fourth insulin company. We do tip our hat to Sanofi management who said at the time of Sanofi's Aventis acquisition that they were not enthusiastic about inhaled insulin. Sanofi-Aventis chairman Jean-Francois Dehecq should be lauded, of course, for recovering so much of Aventis' investment into inhaled insulin. We still remember vividly his words on the company's third quarter 2004 conference, when he noted that inhaled insulin was "*charming at first glance*," but that the market access was questionable and expressed doubt in particular that the European healthcare system was ready and willing to pay for something that was "essentially the same, but much more expensive." Touche. The big question now is whether another company could create a successful inhaled insulin product. We are cautious still due to perceived safety (especially since the Exubera database, which had been growing nicely, is now kaput), but we also note again that taking insulin is just darn hard to teach and we're happy to see those next in line working hard on that front. Last, we also tip our hat to Morgan Stanley analyst Jami Rubin who was the first analyst we remember who

went against the grain from the start and forecast that the inhaled insulin uptake would be slow, given the difficulties. For us, it's hard to say if any of the other companies can be successful, but we certainly can sound our now-familiar theme that we hope more alternatives will be developed. The other big question – what will happen to the world's second-largest insulin plant in Frankfurt, Germany?

- **Novartis – Galvus not any nearer**: The Galvus news was not positive on this call for Novartis. While Galvus was not mentioned in the presentation, in the question and answer session, management expressed disappointment that there was "no news" with regards to FDA discussions. Last quarter, management had expressed optimism that the FDA would clarify what it needs for approval by August. However, management's tone seemed more pessimistic this quarter, explaining that they had received no clarity, and did not expect clarity from the FDA any time soon. We wonder if this is "safety first" again – perhaps there is more here that meets the eye, or perhaps the FDA is just overloaded. Management said the FDA has only offered moving targets, asking for additional patients and longer follow-ups; no agreements have been made and discussions continue. In response to a question of whether outcome studies will be required following an FDA mandated Galvus trial, managements response was simply, "*your concern is our concern*." The one positive update on Galvus was that Steven Johnson's Syndrome has not been seen in the Galvus clinical program.

- **Amylin – Continues forward, awaiting LAR:** Amylin announced its 3Q07 results October 17. It reported product sales of $177 million, up 28% from $147 million in 3Q07 and up ~6% from last quarter. Byetta sales came in at $161 million, up 27% from 3Q06, while Symlin net sales brought in $16 million, up 31% from 3Q06. Product revenue results were a little disappointing. We suspect primary care doctors don't have enough time to really learn new diabetes treatments, even easy ones - the hallmark of simplicity for this product is one of the biggest benefits in our view. We wonder how much "physician inertia" (as the ADA calls it) exists – we know the reimbursement is poor for spending any real time with patients. We wonder the extent to which some of this will be addressed by patients, who may begin asking doctors more about Byetta, now that there is more direct to consumer marketing (click here for the commercial). We found the call very encouraging from a strategic perspective, especially with respect to LAR and the INTO obesity pipeline and we were mightily impressed with the 92% gross margin. This is very impressive so early in the product's lifecycle – especially for a peptide but even for a small molecule! As noted in our editor's letter this issue, we are worried about the recent FDA decision not to approve Symlin for type 2 use for people on basal insulin. That said, we do not believe this will have an impact on Symlin obesity indications in the pipeline since A1c efficacy is a moot point for the obese. Earlier in the week, the FDA announced it had updated the Byetta label for pancreatitis – this seemed a relative non-event since there was no new news on this front and rates have been declining (30 in over 700,000 on the drug). Management did say that pancreatitis was already a targeted surveillance event and that there were no reports of it in the LAR trial – that was good news and we are sure this will continue to be monitored closely. Other positives in the call – the $1.1 billion cash balance.

- **Abbott – Blood glucose monitoring up 14%:** Abbott reported its 3Q07 results October 17 and showed impressive momentum in terms of blood glucose monitoring results, surpassing expectations for the quarter. Abbott Diabetes Care (ADC) reported worldwide sales at ADC of $322 million, up 14% from a year ago and up just under 5% from last quarter – impressive sequential growth. ADC's US sales of $146 million rose 10% from last year, driven by the successful launch of the FreeStyle Lite meter in June – good growth in this difficult market. International sales of $176 million at ADC rose 17% (10% without positive 7% impact of exchange). On the pipeline front, management said the FreeStyle Freedom Lite would be launched next year in the US. The franchise topped Abbott's Medical products section at $146 million in U.S sales (up 10% from 3Q07 and 3% from last quarter). Global ADC sales were $322 million, up 17% from last year and just under 5% from last quarter.

Management reported double-digit blood glucose monitoring sales in emerging markets, mentioning specifically that the company was considerably outpacing market growth in China. They expect continued double-digit growth as they continue to introduce new products and the look to further strengthen their hold in Russia, southeast Asia, and Latin America. Also on the pipeline front, management said that a fully integrated meter was in development that would combine lancing and testing – this will compete against Roche's Accu-Chek Compact Plus meter, which is the only integrated meter on the market currently. Management said it planned to launch the FreeStyle Freedom Lite in 1Q08 in the US and is already available in Europe. One advantage of the Lite is the no-coding feature – Bayer pioneered this technology and Roche also has a no-coding feature on its Compact.

Abbott's robust lipid management business got a lot of visibility on the call. US sales of TriCor rose 13% from last quarter to $300 million while Niaspan contributed $167 million (no growth listed as Abbott didn't own the product last year). TriCor was presented as the best therapy on the market for lowering triglycerides and our sense is this drug is so well-established that it will continue to do very well in the current environment where safety (real and perceived) is so paramount.. The importance of cardiovascular health is also a growing trend – we're hearing more about "it's not just about glucose" and we suspect cholesterol will grow further in importance. Management also pointed out that the new film-coated Niaspan was enjoying gains in dynamic scripting share. We're clearly focused on this as most people with diabetes have cholesterol issues. Abbott forecasted full year Niaspan sales in excess of $650 million. – this is one of the products that came from the Kos acquisition. Management announced plans to advance plans for a 2009 filing of the regulatory application for a fixed dose combination of ABT-335, and Astra Zeneca's Crestor. With regards to Simcor – combination therapy for LDL and HDL cholesterol - we look forward to hearing the Phase 3 clinical trial data to be presented at the AHA meeting from 2nd- 7th November in Orlando.

- **Roche—Diabetes Care up 3% year to date:** On October 16, Roche reported its 3Q07 results. On the diabetes technology side, blood glucose monitoring appears to had a weaker quarter than its peers, with negative quarterly growth (up 3% year to date) after a 5% increase a year ago. Diabetes Care overall was flat, with insulin pump sales up, bolstered by the addition of pump revenue in the US; recall that Roche returned to the US market in late October of last year. Year to date, pumps rose 15%.

  We continue to wonder the extent to which glycemic dependent drugs Byetta and Januvia are dampening testing frequency in type 2 patients. On one hand, anytime people take new drugs, they test more. On this same hand, we suspect patients on these drugs are coming onto diabetes therapy relatively sooner than they otherwise would. On the other hand, to the extent they are dropping SFUs and going onto Byetta and/or Januvia, they are likely testing less, as SFUs are associated with hypoglycemia whereas Byetta and Januvia are not. What will be interesting to see over the long term is the durability of these new agents – it is early to tell on this front. We also wonder the extent to which some patients might be testing a little more than usual because they are getting positive results. That might just be us! There is no data on this. In terms of the weaker international blood glucose monitoring results, Roche's press release actually mentions poor reimbursement in the UK and Germany – we believe the impact of poorly designed studies like DIGEM is being felt though at least for this quarter, it appears to have been felt most by Roche. Broadly speaking, however, we are concerned these studies are not well designed or understood. The company also mentioned both prices and volume were down in a US market it characterized as weak - the ongoing impact of managed care no doubt, plus strong competition from some peers.

  On the drug side, Roche management said that GLP-1 extended release phase 2 results will come before the end of the year - this has been discussed as once-weekly and once every two weeks and is

currently scheduled for FDA submission in 2010. Interestingly, Roche's presentation slides suggest that weight loss might be associated with its DPP-4 inhibitor, which began phase 2 in Q3 - recall that a year ago, Roche dropped R1438 due to "non-differentiation." We wonder whether true weight loss in the DPP-4 inhibitor class could be seen and question what the mechanism would be. Also on the pharma side, development continues on PPAR aleglitizar, in phase 2 - this is noted as a post-2010 submission, along with the un-named DPP-4 inhibitor and the CETP inhibitor R1658 for dyslipidemia, which seems to be generating more attention as time goes on.

- **J&J—On a roll with best performance for LifeScan in ten quarters**: On October 16, J&J reported its strongest quarter with regards to growth since early 2005. LifeScan sales of $585 million for the quarter rose a standout 16% (13% excluding foreign exchange). Management said the OneTouch Ultra franchise, especially the catchy UltraMini, contributed strongly to revenue growth this quarter, as did robust Animas sales, up 30%. Management said four million people with diabetes are estimated to use OneTouch products; we believe Animas' installed base is at least 30,000[1]. On the consumer front, J&J has done an excellent job in our view appealing to patients, making its products highly attractive, using consumer electronics in very smart ways – e.g., its savvy color pump screens, very small pump, the UltraMini hyper-portable color blood glucose monitor. Anyone who thinks this is not important would seem to be mistaken, given the success J&J has had in this regard - we've heard great things about the impact of such products at camp, for example. In contrast to other large companies looking to enter diabetes, this is one established company that does its patient research. Overall, J&J LifeScan seems very on its game from this marketing perspective. This is critical, since it has become difficult in this mature product category to differentiate on features.

  Elsewhere in new products, we understand LifeScan is aiming a new product, the OneTouch Select, at uninsured and underinsured patients with a new mail-order low-cost meter to be launched shortly. This is a fast-growing segment and given that 70% of patients with diabetes in the world don't currently test blood glucose (at all), we think this introduction could be extremely important entry for J&J. These are among the highest of the high need patients in our view, so we are also so glad to hear this is an area of intense focus.

  Earlier on October 16, J&J announced the creation of the J&J Diabetes Institute, to be led by former Acting Surgeon General (and type 1 diabetic), Dr. Kenneth Moritsugu. This is a very serious step and investment – in establishing this institute, where thousands of healthcare professionals will be trained, J&J is taking strides to improve training for the those who care for patients with diabetes. To start, four institutes will be built in the US, China, France, and Japan. A significant part of the teaching will focus on standards of care in diabetes, reimbursement, pattern recognition, patient communication while the balance will focus on products; currently the pumps are really the only products that require extensive teaching. In our view, the J&J Diabetes Institute represents a prime example of smart leadership putting J&J's breadth and depth to effective use - with this move, J&J effectively puts the rest of industry on notice to step further up as well. We imagine the investment for this project must be upwards of $30-50 million with sizable annual costs – but what payback for patients, HCPs, payors, and families.

  On the call, Nick Valeriani, who leads the medical devices and diagnostics division for J&J, gave a very inspiring and inspired talk about J&J's vision for presence in metabolic disease and diabetes. In short, we found it very forward-looking, even profound, addressing head-on the challenges of diabetes

[1] It is an interesting time in the pump market – we think Medtronic, Insulet, and Animas are all expanding the market with current and new products. We believe broader CGM reimbursement will be an important driver for the market - we estimate this should happen c. 2010.

care. Overall, we see J&J stepping up and raising the bar for itself and industry in expressing commitment to patients and healthcare providers.

On the pipeline front, Valeriani noted that LifeScan's integrated pump/meter, in the works, was on track for 2008 regulatory submissions in the US and Western Europe. He forecasted a market opportunity of $9.7 billion by 2011 for the SMBG market – we admit our recently revised model only goes to 2010, where we forecast $8.9 billion. Valeriani said there were two continuous programs, one of which had seen some early testing. He expressed concern over accuracy in continuous, especially at low levels. On continuous, we hope J&J does go into continuous in some bigger way in the future - we have come to think these products can make a big difference - and what a place for continuous to be taught, the J&J Diabetes Institute! From a product perspective with continuous, we hope to see continued simplification but more settings that can be set by users. He also positively characterized disposable pumping, terming it important and mentioned this may be an area pursued in gestational. Too, there is a new meter that has been submitted in Japan – traditionally this has been a very tough market to crack for western manufacturers.

On the conference call, the commitment to diabetes and obesity didn't end with discussions of LifeScan and Animas. With the approval of gastric band Realize in the US at the end of September, J&J is now also officially in the metabolic disease/obesity business at Ethicon-Endo Surgery. Management was quick to cite recent NEJM data on bariatric surgery – very smart to focus on evidence (see DCU from last month for our literature review on this NEJM issue). Realize will be marketed by Ethicon Endo's Bariatric Edge and should be available in early 2008. J&J has been looking for this approval since it purchased Obtech in 2002 for $110 million - it was a long term investment given that a rigorous three year trial was required by the FDA. This device is said to be doing well in Europe (over 100,000 have used it) and we agree with smart investors in this field who think J&J might be able to give Allergan a run for its money given J&J's very strong relationships with surgeons here in the US. Key will be making sure there are enough surgeons trained and we assume a big investment will be made here; the company says at least 200-300 surgeons will be trained by the first quarter of 2008. We expect that well over 200,000 bariatric surgeries (all together) will have taken place this year – that's up from about 70,000 in 2002, the year J&J purchased what is now Bariatric Edge. The purchase price looks cheap at this point even given the longish wait and certainly the market has been booming - it is especially attractive for those with diabetes given almost immediate resolution of diabetes seen by so many patients. Pricing hasn't yet been disclosed; in general, the cost of banding is $16,000 - $25,000 all in - the hospital purchases the device.

Last, we are always surprised to see nothing diabetes related in the pharma pipeline (at least the phase 3 pipeline discussed) – this is a major gap but one that we're sure has been/is being addressed in the earlier-stage pipeline. On a related note, biomarkers were discussed, which could be exciting on the pre-diabetes and metabolic disease front.

- **Orexigen—Seeking obesity indication for approved drugs:** On October 10 at a BioInvestor Forum, management explained that they are using an unconventional business model of testing previously approved drugs for new indications (specifically obesity). The company hopes to benefit from the safety data of previously approved drugs, thus expediting speed-to-market and reducing development costs. Orexigen has two late-stage products with favorable phase 2 results. Contrave is a combination of bupropion SR and naltrexone SR, and is in phase 3. Empatic is a combination of bupropion SR and zonisamide SR and is in phase 2b. Both had good data shown at NAASO – we'll discuss that next issue. The company stated that it is planning to advance additional compounds through regulatory trials. Bupropion, an antidepressant in its original incarnation, leads to elevated dopamine, which depresses appetite and increases energy expenditure. But this also leads to release of endorphins which increase the craving for food. This is why Contrave has the combination of

bupropion and naltrexone, which inhibits endorphin release. Similarly, Empatic has bupropion and zonisamide, which depresses mechanisms that increase appetite.

Management speaks of 2010 (NDA filing second half 2009) as the launch date for Contrave. It will focus on females with mild-to-moderate obesity, with an emphasis of the behavioral aspects leading to obesity. The Empatic trial initially suffered from a high dropout rate of 37% (this is of course not that high compared to many obesity trials), but discontinuation rates decreased significantly in a followup Phase 2b dose optimization trial. In this trial, Emaptic showed weight loss benefits similar to those shown by Contrave. Empatic will follow in the footsteps of Contrave in terms of clinical trials, and will be about 12-18 months behind. One more phase 2 study is currently needed to demonstrate superiority of the combination over monotherapy. Phase 3 trials for Empatic are expected 1H2009. Empatic will focus on the moderate-severe obesity market, including patients with comorbidities, such as diabetes. The overarching rationale behind Orexigen's pursuits is that obesity is an addictive disorder. This view has been validated somewhat recently, and was one of the main takeaways of Dr. David Kessler's lecture at the Cleveland Obesity Summit. The success of Contrave and Orexigen is in the remaining steps of development, of course, but it's good to see some optimism about drug development in this area.

- **DiaKine—NIH to sponsor preclinical testing of type 1 diabetes drug DT 22669:** On October 9, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the NIH, said that it would sponsor preclinical testing of DiaKine's oral diabetes drug DT 22669 in a rodent model of type 1 diabetes. Preliminary studies of DT 22669 in animal models suggest that the drug may halt, or perhaps even reverse, the progression of type 1 diabetes if treatment is initiated promptly after diagnosis. The drug could potentially also be used to protect islet transplant cells in type 1 diabetes patients. DT 22669 functions by modulating inflammatory cytokines, a part of the body's immune response implicated in the auto-immune destruction of beta-cells. The fact that NIDDK is sponsoring this preclinical trial suggests that the institute may be optimistic about the potential of this oral agent; it is, of course, very early in the development of this drug. Its side effect profile and efficacy are largely unknown, and it will be a long period of time before the compound is administered to a person even if all preclinical trials are successful.

- **Insulet–Bulking up agreement with Flextronics:** Insulet Corporation is taking action to address the excess demand for its popular disposable insulin infusion device, the OmniPod. On October 4, the company announced an agreement to outsource production of the pump to a Flextronics International subsidiary. Flextronics and Insulet originally had an agreement where the contract engineering company assembled some components of the pump, but Insulet had been missing out on business as it struggled to meet demand for the pump. With the new manufacturing agreement, Insulet expects to have enough supply to turn a profit in 2009. Medtronic of course has the Paradigm pump with integrated CGM, a great selling point – but Insulet has what we consider equally real innovation, a tubeless (and thus more discreet) pump. All this means the pie should be getting bigger – and if recent impressive sales from both companies are any indication, the market is certainly expanding. Animas is also adding to the market expansion – although it doesn't have a CGM hook or a disposable pump, it does have a cool new screen (we don't underestimate the power of sexy ((it's all relative)) consumer electronics) – see J&J update above. Our recent market analysis suggests that if industry pump revenue continues to grow at a pace of ~15% per year, this would result in close to 37-40% penetration of the type 1 market by 2012. We believe physiologic therapy is better for all type 1s and could be appropriate for many type 2s though the latter group still has some reimbursement challenges. Can the current industry work on those? – absolutely. We are especially hoping that type 2s can benefit from simpler insulin delivery moving forward.

- **Novo Nordisk—Contemplating sale of engineering and IT divisions:** On October 4, Jesper Brandgaard, the chief financial officer of Novo Nordisk, said that the company was not the right owner for its engineering and information technology (IT) divisions. Sales of units are not expected in the very near term however, as Novo Nordisk would like the engineering division to reach an operating profit margin of 5%, and the IT division to derive at least half of its revenue from outside the company; this could take over 18 months and three years, respectively. Novo Nordisk appears to also be contemplating the sale of its hormone replacement division, although such a sale is unlikely to occur in the near future because of ongoing lawsuits about the safety of hormone replacement. Selling these units would allow the company to invest further into the ever-growing diabetes care market. Novo Nordisk has already begun concentrating further on the diabetes market, as indicated by the sale of its large stake in Dako Denmark A/S, a cancer diagnostics company, in February 2007. Currently, over 70% of Novo Nordisk's sales pertain to diabetes.

- **Garvan Institute of Medical Research—Enzyme PKCepsilon a novel target for treating type 2 diabetes:** Medical researchers Trevor Biden and Carsten Schmitz-Peiffer at the Garvan Institute of Medical Research in Sydney, Australia, have identified an enzyme called PKCepsilon that is potentially involved in blocking the production of insulin in type 2 diabetes. The researchers engineered a line of mice lacking the PKCepsilon enzyme (PKCepsilon knock-out mice), and found that the mice did not develop type 2 diabetes even when fed a high-fat diet leading to insulin resistance. A patent is pending, and the researchers are now approaching pharmaceutical companies about developing a drug to target PKCepsilon. While the discovery of the PKCepsilon is extremely exciting, it is of cousre too early to determine whether the discovery will result in successful therapies targeting the enzyme, and even if all goes well for PKCepsilon-targeting therapies, it would likely be close to a decade before a PKCepsilon-targeting drug is on the market. Still! Look how far diabetes research has come since 1997!

- **Living Cell Technologies—$2.4 million capital injection for DiabeCell:** On October 4, Living Cell Technologies (LCT) signed a non-binding letter of intent to sell approximately 22.4 million ordinary shares, worth $2.4 million, to U.S.-based investment group NaviGroup Management. The agreement comes at a good time for LCT, whose 12-month clinical trials for DiabeCell in Russia and New Zealand are to begin late this year—the company plans to use the funds as working capital for the clinical trials, and to grow its source of islet transplant cells—its pig herd—to meet clinical requirements.

- **Home Diagnostics—HealthVault test:** HDI announced on October 4 that its TRUEtrack and TRUEread blood glucose meters will operate on Microsoft's free HealthVault system, which allows users to store and manage their records and share them with their physician or healthcare team. We are very eager to see where this technology goes – we have a lot to learn in this area of technology. As usual, simplicity will be key – that's always required in getting patients to add more steps. Although some have pointed out it isn't clear who will pay for the additional time a physician would take to analyze the data, we point out that data that can be analyzed more easily by patients would certainly be a win.

- **Nastech—Second try at phase 2 for PYY nasal spray:** On October 1, Nastech announced that it is starting another six-month phase 2 clinical trial of Peptide tyrosine (also called peptide YY or simply PYY) nasal spray in obese patients. This trial will enroll 510 patients for six months. Patients will be randomized to nasal PYY (three times daily), the active comparator sibutramine (Meridia, Abbott), or placebo. As a reminder, PYY is a hormone that plays an important role in satiety. When activated, PYY3-36 binds to the Y2 receptor in the hypothalamus, which in turn inhibits NPY, an appetite signal. Therefore, PYY indirectly acts to reduce appetite. Obese people have a deficiency in PYY, much in the way obesity is associated with a deficiency in GLP-1. Nastech's new phase 2 trial

follows disappointing results from a previous phase 2 trial of nasal PYY conducted in partnership with Merck. In this first trial of 133 obese patients, nasal PYY taken 20 minutes prior to a meal produced 8.1 lbs of weight loss over twelve weeks, compared to 6.1 lbs for placebo (a difference of 2 lbs). Merck subsequently discontinued its collaboration with Nastech to develop PYY, and Nastech now plans to bring the drug through phase 2 before looking for another partner. The current trial has several differences from the first phase 2 trial: it is longer, will have an active comparator group, and will include an early dose optimization period in which patients may either escalate or decrease doses; this should reduce the high attrition rate seen in the previous study. We would be surprised to see nasal PYY produce more than modest weight loss in monotherapy, but the peptide may be promising in combination with other hormones involved in regulating energy balance such as GLP-1, cholecystokinin (CCK), leptin, ghrelin, and adiponectin. Amylin is currently working on developing a triple combo therapy for obesity with pramlintide, leptin, and PYY. There is considerable interest in combination hormone therapy, because many hormone therapies are thought to be synergistic.

Nastech has other nasal technologies in the pipeline as well that we will be watching. On September 26, Nastech announced the initiation of a phase 2 clinical trial for its rapid-acting insulin nasal spray. The randomized, crossover design study will enroll 20 people with type 2 diabetes and is expected to begin in October. It will compare postprandial control with Insulin Nasal Spray vs. insulin aspart (NovoLog, Novo Nordisk). In phase 1 studies, the spray had a more rapid peak effect than either NovoLog or inhaled insulin (Exubera, Pfizer), was well tolerated, and did not cause significant hypoglycemia – we are still skeptical about this approach, however, about absorption, and about use in the "real world". Nastech is emphasizing the product's rapid onset of action, ease of use, and non-invasive approach (nasal insulin does not get absorbed in the lungs, thereby avoiding concerns about pulmonary delivery – although Pfizer had successfully documented some long-term safety of pulmonary insulin delivery before it pulled Exubera). This is one of the a few products that may lead to more patient-friendly and rapid acting insulins, though we note that form factor and ease of dosing/use are extremely big challenges, as Exubera's sub par performance demonstrated.

- **Medco—New plans for seniors in 2008, including diabetes pharmacists:** Medco, a pharmacy benefit manager (PBM) company that currently operates the nation's largest mail-order pharmacy operation, introduced three new Medicare prescription drug plans aimed at seniors for 2008 on October 1. Enrollment begins on November 15 and details of the plans can be found on Medco's website. What was very interesting to us here was Medco's decision to offer its Medicare PDP plan members access to licensed Medco pharmacists who are specially trained in specific chronic conditions like diabetes, cardiovascular disease, cancer and pulmonary conditions, as well as 24/7 Medicare Advisors who can help members identify and analyze lower-cost medication options.

- **Amylin—FDA approves Symlin pen and delivers low blow to Symlin**: The Symlin pen was approved in early October – this is excellent news for patients who dislike using vial and syringe for Symlin and we expect it will generate at least a small bolus of new users who did not want to try to the drug until the pen was approved. As discussed above, the FDA declined to approve the indication for Symlin use with basal insulin for type 2 patients – this was unfortunate and even more unfortunate that patients do not even know – there was not an FDA press release on this decision, needless to say. Granted, Symlin is a complicated drug in that the titration can be complicated. But it can do a lot for patients in evening out their blood glucose variations. So rather than having a lot of hyperglycemia then prompting a lot of hypoglycemia, for some patients, Symlin evens out the path. It is known to work specifically against post-prandial hyperglycemia - recall that the International Diabetes Federation just put out new stricter guidelines on post-prandial blood glucose. This prompted a slew of stinging patient blogs wondering how in the heck patients were supposed to get their post-meal

scores lower. (We loved Amy Tenderich's of DiabetesMine's "Institutionalizing Frustration" take on this).

- **DexCom—Making a case for CGM and talking up third-generation sensor:** On September 27 at the UBS 2007 Global Life Sciences Conference, President and CEO of DexCom Terrence Gregg gave an overview of the mechanism and utility of continuous glucose monitoring. He explained that CGM fills in the gaps for the time between finger-sticks and gives critical trend information crucial to safe and effective glucose control. Gregg also described four studies that showed that CGM enables patients to reduce A1c without increasing fear of hypoglycemic events. He added that DexCom has refocused its sales force to reach out to healthcare providers with the message of changing the paradigm of fingersticks, which he likened to insulin because while it is extremely important, is still just a tool – not a solution. He cited progress toward obtaining reimbursement, such as the large one-year JDRF sponsored clinical trial aimed at proving the sustainability and efficacy of CGM. In addition, HCPCS codes for CGM will be implemented in January. While they do not guarantee coverage, of course, it's a good step in that they give payors/healthcare providers a framework in which to bill for the technology. Gregg stated that the inconsistency of reimbursement between patients remains another challenge.

  Gregg said that DexCom's third generation product is in the works and could boast a sensor that is 75% smaller than its predecessor with a smaller, thinner gauge needle. This should reduce any remaining insertion trauma (the second gen had big improvement over the first gen) and allow for cleaner readings of interstitial fluid glucose levels. DexCom also promises significant overall improvement to the software and receiver. We were very impressed to hear that that pivotal trials of this device would be completed in 4Q07 with commercialization expected mid-2008.

  DexCom will be applying for a CE mark to allow for expansion into the EU markets next year, particularly in countries with decent reimbursement. DexCom is also developing a sensor specifically for the intensive care unit (ICU) market. Tight glycemic control in ICUs is important in decreasing mortality and morbidity, but this means nurses are administering 12-48 finger-sticks every 24 hours in an effort to maintain control. We think although many hospitals say they are practicing tight glycemic control, few are probably doing the real thing – it's too labor intensive currently. Gregg pointed out that CGM technology in the ICU could lead to faster discharge rates since hyperglycemia slows wound healing and CGM decreases the amount of time patients spend in the hyperglycemic range. He added that DexCom was looking to partner with a company that has assets in the ICU already; their goal is to first develop a standalone product, get this approved,and then partner through a distribution agreement with a company that already sells products into the ICU. In his view, the ultimate product is one that is integrated into the ICU system.

- **Medtronic—STAR 3 trial to escalate adoption of CGM:** At the UBS Global Life Sciences Conference on September 26, Medtronic CFO Gary Ellis spoke broadly about Medtronic's businesses with a brief mention of the diabetes franchise – 23% growth this quarter - towards the end of his presentation. He pointed out that Medtronic is in a unique position to take advantage of international markets; Medtronic's OUS revenue currently accounts for 1/3 of its total revenue package, but Ellis said this figure was on the rise and predicted that it would surpass US revenue in five years despite the fact that technology tends to be adopted faster in the U.S. Ellis also asserted that the STAR 3 trials should help escalate adoption of CGM therapy. As a reminder, STAR 3 is a randomized study comparing the efficacy of the MiniMed Paradigm REAL-Time System versus multiple daily injections (MDI) in type 1 patients naive to pump therapy. The primary outcome is change in A1c from baseline to 52 weeks. The trial aims to improve upon STAR1, which had mixed results and was negatively impacted by patient compliance as well as some meter issues. With regards to partnerships, Ellis highlighted what we viewed as standout deals with J&J and Bayer, which will give these two

companies exclusive rights to supply blood glucose meters to Medtronic patients inside and outside the US, respectively. The deals were worth hundreds of millions in blood glucose monitoring revenue – pump patients are among the most frequent testers around and thus among the most profitable patients. We would see over time however that as these patients shift to continuous, they may be less valuable.

- **GlucoLight–Awarded patent for non-invasive blood glucose monitoring technology:** On September 26, GlucoLight was awarded a U.S. patent for a blood glucose monitoring technology used in the company's Sentris-100 glucose monitor (not yet commercially available). The technology uses optical coherence tomography to non-invasively monitor blood glucose concentrations. In other words, as we understand it, the monitor shines a light on a person's skin and then collects the light that is reflected back. By monitoring the spectrum of light that is sensitive to glucose concentration, the technology can monitor glucose concentration in the blood without the need to break skin. The Sentris-100, as a reminder, is a non-invasive blood glucose monitor for the acute care environment that is currently in clinical trials. GlucoLight completed its first "clamping study" and ICU clinical study of Sentris-100 earlier this year and is making design and technological adjustments to the product. We laud work on this front although we note that non-invasive monitoring has been a historically disappointing area of development, as it has been difficult for companies to develop a device that is accurate, easy to use, and portable.

- **Transition Therapeutics—Exciting pipeline and bold ambitions:** At the UBS Global Life Sciences Conference on September 26, Tony Cruz, chairman and CEO of Transition Therapeutics, delivered an upbeat and excited review of the company's diabetes drug pipeline. Transition's approach to diabetes treatment, its Islet Neogenesis Therapy (I.N.T.) program, focuses on using gastrin to increase beta cell function, stimulate islet cells to produce insulin, and create new islet cells. E1-I.N.T, the program's lead compound, is a GLP-1 that is being developed in partnership with Novo Nordisk. Data from the early phase 2 clinical trials looks promising - patients with type 1 and type 2 diabetes were put on E1-I.N.T for four weeks, then followed for 24 weeks. In the one to six months post treatment—when patients were not undergoing any diabetes treatment at all — A1c levels dropped 0.94% to 1.21% and more than 50% of the subjects had a greater than 1% drop. This is quite good. More strikingly, for the subjects whose A1c levels declined more than 1%, insulin production increased by 60-100% in the one to two months following treatment and was sustained for six months, which suggests that gastrin may improve beta cell function. The six-month improvement at the price of a one-month treatment appears promising. Transition also has two other products in the pipeline: gastrin alone and gastrin + GLP-1 analogs. Transition is adopting a wait-and-see approach on E1-I.N.T. until these two therapies finish phase 2 testing. The company is expecting to complete two phase 1 studies in the remainder of 2007 to increase its flexibility with gastrin. It also plans to initiate a phase 2 study on gastrin + Metformin and GLP-I.N.T. in the beginning of 2008. A study on the efficacy of gastrin + Byetta is also in the works. Cruz also discussed Transition's corporate strategy of taking products from early stage discovery to phase 2, and then finding a partner to help take the product to market. He hinted that Transition now has four or five targets in progress, with at least two lead molecules that could enter preclinical development by the end of the year. This is one to watch.

- **Eli Lilly—Enthusiastic about AIR insulin:** On September 25 at the UBS 2007 Global Life Sciences Conference, Bryce Carmine, President of Global Brand Development at Eli Lilly, spoke enthusiastically about AIR Insulin, Eli Lilly's inhaled insulin product. Carmine stated that Eli Lilly and AIR insulin partner Alkermes are "increasingly confident in the safety" of AIR Inhaled Insulin and are planning EU and US submissions in 2009. Among its advantages that we believe would be very important in the wake of the Pfizer exit from this market are small size and simplicity. The partners presumably hope and expect that these advantages will distinguish AIR from Pfizer's

Exubera. As expected, the company will press on with phase 3 trials. Carmine also reiterated that exenatide LAR results are expected this quarter . Past study data show dose-dependent reductions in A1c and body weight, and Carmine again emphasized enthusiasm for the product: "*Byetta may well have ushered in a new era"* in controlling both glucose and body weight in diabetes patients, he said. The company continues to express enthusiasm on Byetta classic - US monotherapy submission is expected in the first half of 2008 and we believe this would be a very important indication to be added. Carmine did not comment on the company's GLP-1 analog, currently in phase 1, though he did say that he was "pleased with qualities of the compounds" in the company's R&D lab. We imagine more GLP-1 experience is a positive for Lilly just so they can better understand this important hormone. A detailed update on the pipeline is expected in December when Eli Lilly holds its annual R&D meeting in New York.

In other news, on October 8, Eli Lilly updated the labels for Zyprexa and Symbyax, both psychiatric drugs, to include new warnings for weight gain, hyperglycemia, and dyslipidemia. Both drugs already had some label information about these risks, and in 2003, the labels of both medications were updated to include an FDA-mandated antipsychotic class warning about monitoring for diabetes. However, the company has been accused of playing down the health risks of Zyprexa. Over the past two years, the *New York Times* has published an impressive series of articles by key reporter Alex Berenson on this topic – best place to see the background on this is www.nytimes.com. Eli Lilly has spent more than $1 billion settling lawsuits regarding safety concerns about Zyprexa.

- **Digital Healthcare—FDA approves Retasure retinal risk assessment system:** On September 19, Digital Healthcare gained FDA approval to pre-market Retasure, a non-invasive retinal digital imaging tool to help health care professionals assess diabetes retinal risk. Images from Retasure can be transmitted from the clinic to an off-site ophthalmologist via Digital Healthcare's iP technology platform. The Retasure system requires no pupil dilation, and it may be operated by non-clinicians. Advancements in retinal screening with regards to convenience for patients are important because they encourage increased patient compliance for regular retinal assessments. Currently, only about half of all people with diagnosed diabetes in the United States receive regular retinal risk assessments.

- **Biodel—VIAject pharmacokinetic data presented at EASD:** At EASD on September 18, Dr. Solomon S. Steiner presented data about the pharmacokinetics and pharmacodynamics of Biodel's insulin VIAject, as compared to insulin lispro (Humalog, Lilly) and regular human insulin when injected subcutaneously immediately before a meal in patients with type 1 diabetes. VIAject became effective after 13 minutes, compared to 29 minutes for lispro and 33 minutes for human insulin – a statistically significant difference. Maximum effect was after 34 minutes for VIAject, compared with 63 minutes for lispro and 139 minutes for regular human insulin. VIAject also cleared out faster than either lispro or human insulin, reducing the risk of 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. A number of members of the audience objected to the study, pointing out that study design advantaged VIAject with respect to carbohydrate dose (120 g) and timing of insulin administration. In rebuttal, the speaker explained that most patients do 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. Even if the trial was designed to favor VIAject, the pharmacodynamic and pharmacokinetic data are impressive and suggest that we are entering into an era of even more rapid bolus insulins.

- **Diamyd Medical—Encouraging immunological results for diabetes vaccine:** Diamyd Medical is attempting to develop a diabetes drug that may reduce autoimmune destruction of beta cells by inducing immune tolerance through administration of the beta cell autoantigen GAD65A.

Evidence demonstrating a lasting effect of the drug was presented at EASD on September 18. In a placebo-controlled trial, subjects who received the Diamyd drug had an immune response specific to GAD65 that persisted until 15 months after administration. The effect was not observed in subjects who received placebo. This study provides an immunological analysis of a previous phase 2b clinical study that found beta cell protection in children with type 1 diabetes after administration of the Diamyd drug. Notably, the present study found evidence of a biomarker that correlates with these improved patient outcomes. The protective effect appears to be mediated by T-cells induced by the vaccine that rebalance the immune system. Phase 3 trials for Diamyd are planned for this coming year. We need to study this further before understanding the promise for the area and for beta cell transplants more broadly.

- **Isis—Collaboration with Ortho-McNeil (J&J): On** September 13, Isis Pharmaceuticals announced that it will collaborate with Ortho-McNeil, Inc., a Johnson & Johnson company, to develop its two lead diabetes drug candidates, ISIS 325568 and ISIS 377131. Both ISIS 325568 and ISIS 377131 target liver production of glucose, thereby reducing blood glucose, although their mechanisms of action differ. ISIS 325568 selectively inhibits the production of glucagon receptor (GCGR). Glucagon is a hormone that stimulates the production of glucose in the liver, and therefore inhibiting GCGR should reduce excessive liver glucose production and lower blood glucose. ISIS 377131 instead targets the glucocorticoid receptor (GCCR). Glucocorticoids promote breakdown of protein and lipids from storage, resulting in increased liver glucose production. As part of the agreement between Isis and Ortho-McNeil, Isis will receive an upfront licensing fee of $45 million, and up to $230 million in payments along with royalties on sales pending successful development and approval of ISIS 325568 and ISIS 377131. Isis received clearance under the Hart-Scott-Rodino Antitrust Improvements Act for its collaboration with Ortho-McNeil, Inc. on October 2. The same day, Isis announced that it had received $5 million from Ortho-McNeil for initiation of a phase 1 study of ISIS 325568.

- **Xoma—Another phase 1 trial for compound Xoma 052**: On September 12, Xoma, Inc. announced that its monoclonal antibody targeting Interleukin-1 beta (IL-1 beta), Xoma 052, was entering a second phase 1 trial in patients with type 2 diabetes. The trial will enroll up to 36 subjects in Europe; another phase 1 trial of Xoma 052 is ongoing in the US. As with other phase 1 trials, the primary purpose of the trial is to assess safety and pharmacokinetics. The drug is designed to treat type 2 diabetes, rheumatoid arthritis and other diseases of inflammation.

  Like many companies, Xoma is betting based on an increasing body of evidence that inflammation plays as important a role in diabetes as it does in cardiovascular disease. IL-1 mediates inflammation, and therefore blocking IL-1 can reduce inflammation. Much of the excitement about IL-1 as a treatment target for type 2 diabetes began after an April 12 article in the *New England Journal of Medicine* demonstrated that inhibiting IL-1 leads to improved beta cell function and glycemic control in people with type 2 diabetes. Xoma hopes that the safety profile will be similar to the approved IL-1 blocker kineret anakinra (Kineret, Amgen), but will have the advantage of a longer half-life and greater bioavailability (thereby requiring a lower dose for equal potency). IL-1 blockade is relatively safe, as other IL-1 blockers are already on the market (though they have side effects including but not limited to increased infections, gastrointestinal disturbances, and potentially an increased rate of lymphomas). At the same time, Xoma 052 is a unique chemical entity and may have unexpected interactions, or it may prove not to be as effective as other IL-1 blockers. We emphasize that more research is needed to determine whether inflammation truly does play as important a part in diabetes as the preliminary evidence suggests that it does.

- **Sirtris—SRT-501 (resveratrol) may improve blood pressure**: Sirtris is a company we continue to watch – it was founded in 2004 and as the name of the company suggests, is exclusively

involved in developing therapeutics that target sirtuins, a class of enzymes that play a role in aging. Sirtuin activation has been shown to mimic the benefits of calorie restriction by increasing lifespan and lowering the incidence of many diseases related to aging, including diabetes. One molecule that has been shown to activate SIRT1 is resveratrol, a natural product that is present in red wine, though only in sub-therapeutic amounts. Sirtris has developed a proprietary formulation of resveratrol called SRT501 that achieves therapeutic levels in the blood in animal models. SRT501 is currently in phase 2 testing for the treatment of type 2 diabetes.

Findings published in the September 12 issue of the *Proceedings of the National Academy of Sciences (PNAS)* by Mattagajasingh et al, indicate that activation of SIRT1 increases the release of nitric oxide (NO) by vascular smooth muscle. Blood vessels use NO to increase blood flow, and a diminished supply of NO is implicated in vascular diseases such as hypertension, as well as vascular inflammation and endothelial dysfunction. Given that many type 2 diabetes patients also have lower levels of NO and, consequently, have hypertension, SRT501 could potentially be used to treat not only type 2 diabetes, but also the highly associated condition of hypertension. As combination therapy and the idea of treating multiple risk factors are coming into view, a single drug to treat multiple risk factors is exciting. At the same time, we underscore that SRT501 and other activators of SIRT1 are in the very early stages of clinical testing, and there is by no means a guarantee that they will survive through phase 2 and 3.

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

4. Interview with Dr. Steven Nissen: Thoughts from an industry watchdog

Dr. Steven Nissen, chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, caused a firestorm this year when the New England Journal of Medicine published his meta-analysis of Avandia, which showed that patients taking the drug had a 43 percent increased risk having a heart attack. The FDA issued a black box warning for the drug, which last year generated more than $2 billion in sales for GlaxoSmithKline but is now attracting few customers. Dr. Nissen is no stranger to controversy: his expressed concerns that Vioxx might cause blood clots contributed to Merck's decision to withdraw the drug in 2004. In November of 2005, he and two colleagues published a paper in JAMA indicating that the PPAR modulator muraglitazar (Pargluva, Merck and Bristol-Myers Squibb) increased death and major adverse cardiovascular events in patients with type 2 diabetes. The drug had been reviewed positively by an FDA endocrinologic and metabolic drugs advisory committee (8 to 1 vote in favor of approval), but its development was halted largely in response to Dr. Nissen's analysis.

In speaking with Kelly Close, he described how he discovered Avandia's problems, how endocrinologists need to rethink their glucose-centric" approach to diabetic care, and how the FDA advisory panel meetings often fall short. "Courage," he said, "is very rare." An excerpt of our discussion is below; the entire conversation is available in the lower left hand corner of the Diabetes Close Up website at www.closeconcerns.com.

Kelly Close: Thank you so much for taking the time to speak with us. To start with, we're curious about how, as a cardiologist, you first became interested in studying PPARS.

Dr. Steven Nissen: Well, it actually goes back quite a long ways. I was aware from the very beginning that there were a lot of issues with PPAR drugs, which affect a very large number of genes. We don't know what most of those genes do. Whenever you see a drug like that, you always worry about off-target effects that the drug was not designed to produce. My concerns accelerated in September of 2005 when muraglitazar came before the FDA for approval.

Kelly: Yes, we were actually at that hearing. It was actually a very tepid sort of advisory panel session, which is quite ironic in hindsight.

Dr. Nissen: I did not attend the hearing, but I did have an interest in the class of drug. The night before the hearing, I looked at the FDA's briefing documents and immediately saw that there was a rather large excess of adverse cardiovascular events in the patients who received muraglitazar. And they were serious events: death, stroke, heart attack, that sort of event. So I assumed that the FDA advisory panel would recommend unanimously that muraglitazar not be approved.

As you may recall, they actually voted 8 to 1 to approve the drug. I was just shocked. I immediately went into action and took the data from that FDA advisory panel, analyzed it independently with my statistician, and published in JAMA a few weeks later that the drug was doubling the risk of the really serious cardiovascular consequences of diabetes.

It is important to realize that there's something you don't know and that no one outside of a relatively limited circle knows. But there have been at least 50 of these drugs for which investigational new drug applications, or INDs, have been submitted to the FDA over the last seven or eight years, and virtually every drug has had its development program terminated for toxicity.

Kelly: Is that because all of them had to go back and do two-year toxicity programs?

Dr. Nissen: Well, that was certainly one of the things that happened, but the other thing was that many of them were just killed by their manufacturers when safety issues arose. And the safety issues were cardiovascular for many of these drugs. In fact, some of them actually produced direct myocardial necrosis. But none of those results were ever published. The problem, of course, is negative publication bias. When drugs fail, companies routinely simply bury the data, and we never see it in the scientific community. I was well aware of this.

Then in September of last year, the DREAM trial was published, and if you will excuse the pun, the DREAM trial was a nightmare. There was a drug, rosiglitazone, which reduced the incidence of new-onset diabetes by 60 or 70%. But all of the cardiovascular events were going in the wrong direction. If you go to that publication in Lancet and look at table two, you'll see that death, heart attack, stroke, liver failure – I mean, everything – is going in the wrong direction. There's a P-value of 0.08 for cardiovascular harm.

You want to prevent diabetes to avoid the complications of diabetes, the most important of which is heart disease. Eighty percent of all diabetics will die of cardiovascular disease, so this was very troubling. I actually wrote a letter to the editor – to the Lancet – that appeared in December of 2006 in which I pointed out this rather extraordinary paradox: that the drug was preventing diabetes, but it seemed to be causing cardiovascular harm.

Then the ADOPT trial was published, and the same thing happened. It showed a 33% excess of major adverse cardiovascular events. Clearly, myocardial infraction was going in the wrong direction with rosiglitazone. This got my attention because the only two large long-term trials were going in the wrong direction. So I finally went back to the FDA Web site and extracted the original approval data for rosiglitazone.

What I saw there was that at the time of approval in May of 1999, in studies including about 2,500 patients, the hazard rate, or the relative risk of myocardial infraction, was 1.8 compared to comparators. So I now had three pieces of data: the original approval package, which showed a rather striking excess of cardiovascular events; DREAM; and ADOPT. That's why we went on and did the meta-analysis, which was only possible because of the Spitzer lawsuit.

Now the really big shocker was that just as I was getting ready to publish the manuscript, I learned that GlaxoSmithKline, the maker of the drug, had actually done its own analyses beginning in September of 2005. They actually submitted to the FDA about the time the muraglitazar panel occurred that their own analysis showed a statistically significant 31% increase in myocardial ischemic events.

Kelly: That was the one you found on Google a little randomly, as we understand it?

Dr. Nissen: Well, we found a clinical trials registry. But the bottom line was we then knew that the company, in analyzing all of its own internal data, had found the risk. They'd informed the FDA of this risk. But neither the FDA nor the company informed any of the rest of us. This to me was simply shocking. I personally believe in the right of patients and providers to know the totality of information on the benefits and risks of drugs.

Kelly: What do you think that says about the FDA panel process? I know that the FDA is very concerned about bias and so very often, the people who have done all of the work and all of the investigations and so forth are not necessarily the ones that are on the panel.

Dr. Nissen: Actually, the problem is that the FDA is not concerned about bias and they end up putting together relatively poor panels. That's why in the recently passed House Resolution 3580, there are new restrictions on who can serve on FDA panels.

Kelly: What do you think it says about endocrinology that it took a very noted cardiologist to intervene in this matter?

Dr. Nissen: Endocrinologists have a serious difficulty. They've spent their entire lives believing that the most important thing about treating diabetes is to reduce hemoglobin A1c, so they've had a very glucose-centric view, and I simply don't agree. I believe that the reason you want to lower HbA1c is to reduce the complications of diabetes. This singular focus on blood sugar – because that's what they could measure every day with finger sticks and all of that – has led to a misunderstanding of what it is that we're trying to accomplish when we give these drugs. With a PPAR like rosiglitazone that causes myocardial infarctions, fractures, macular edema, and heart failure – I don't really care if it lowers blood sugar. It's not of benefit to patients.

Kelly: When you testified before Congress, you were criticized by some of the Republicans for taking your concerns to the House Democrats instead of the FDA.

Dr. Nissen: Actually, what's interesting is that I wasn't able to deal with them very effectively. It was actually a bi-partisan group in Congress that I met with.

Kelly: Right. I suppose the broader question from a patient perspective is that, when your meta-analysis came out from the New York Times, which got it from the Web site of the New England Journal of Medicine, it just kind of blindsided everyone. It caused a lot of anxiety. In retrospect, was there a better way to disseminate the information so that so many people were not left so concerned?

Dr. Nissen: Actually, I think we did exactly the right thing. And let me make a couple of comments about this. First of all: the idea that I should have told the FDA first. The FDA already knew! The company had told them two years earlier that the drug was causing this effect. I knew that. So why would I tell the FDA something that they already knew? I went to the Congress because the FDA had chosen not to act.

Second point: it is very important to understand that when these things are handled in a quiet fashion, you don't get change. Do you know that when you put a black box warning on a drug that its sales are rarely affected at all? If the FDA had quietly relabeled rosiglitazone, people

would have continued to be exposed to the drug. The reason that it's a good thing that the media jumped all over this is that the drug is effectively not being used anymore.

Unfortunately, in this current environment where the FDA is unwilling to act, and is really impotent in many ways, the only way we get action is to directly inform the public. I would argue that while it made life tough and did create some anxiety, it also meant that a lot of people that were being harmed by a drug got to talk to their physicians about it. A lot of physicians had the opportunity to change the therapy for their patients. Frankly, wide public discussion of the Avandia affair has led to much more good than harm.

Kelly: Rosiglitazone works on insulin resistance, which is very different from insulin and any of the other drugs out there. Do you think there is a need now for more drugs in this class that are safe?

Dr. Nissen: Well, you saw a manuscript in JAMA about pioglitazone. Remarkably, pioglitazone actually reduces cardiovascular complications.

Kelly: It does reduce cardiovascular complications, but it also causes weight gain and edema and some of those other side effects such as fractures.

Dr. Nissen: They are concerns, although there are companies that are working on what is known as selective PPARS. These are selective PPAR modulators that are designed to turn on only some of the genes that PPARs turn on. I think that eventually we're going to be able to figure out how to make these molecules help people rather than harm people. We would have never gotten there if somebody hadn't done what I did, which was to take on the company and the FDA and get this debate out in the public arena where it belongs. And so, that was really the essential public health consideration here.

If Vioxx had stayed under the radar screen for three more years after we published our original analysis to suggest that it was causing harm… Well, I was absolutely hell-bent that we weren't going to let that happen again. We were going to get this thing out in the open and let it get hashed out in the scientific community, even if it was unpleasant for me personally to do that. To my dying day I will believe that was absolutely the only reasonable thing to do.

Kelly: So from a patient perspective, one might be optimistic that there might be some drugs in development – the selective PPARS – that would have a favorable lipid profile and not the same side effects. How far in the future are these treatments?

Dr. Nissen: They're still a ways away. However, keep in mind that at least from the point of view of cardiovascular safety, pioglitazone is a really good alternative. That's why most endocrinologists have taken their patients off of rosiglitazone and put them on pioglitazone. You can make the switch immediately, there's no difficulty in doing it, and it seems like a very rational approach. It's the approach most people are taking.

Kelly: You know, at AADE, Dr. Nesto had argued that any potential difference in cardiovascular risk between rosiglitazone and pioglitazone would be eliminated if the patients were on a statin, which I guess the patients should be on anyway.

Dr. Nissen: That's just utter unscientific nonsense… We don't know what the mechanism is. We do know that rosiglitazone raises LDL-cholesterol by about 20%, but that may not be the mechanism of harm, so this idea that you can mitigate the problem… Now it's also important to understand that Dr. Nesto is a consultant for GlaxoSmithKline. I would put that into context when you consider his remarks.

Kelly: Oh, that's interesting. But you had complained that diabetologists were not putting enough patients on statins. Can you talk about that more broadly?

Dr. Nissen: Well, our guidelines suggest that if you have diabetes, you should be on a statin, and yet when you look around the country, only 40 to 50% of diabetics are actually on statins. This is why I'm troubled by the glucose-centric approach to care. We know statins reduce the risk of the most lethal complications of diabetes by 25 to 35%, and yet they're not being used. There's questionable evidence whether lowering blood sugar protects against cardiovascular end points and certainly in some cases, like rosiglitazone, it increases it. So my view is that we've got to get endocrinologists to think more broadly about the risks to their patients and not focus exclusively on blood sugar.

Kelly: As you have said, most diabetes patients do die of cardiovascular disease. Can you talk a little bit about the changing roles of the endocrinologist and cardiologist and if the fields are moving together?

Dr. Nissen: They are moving together. I refer to myself as a diabeto-cardiologist. My practice at the Cleveland Clinic is full of diabetic patients and I treat their diabetes also. I do not, in general, refer them to endocrinologists for management of their diabetes. I manage their diabetes myself. And I've done that for many years.

Kelly: Wow. Okay.

Dr. Nissen: Only if they have very complicated issues managing insulin regiments or so on do I refer them for a consultation. I think that a cardiologist should manage diabetes. Now I'm very careful how I manage them, and you can bet they get statins. Almost all of them, if they have acceptable renal function, get metformin. I'm very cautious about sulfonylureas because of the cardiovascular issues with that class of drugs. And I do use pioglitazone in some patients if they have good ventricular function and are not at risk for heart failure.

Kelly: There's a lot of safety concern about some of the newer medications. There's less concern, perhaps, with the peptides because they're naturally occurring, but there is concern about some DPP-4 inhibitors and other drugs. Can you talk a little bit about safety since there are no long-term data?

Dr. Nissen: Yes. Here's the most important principle, and it's one that no one wants to hear: the absence of evidence is not evidence of absence. What that means is that when a new drug comes out, there's an absence of evidence, and then everybody assumes that that absence means that there's an absence of serious concerns.

I am very, very, careful now that I know that Januvia is off to the races. I wish we had more long-term safety data, and I hope it will be okay.

But, you know, there was originally a recommendation from the Institute of Medicine to put a little triangle next to the name of all drugs for the first two years after introduction to indicate to patients and physicians that we don't have a lot of long-term safety data with the drugs.

It was a good idea but, of course, it didn't happen. My concern is that people just jump on these bandwagons and then we find out later what the issues are. I always worry about it. It doesn't mean I don't use new drugs, but it means that I have a "show me, I'm from Missouri" kind of an attitude about this. Frankly, I think the agency standards for approval for a new diabetic agent are too low.

Kelly: What about phase 4 trials? Can you talk about those? Sometimes they're just not practical; patients don't even want to stay in very long-term trials, especially with all the new drugs coming out.

Dr. Nissen: Look, let me just tell you that it's always possible. I think industry will tell you that it's not possible. But let me tell you, we do it all the time in cardiovascular medicine. We don't get those 15,000-patient trials in diabetes and we need them. You could randomize patients to a regimen that includes a DPP-4 inhibitor versus a more conventional regimen and collect safety data long-term. You could launch that kind of a study even before the drug is actually approved, and it would be highly desirable. How did we get into the rosiglitazone fix? We got into it in part because the company did not do long-term prospective randomized trials. I think patients and providers should demand them. I could fashion a trial regimen very easily that would include a DPP-4 inhibitor in one arm and wouldn't include it in the other.

Kelly: Do you think you can get people to stay on metformin or whatever it is for the comparator arm for five to seven years?

Dr. Nissen: Well, metformin plus or minus other therapies. These are not hard studies to do. It's just that there hasn't been the discipline to do them.

Kelly: Hmm. Okay. I need to think about that from a business perspective. But in the meantime, switching gears, how you feel about pay-for-performance for clinicians?

Dr. Nissen: I would pay physicians for getting HbA1c's below 7%. Having said that, I'm not centered around glucose; I'd also pay them for getting blood pressure down. In the United Kingdom, you get paid according to what percent of your patients get their LDLs below 100 mg/dL. So you get paid for performing well and getting your patients' cholesterol levels down. And guess what? Utilization of anti-cholesterol medications went way up.

Kelly: Have you felt more optimistic, say, in the last year that we're actually moving towards pay-for-performance?

Dr. Nissen: Ah, no. There are powerful lobbying forces that are fighting these kinds of reforms. Unfortunately, we are up against a very, very powerful lobby that is really not necessarily in favor. I'm in favor, but the AMA (American Medical Association) is adamantly opposed. I think we're going to have to create a lot of public pressure to do this, and it has to be done right, which means – this is a very important point – it should not be done via claims data. You have to have a real prospective collection tool that puts this into a registry so you collect all variables and all the co-variance that affects what the performance is really going to look like. What you don't want to do is penalize physicians because they take on the sickest patients.

Kelly: Right, exactly. There does seem to be some concern about that, especially with endocrinologists, because they tend to have the patients who have the most complications.

Dr. Nissen: There are ways to handle that, but it's got to be done correctly. The way the government is currently talking about doing it is not very thoughtful.

Kelly: So do you think that there's any reason that Avandia should stay on the market?

Dr. Nissen: Well, let me put it to you this way. I have deliberately avoided calling for its removal, but I would refer you to the statements. Did you go to the FDA advisory panel meetings?

Kelly: Yes, we did.

Dr. Nissen: Do you remember what Drs David Graham and Gerald Delpan said?

Kelly: Yes, they made some very ardent arguments for its withdrawal.

Dr. Nissen: Dr. Delpan heads up the Office of Surveillance and Epidemiology in the FDA. This is the first time in history that he has ever called publicly for the removal of a drug from the market. He had to be pretty damned convinced before he would do that.

I was very disappointed in the performance of that advisory panel, frankly. I mean, there's logic to voting 20 to 3 that the drug increases cardiovascular risk, but then to not recommend decisive action is a little hard to understand.

Kelly: How would you explain that?

Dr. Nissen: Well, let me tell you something that you need to understand here: In these matters, courage is very rare. No one understands the FDA better than I do as an outsider. These panel meetings are in front of all your peers, knowing that the pharmaceutical industry is with whom everybody works and is really keen on not having you take decisive action. People just don't stick their necks out. And that's exactly what you saw.

Kelly: That's interesting.

Dr. Nissen: That's what leads to the Vioxx's and the Avandia's of the world. We need to do better because all drugs have risks, and we can only feel good about drugs when the benefits exceed the risks. For the last eight years we have been giving patients with diabetes a drug whose risks clearly exceed its benefits for the vast majority of people.

Kelly: Can you talk about what methods you would want industry to adopt to improve the process?

Dr. Nissen: Well, I would say to industry that we need greater transparency. When GlaxoSmithKline found the risk, they needed to inform the patient and provider community. I demand that kind of transparency. I would argue that when they found this risk, they had an obligation to inform all of us. If there's contradictory information out there, fine. But we have to get the totality of the information out in the public domain so that patients and providers can make rational decisions.

Kelly: This has really been terrific; we appreciate your taking the time to speak with us.

5. Conference Report: EASD

September 17-21 • Amsterdam, the Netherlands • http://www.easd.org/

The weather wasn't great but the talks were fantastic at the 43rd Annual Meeting of the European Association for the Study of Diabetes (EASD). Compared to its American counterpart, the annual meeting of the American Diabetes Association (ADA), EASD was very focused on basic science and insulin therapy. As at ADA, incretins garnered quite a bit of interest. Consistent with the meeting's focus on insulin therapy, the highlight of the meeting was the interim report from a three year study conducted by the Investigators in the Treating to Target in Type 2 Diabetes (4-T) Study Group, which we review independently on page 34.

- **Name of the game at EASD? Intensification.** Whether with regard to glycemic control, micro/macrovascular event prevention, or insulin initiation, presenters and chairs cited over and over again the need for faster, tighter, and more comprehensive management. Some of the field's leading researchers levied a call to providers to literally increase their aggression in fighting diabetes—modify a management regimen *before* it fails, they say, and before inadequate management raises a patient's risk of poor health outcomes. Highly respected Dr. Vivian Fonseca (editor of *Diabetes Care*) at

Sanofi's symposium on Day 1 could not have made this theme more clear: good management means ambitious goals. An enormous amount of data presented throughout the week supported this culture of intensity. Hyperglycemia and hyperlipidemia both contribute to progressive beta-cell loss in type 2 diabetes. Hyperglycemia is directly atherogenic by increasing plaque, cell death, and oxidative stress. Formal diabetes management systems are associated with higher numbers of prescribed therapeutics and also with maintained lower A1c. Postprandial glucose must be controlled in addition to fasting plasma glucose. Intensive therapy has been found to be less expensive than more casual management because it is associated with lower rates of complications. The ADDITION study specifically compared the effects of intensive and routine care and found 'spectacular' results including huge improvements in almost all indicators of diabetes and cardiovascular health under intensive care. One study found that hypoglycemia in the hospital does not increase the risk of future cardiovascular events or affect mortality; thus, hypoglycemia should not be a deterrent for more intensive glucose control. (From a patient perspective we question this.) In sum, both the data and the researchers are shifting further toward intensive therapy.

- **Appropriately enough, given the theme of intensification, several talks at EASD predicted a trend towards more insulin therapy.** Insulin, no longer just the heavy-duty machinery for reining in glycemia, should be considered a 'positive therapy' for positive results. Early initiation of insulin is associated with tighter glycemic control in the short-term and reduced rates of cardiovascular events and hypoglycemia in the long-term, in addition to improved micro- and macrovascular health more generally. The need for providers to 'get positive' (and get *persuasive*) on insulin therapy is clear. Presenters demonstrated widespread agreement on the benefits of early insulin initiation (and general consensus on the negatives, namely, weight gain) while in-session surveys showed that attendees believe needle fear is the #1 reason patients do not want to start insulin (we would urge study of patient research on this point). Furthermore, data on patient opinions show that few believe insulin will help them manage their diabetes better, and almost a third of physicians postpone insulin as long as possible. This places the onus on providers to demonstrate the benefits of insulin to patients. Data collected since the late 90's have shown increasing use of insulin alone and in combination therapy. Discussion of insulin at EASD suggests these numbers will only increase.

- **All things continuous!** Continuous glucose information and continuous subcutaneous insulin infusion (CSII) both yield better control and higher patient satisfaction. Several presentations throughout the week suggested that continuous monitoring translates into better management. Pumps also yield better results, particularly in groups such as children, overweight individuals with type 2, and pregnant women with type 1. CSII is associated with less fear of hypoglycemia, less concern about diet restrictions, and higher treatment satisfaction despite the complexity of operation. These positive results call for continuous information and infusion united in the same device – excellent for Medtronic, with its Paradigm CGM pump. Unfortunately, what looked like a terrific symposium on diabetes technology was cancelled – this was sad to see. Organizers said this was due to low interest but we did not think the symposium was well-marketed.

- **Two stand-alone treatment models presented at this conference were particularly intriguing.** First is Dr. William Polonsky's (US) new assessment model to facilitate behavioral change, called the Tipping Points program. Providers follow a simple chart to determine what factor most strongly contributes to poor glycemic control. Dr. Polonsky also presented a self-evaluation form to assist patients and providers in recording and incorporating SMBG data into management. We continue to be extremely impressed with Dr. Polonsky's research. Second, Dr. Martin Pfohl of Germany described a new model of insulin therapy to facilitate implementation called Basal Plus, which adds a once-daily injection of rapid-acting prandial insulin to improve control. The effectiveness of this model is currently being tested in a number of ongoing trials. Between these trials

and the recent release of data from the 4T study, it seems research is on track to guide providers as they follow new trends to earlier and more intense insulin initiation. This one looks to bring in simplicity – very laudable and we will be eager to see how it works, on the efficacy as well as side effect fronts.

- **Genetics research has exploded, and new insights on cause and cure are anticipated with great excitement.** The growing role of genetics in understanding and treating diabetes was at the forefront of the conference. In the opening lecture we heard about how groups around the world have joined forces in making large sample sizes available for genetics research. As a result, in recent years, genetics research has made bigger strides using large-scale studies with huge quantities of data. The number of type 2 diabetes-related genes continues to increase and demonstrates rapid advancements in the field. Research strategies are changing as well, thanks to the availability of larger data pools. Instead of basing research on hypotheses, researchers can now use raw genomic data to generate new hypotheses. These findings allow for the exploration of new treatment pathways as they implicate specific genes and processes in the diabetes pathway. One exciting area of research presented at EASD includes that of zinc transporters, a family of proteins specific to islet cells in the pancreas. Overexpression of these transporters has been found to be associated with beta-cell protection from stress-induced apoptosis. Furthermore, the prevalence of autoantibodies has been seen to increase as C-peptide and beta-cell mass decreases, and as children with type 1 diabetes grow older.

- **Genetics plays a huge role in diabetes risk.** Researchers have discovered numerous genes this year that are linked to weight and type 2 risk. Additional genes link diabetes and cancer, as well as diabetes and heart disease. Without a parent with diabetes, a person has a 10% chance of developing type 2 diabetes. With a single parent with diabetes, the chance rises to 30-40%; both parents raises the risk to 70%, and a monozygotic twin with diabetes raises a person's risk to nearly 100%. Research has confirmed the role of several specific genes that increase the odds of type 2 and obesity. Genetics also seems to strongly contribute to an individual's ability to lose weight through exercise.

- **Genetics isn't the whole story.** For example, the prevalence of type 1 diabetes has been rising at a steady rate of 3% per year for the past several decades. Genetics cannot explain such rapidly rising rates of disease, so genetics is only partially responsible. On-going initiatives have begun to explore environmental factors that might influence risk for type 1 diabetes, and research in this area will likely increase.

- **Echoing the intensive theme, we learned that when it comes to reducing cardiovascular risk, the best tactics involve intense treatment.** Cardiovascular risk is best reduced through tight control and intensive therapy, including early insulin initiation. The importance of glycemia in cardiovascular health is indisputable; 69% and 39% of patients admitted for acute MI or stroke test positive for impaired glucose tolerance (IGT) and undiagnosed type 2 diabetes, respectively. Furthermore, the most common risk factor for CV events in individuals less than 45 years is undiagnosed metabolic disorders and obesity. Study results indicate that glycemic control following an acute MI not only strongly predicts risk for a future event, but also survival rate. Importantly, the American College of Cardiology seems to agree with these conclusions, as it is working on new guidelines that demand glucose testing before patients admitted to a hospital for acute cardiovascular conditions can be released.

- **Insulin therapy may support cardiovascular health.** Early insulin initiation is linked to improvements in cardiovascular risk factors such as size of infarction and inflammation, as well as CV event rates. Insulin reduces inflammation through numerous mechanisms, such as reduced cytokine adhesion and platelet aggregation and improved vasodilation and reduced apoptosis. While insulin

was a hot topic in cardiovascular risk, very little was discussed about waist circumference, which we found surprising considering the emphasis placed on the importance of measuring waist circumference at the Prediabetes Congress in April. However, the International Chair on Cardiometabolic Risk has taken measures into its own hands with the launch of an informative website on Metabolic Syndrome. We will be checking this out and reporting back.

- **The jury is still out when it comes to cardiovascular health and TZDs.** Several meta-analyses referenced at EASD suggest an association between treatment with rosiglitazone (Avandia, GSK) and increased risk of myocardial infarction and heart failure. Several speakers, however, criticized the role of meta-analyses in guiding treatment protocols, calling for head-to-head studies comparing drugs within the class (namely rosiglitazone and pioglitazone (Actos, Takeda) as well as between classes.

- **Talk of glycemic control followed the general theme: the more intense, the better the results**. The hot topic in glycemic control at this year's meeting was postprandial glucose (PPG). In discussing intensifying glycemic control, speakers focused on postprandial control and its contributions to the risk of future micro- and macrovascular events. Experts still debate the relative contributions of FPG and PPG. Some experts say that recent evidence on oxidative stress markers shows strong correlations with rising PPG. Others suggest that no study shows additional outcome benefits in targeting PPG above A1c. But regardless of whether FPG or PPG carries more weight, achieving normal A1c levels requires addressing both. In accordance, the IDF has released new guidelines for postprandial control. The IDF believes that control of fasting glucose is necessary but not sufficient for adequate glycemic control for any A1c level. New PPG targets approximate 'normal' glucose tolerance, set at 140 mg/dl at two hours after ingesting a 75 g carbohydrate meal.

- **Intensive management will require a greater role for the patient.** To meet PPG targets, the IDF recommends that people taking insulin test three times a day, varying the timings of these measures, but including one test at two hours after a meal. These guidelines might affect individuals with prediabetes, too, since the guidelines are based on PPG. Shifting towards earlier insulin initiation also places greater responsibility on the patient, since insulin therapy often requires patients to be more involved in dosing and administration.

- **Finally released, "The Equation" and a new system for reporting blood glucose.** Results from the ADAG trial have identified a new equation to make numerical assessments of glycemic control more accessible to patients. The equation: AG (average glucose in mmol/L) = 1.583 x HbA1c - 2.52, where $R^2 = 0.836$. (Note that 1 mmol/L = 18 mg/dL) With this system, providers will have three numbers: the usual A1c percentage, the new IFCC version in mmol/L, and the new estimated average glucose. What are the implications? Hopefully, patients will find it easier to integrate this information into their management behaviors and improve control because the eAG scale matches that of glucose meters. Also, manufacturers of A1c equipment will need to update their software. The equation yields a linear correlation over a wide range of A1c. This means:

    - 6% = 126 mg/dl
    - 7% = 155 mg/dl
    - 8% = 182 mg/dl
    - 9% = 211 mg/dl
    - 10% = 239 mg/dl

- **In the wake of The Equation, some asked, which measure is most important, A1c or blood glucose?** The ADAG trial showed no difference between LifeScan and CGM data. Perhaps A1c is not the gold standard, at least for correlating cardiovascular disease with glucose levels. After all,

data presented at EASD showed that patients with the same A1c can have different 'area under the curve' PPG. For these patients, high PPG values may be a better indicator of inflammation and CVD risk than A1c. On all fronts, we believe it's the combination of data that will most help patients connect the dots.

- **Obesity is a disease, and it's time to treat it like one.** This year at EASD, talks about obesity focused on therapeutics and medical procedures rather than lifestyle intervention. Regardless of what side of the debate speakers fell, all agreed that it is time to take obesity seriously. What does 'get serious' mean? Well, mainly drugs and surgery, what one speaker termed 'sophisticated' treatment. Research has shown that surgery is a powerful and effective intervention to get morbidly obese individuals on track towards better health. Furthermore, data suggest that the effects of surgery are lasting, with participants in one study successfully maintaining weight loss for 12 years, and even after regaining the weight, demonstrating a 30% reduction in all-cause mortality. Given such positive results, why don't providers recommend surgery more often? NICE seems to be in agreement, recently adding drug treatment and surgery to recommended treatment timelines.

- **Obesity is more complicated than 'energy in equals energy out.'** If obesity is a disease, causes of obesity include more than overnutrition and sedentariness. Other factors like hormones, adipokines, and inflammation complicate the disease pathway and thus complicate treatment as well. Beyond exercise, several approved and pipeline products show successful results in treating weight loss.

- **Data on Merck's CB1 receptor antagonist for obesity, taranabant, show promising results.** Taranabant is an inverse agonist that blocks endocannabinoid signaling pathways by occupying the receptor site CB1-R, similar to the mechanism of action of Sanofi-Aventis' stalled rimonabant. Through occupation of these receptors, taranabant suppresses appetite and food cravings in humans and mouse models. In trials, 12 mg of taranabant suppressed calorie intake by 22% overall and 27% at lunch specifically. We're very interested in whether taranabant produces the same psychiatric side effects as rimonabant but we unfortunately were not able to learn anything on this frnt.

- **Discussion of insulin-treated diabetes tended to question widespread, automatic use of Lantus (glargine, Sanofi-Aventis).** Between results from Treating to Target in Type 2 and various head-to-head studies, Lantus did not always come out ahead. And with the market opening up to insulin use, this could mean serious change for prescription trends as Levemir or prandial insulin become more commonly used options.

- **Pharmacokinetics data and insulin analog comparison studies took center stage numerous times throughout the week.** Presented data centered on head-to-head trials of glargine *(*Lantus, Sanofi-Aventis) and detemir (Levemir, Novo Nordisk). Glargine was found to have significantly longer duration than detemir, (24 vs. 17.5 hr), which recommends use of detemir as a twice-daily insulin, at least in individuals with type 1 diabetes. The long-duration benefits of glargine, however, may be linked to higher rates of post-exercise hypoglycemia in comparison to detemir. Both drugs resulted in similar brain response in states of euglycemia and hypoglycemia, though onset of action was somewhat delayed for detemir. These two analogs are further set apart with respect to weight gain. While glargine is associated with weight gain, detemir is associated with relative weight loss (weight neutrality). Glargine also compared less favorably to Humalog 75/25 (Eli Lilly) in A1c improvements. Premixed Humalog plus metformin yielded better results than glargine plus metformin, likely because it lowered PPG more effectively. Unfortunately, premixed insulins also tend to come with slightly more weight gain and higher rates of mild hypoglycemia.

- **What are the implications of earlier insulin therapy for rates of insulin-related weight gain?** Insulin therapy should not be postponed due to weight concerns, but at the same time, weight should not be ignored. Right! Lifestyle interventions concurrent with insulin initiation presents a viable option, but data on insulin detemir (Levemir, Novo Nordisk) are also encouraging. Medical representatives for Novo Nordisk at a press conference said it wasn't yet clear why Levemir does not cause weight gain, but the results are very positive. Some suggested explanations referenced Levemir's lower association with hypoglycemia (and thus reduced safety eating) and its potential ability to cross the brain blood barrier, thus stimulating satiety through insulin's appetite-suppressing effects on the brain. These and other explanations are still being investigated.

- **Weight worry is a significant obstacle to insulin initiation and successful glycemic control using insulin therapy.** A large percentage of insulin users worry about weight to some degree, with 25% reporting high weight worry in one study. Alarmingly, individuals who worry more about weight are more likely to report higher levels of non-adherence. For example, in children, one study showed that over 90% of boys and girls omit insulin once per month in order to avoid weight gain. Other methods include fasting and vomiting. These weight 'short-cuts,' however, beyond being disturbing in and of themselves, are associated with poorer glycemic control and increased risk of complications. As evidence, 45% of women with type 1 with complications report under-dosing insulin to manipulate their weight. Forty-five percent! Incredible.

- **Far and away, GLP-1 therapies dominated talk on non-insulin treated diabetes.** One talk we attended focused on the many advantages GLP-1 therapies have over sulfonylureas, such as weight loss or weight neutrality, lower risk of hypoglycemia, and more effective glucose control over a longer duration. Furthermore, sulfonylureas may induce beta-cell apoptosis. At the same time, several reasons justify not abandoning sulfonylureas all together. First, long-term data on GLP-1 therapies is still emerging. Second, speakers said GLP-1 therapies are much more expensive at least in the short term though to the extent complications are avoided, the return is obviously good. There was support for research to continue to assess the effectiveness of a low dose sulfonylurea in combination with other therapeutics, such as a low dose DPP-4 inhibitor. We imagine that sulfonylureas are also getting another look now that the TZD class is under suspicion. We are very interested to know the extent to which side effects of SFUs would be reduced with lower doses and what durability might emerge – ADOPT showed SFU durability to be quite poor, even early in disease progression.

- **Benefits discussed for liraglutide over Byetta include less GI side effects, lower incidence of antibody formation, and a longer duration of action.** Liraglutide covers 24 hours while Byetta covers less, resulting in higher fasting – of course, without a head to head, it is very difficult to make comparisons of efficacy or side effects. Like Byetta, in monotherapy or as an add-on to metformin, liraglutide is associated with a very low risk of hypoglycemia, while in combination with sulfonylureas, there is a greatly increased risk of hypoglycemia. Low doses of liraglutide are associated with glucose control (0.65, 1.25, 1.9 mg/day cause similar A1c improvements), but only higher doses (1.25 mg/day) are also associated with weight loss, which presenters noted were independent of gastrointestinal side effects. This finding is interesting, as it parallels the phase 2 data on Byetta LAR, in which the lower 0.8 mg dose produced A1c reduction without weight loss whereas the higher 2.0 mg dose produced significant weight loss. Finally, liraglutide may reduce systolic blood pressure and other cardiovascular risk factors, and may increase beta-cell mass. We remain enthusiastic about innovation in this area and believe a product by Novo Nordisk would be terrific for the field as their physician and patient education is so strong.

- **Talk on DPP-4 inhibitors positioned sitagliptin (Januvia, Merck) against vildagliptin (Galvus, Novartis).** With Galvus expected to hit the European market in the next couple of months, we were curious to see how Merck and Novartis intended to distinguish their products. Merck

highlighted the synergistic actions of sitagliptin and metformin (Janumet) and did not seem concerned with positioning its drug against Novartis' vildagliptin. As Januvia is the first DPP-4 on the market, Merck feels that Novartis will need to create room for its product. Specifically, Merck touted Januvia's safety profile, though we would argue that evidence for sitagliptin's safety is still in development, pending long-term trials. Merck researchers pointed to the drug's tolerability as a driving force in the market, as well as the synergistic effects of sitagliptin and metformin in combination. The synergy results from complementary effects on GLP-1 by metformin and sitagliptin. Metformin increases total plasma GLP-1 through increased gene expression, but does not increase the percentage of active GLP-1. Januvia, on the other hand, does not increase the amount of GLP-1, but it does increase the percentage in active form. Co-administration of Januvia and metformin is considerably more efficacious than either agent in monotherapy. For patients in better control (average A1c of 7.6%), combination therapy—metformin (100mg twice daily) + Januvia (50 mg)—reduced A1c by 1.0%; patients with A1c greater than 10% experienced reductions of over 3.1%; and overall, mean reductions in A1c were 1.9%, compared with 1.3% for metformin monotherapy and 0.8% for Januvia monotherapy. Combination therapy also significantly reduced PPG and had a greater effect on GLP-1 than either agent in monotherapy.

- **Novartis focused on vildagliptin's effects on insulin and glucagon, as well as its weight neutrality.** According to Novartis, Galvus and Januvia are dissimilar molecules (though we are under the impression that they are more similar than Novartis claims) and Galvus may have particularly beneficial effects on beta-cell function. Novartis is currently conducting a 5-year 3,000-person trial to assess vildagliptin's effects on disease progression. Novartis also emphasized that the company's extensive data on Galvus will give its product a leg up in the market. Interestingly, during a Q&A, a vildagliptin study was referenced similar to the metformin/sitagliptin studies above. Overall results were similar, but one difference of note was that vildagliptin reduced total GLP-1 by about 75% whereas in the study above the total GLP-1 was reduced by about 30% by sitagliptin (we note that a reduction in *total* GLP-1 levels is a normal physiological feedback response to higher levels of *active* GLP-1). The significance of this difference is unclear, but may perhaps indicate an advantage of sitagliptin over vildagliptin. One additional difference is that Galvus has a broader label than Januvia, and can be used as an add-on for sulfonylureas, as well – of course, as of mid-October, so can Januvia in the US though not yet in Europe.

- **Compared to GLP-1 therapies, TZDs were less central at EASD, and most of the discussion focused on pioglitazone (Actos, Takeda).** Meta-analyses on pioglitazone revealed consistent results in favor of pioglitazone in relation to all-cause mortality, myocardial infarction (MI), and stroke. Data from meta-analyses may not be as conclusive as a prospectively designed randomized controlled trial, but the cardiology community does seem to increasingly support Actos. However, enough meta-analyses were presented at this meeting to inspire one attendee during a Q&A to criticize the research field, and request more research based on improving medicine rather than industry and media interests.

- **Recent findings on brain activation during hypoglycemia contradict a major theory on hypoglycemia awareness and unawareness.** Previously, scientists accounted for hypoglycemia unawareness based on differing levels of glucose uptake in the brain in different individuals. However, brain imaging shows that glucose content during hypoglycemia progresses similarly in both aware and unaware individuals. These results suggest that hypoglycemia involves neuronal activation, not just changes in blood flow. Imaging techniques have also identified brain regions activated during hypoglycemia. Individuals who experience hypoglycemia awareness show activation in the regions of the brain responsible for food seeking and anxiety. In contrast, hypoglycemia unawareness is associated with activation of the pleasure stimuli—almost an incentive to remain in the hypoglycemic

state. These findings provide insight into clinical tactics to re-sensitize people with diabetes who are hypoglycemia unaware to recognize when they are experiencing a hypoglycemic event.

- **Increased awareness and changes in clinical practice likely account for reduced rates of undiagnosed diabetes in England.** In the 1990s, studies suggested that as many as 50% of individuals with diabetes were undiagnosed. Now, however, an estimated 20% of cases in men and 11% in women are undiagnosed. While fewer are undiagnosed, rates of diagnoses are rising. Putting these facts together, perhaps rising rates of diabetes actually represent the diagnosis of previously undiagnosed cases. In other words, maybe the numbers are not rising as rapidly as we think. Either way, these figures suggest that current screening tools perform well in the clinic. In comparing Cambridge, Danish, SRQ-Hoorn, Rotterdam, ARIC and FINDRISK risk Scores, one research team found that models based on OGTT provided a more accurate picture of risk than a model based on GP diagnosis. Of the six scores, ARIC performed the best in terms of higher sensitivity and a higher positive assessment, meaning that the risk assessment concluded by ARIC was more accurate than that by a different score. Specifically, participants identified by ARIC experienced a 25% risk of developing or having diabetes.

- **Studies on prevention and risk indicators challenge conventional perspectives on cardiovascular risk.** Perhaps the most significant example, studies from the RISC trial suggests that not just insulin resistance, but also insulin sensitivity and insulin levels are independent contributors to cardiometabolic risk. From a different study, both adiponectin and CRP were found to be independent predictors for the development of diabetes by year 10. Both hormones more strongly predict risk of future diabetes than age, sex, and BMI combined. In addition, combining adiponectin and CRP was even more predictive than age, sex, BMI + adiponectin or age, sex, BMI + CRP.

- **RISC results show widespread benefits of physical activity.** While exercise and lifestyle intervention were not central themes of the conference, impressive data from the RISC trial suggest many benefits from all forms of physical activity. Total activity, not just intense exercise, improves insulin sensitivity, and increased activity is associated with improved insulin sensitivity independently of waist circumference. This is great news for people who work in an office all day—moving during the day is extremely beneficial irrespective of intensity.

- **Prevention requires identification of yet unknown variables.** While genetics plays a large role in determining risk of diabetes, rates of type 1 diabetes have been rising steadily for the past several decades at a rate of 3% per year. These numbers imply that genetics is not the only determining factor, and reducing the incidence of diabetes will involve identifying and understanding environmental factors. Ongoing trials such as TEDDY and DIPP have begun exploration into this field. Examples include viruses that might serve as epidemiological triggers for immune conditions.

- **Genetic mutations leading to renal glycosuria have documented the long-term safety of SGLT2 inhibition in humans.** SGLT1 and SGLT2 are glucose transporters found in the small intestine and kidneys, respectively. SGLT2 inhibition allows blood glucose to be excreted in the urine without severe hyperglycemia. Manifestations of SGLT inhibition (renal glycosuria) include normal plasma glucose, no evidence of renal dysfunction, reduced rates of hypoglycemia, and encouragingly, obesity in this population is extremely rare. Studies in experimental models of diabetes have demonstrated that induction of glycosuria restores normoglycemia and improves beta cell function and insulin sensitivity, reversing glucotoxicity. SGLT1 and SGLT2 are novel targets for therapeutic treatment, with BMS/AZ's dapagliflozin the current lead compound in development.

- **Beta-cell replenishing research has made dramatic progress in recent years.** The biggest hurdle in embryonic stem cell research has recently been crossed: driving the definite differentiation of endoderm cells. This achievement opens the door to a flood of future possibilities. One speaker, Dr.

Philippe Halban, could not contain his excitement, exclaiming, "Decades of multidisciplinary research have transformed science fiction into scientific possibility!"

- **Worrying is a common and troublesome aspect of the diabetes experience.** Many studies presented at EASD mentioned how many people with diabetes worry about various aspects of their illness including weight gain, hypoglycemia, and future complications. Worrying is associated with poor adherence, poor glycemic control, and obesity. Encouragingly, people who used CSII compared to MDI reported significantly lower risk for expressing high fear of hypoglycemia or diet restrictions. Given recent data on insulin omission due to fear of weight gain, it would be interesting to compare adherence levels between those who use CSII and MDI.

- **Diagnosis of diabetes is associated with severe mental illness (SMI), schizophrenia, and depression.** Almost half of people with type 2 diabetes experience depressive symptoms and/or diabetes-related distress. One group found that the suicide rate was proportionally greater among people with diabetes as compared to the general Dutch population (6.4% versus 2.7%). A1c and major depression have also been correlated with history of suicide attempt. In the recently published DiSCO, 2007, out of around 1,000 patients with schizophrenia, 3.5% of were known to have type 2 diabetes, and 12% expressed an FPG greater than 7 mmol/l (126 mg/dl). Diabetes is also associated with increased dementia and Alzheimer's disease. While it has long been thought that anti-psychotic drugs influence blood sugar, no anti-psychotic holds a consistent association with the development of diabetes.

- **Greater attention must be given to depression in diabetes.** The association between diabetes, depression, and adherence exposes the need for new mental health screening guidelines to support providers in identifying patients whose physical health cannot improve without attention to mental health.

- **The role of industry.** This conference involved some talk about the influence of industry on research through its access to major capital. It was said that pharmaceutical companies tend to influence research and development due to the financial obstacles smaller research teams face when attempting to conduct a prospectively designed randomized controlled trial. As a result, many questions pertinent for aggressively preventing and treating diabetes remain unanswered, such as the feasibility and efficacy of a polypill, the significance of specific lifestyle factors, the most significant factors in diabetes for reducing cardiovascular risk, optimal dosing, and the timeline of risk indicators. Speakers said that reigning in the diabetes epidemic will require a unified vision addressing all aspects of prevention, diagnosis, and treatment. Notably, the EU has allocated over 6 billion Euros to diabetes research over the next seven years, and will hopefully begin looking into these much needed areas of research as soon as possible. In another session, speakers discussed the value of drugs compared to their cost. Some attendees polled said that they were not getting value for money in diabetes drugs. While some felt that prices reflect the price of long-term investment from the companies, others felt that too much money turns into profit rather than reinvestment in research. We thought that was absurd. Regardless of which perspective one takes, current drug costs are unsustainable, growing nearly ten-fold faster than the overall economy.

--by Alyssa Shell, Mark Yarchoan, John Close, and Kelly Close

6. Literature Review: Treating to Target in Type 2 Diabetes (4-T)

This publication is an interim report from a three-year study conducted by the investigators of the Treating to Target in Type 2 Diabetes (4-T) Study Group. Novo Nordisk supplied all insulin analogs used in this study. In our view, this was the most important data to be presented at EASD.

The September 21st online issue of the New England Journal of Medicine *includes an interim report from Dr. Rury Holman and colleagues presenting one-year findings from the 4-T study. This ongoing open-label treat-to-target trial is comparing biphasic, prandial, and basal insulin regimens for the treatment of type 2 diabetes . The 708 enrolled patients were randomized to receive biphasic insulin (insulin aspart 30), prandial insulin (insulin aspart), or basal insulin (insulin detemir). All patients began the trial with poor glycemic control (Alc 7% to 10% with an average of 8.5%) despite maximum tolerated doses of oral anti-diabetic therapy (metformin or a sulfonylurea, but not a TZD). In the interim report, the overall efficacy of insulin add-on therapy was disappointing, with a minority of all patients reaching the A1c target of 6.5% - we applaud the aggressive goal. Although basal insulin was less effective than either prandial or biphasic insulin, insulin detemir led to less frequent hypoglycemic events and less weight gain – meaningful positives in our view, though clearly "not enough" since so few reached goal. For patients with baseline A1c <8.5%, all three insulin formulations were indistinguishable, which from our view is a win for insulin detemir, as it seems the easiest formulation (though about a third had to take it twice a day rather than once a day). These data suggest that basal insulin should remain first line insulin therapy for patients with type 2 diabetes who are not at glycemic goal on oral agents. The fact that only a minority of patients reached the target A1c of 6.5% reflects, in our view, the importance of combination therapy. We will be very eager to see three-year results – we believe these results were actually a win for GLP-1, which data shows prompts weight loss rather than weight gain and which benefits from being easy to use (once a day injection). More details on 4T:*

- **This open label, randomized trial compares three insulin regimens** as add-on treatment in 708 type 2 diabetes patients with poor glycemic control despite maximum tolerated doses of oral anti-diabetic therapy (metformin or a sulfonylurea). Patients were randomized to receive biphasic insulin (N = 235), prandial insulin (N = 239), or basal insulin (N = 234). Biphasic insulin was provided as twice daily injections of insulin aspart 30 (NovoMix 30). Insulin aspart (NovoRapid or NovoLog) was used three times daily in the prandial group. Once daily insulin determir (Levemir) was used as the basal insulin regimen, though patients have the option of titrating to twice daily dosing. In addition to insulin therapy, patients are maintained on their previous oral anti-glycemic drugs throughout the trial.

- **This trial has a treat-to-target design, with insulin dose escalation according to a pre-established algorithm in patients failing to achieve adequate glycemic control.** Patients are monitored closely throughout the trial with scheduled site visits at weeks 2, 6, 12, 24, 38, and 52 during the first year, as well as "interim telephone contact." Prior to each site visit or telephone call, patients recorded three capillary blood glucose levels spaced throughout the day. These values were used to calculate changes in insulin dose; for patients assigned to basal insulin, a second daily dose was added if plasma glucose monitoring suggested waning insulin coverage. In addition to the pre-established algorithm, patients and physicians were encouraged to amend doses between visits when such changes were "deemed appropriate."

- **Hypoglycemia was carefully monitored throughout the trial and used to limit dose escalation.** Hypoglycemia was classified into three grades: 1 (symptoms of hypoglycemia with self measured plasma glucose ≥ 56 mg/dL), 2 or minor (symptoms with self measured plasma glucose < 56 mg/dL), and 3 or major (if the patient required assistance from a "third party").

- **After 24 weeks of therapy, additional insulin preparations were added to the treatment protocol for patients with "unacceptable" glycemic control** (A1c > 10% or two consecutive A1c measurements > 8%). Patients who received additional insulin therapy were also discontinued from sulfonylurea therapy. Prandial insulin aspart was added at midday to bisphasic insulin

regimens; insulin detemir was added before bed to prandial insulin regimens; and three daily doses of prandial insulin aspart were added to basal insulin regimens.

- **Patients were excluded if they had received previous thiazolidinedione (TZD) therapy** or if they had a history of significant cardiovascular disease. Patients receiving TZD therapy were excluded due to concerns about the increased risk of heart failure and bone fracture as well as cost. Patients with other macrovascular diabetes complications, liver or kidney disease, hypertension, or a significant history of hypoglycemia were also excluded.

- **At baseline, mean age was 61.6 years and mean A1c was 8.5%**. The average duration of diabetes was nine years; more than 90% of the patients were white and most were overweight (average BMI 29.8) and male (64.1%).

- **The primary endpoint of this trial was the drop in total A1c at the end of one year.** The proportion of patients who achieved an A1c below 6.5% served as a secondary endpoint. The proportion of patients with unacceptable hyperglycemia, and the degree of weight gain were also compared across all three treatments. The rate of hypoglycemia was closely monitored throughout the trial, serving as a counterpoint to dose escalation. In addition, the percent of patients achieving an A1c below 6.5% without significant hypoglycemia was compared across all treatment regimens.

- **The average reduction in A1c was similar in patients treated with biphasic insulin (1.3%) and prandial insulin (1.4%), and was significantly greater than the reduction in patients receiving basal insulin (0.8%).** Subgroup analysis showed that the greater beneficial effect from biphasic and prandial insulin was only observed in patients with baseline A1c > 8.5% and was associated with a decrease in average prandial glucose but not a decrease in average fasting glucose.

- **A minority of patients in all groups achieved the target A1c of 6.5%.** Although patients receiving biphasic insulin or prandial insulin were significantly more likely to achieve target A1c levels (17.0% and 23.9% respectively) than patients receiving basal insulin (8.1%), all three regimens were largely unable to achieve tight glycemic control. A1c fell below the ADA's target recommendation of 7.0% in 27.8% of patients receiving basal insulin, compared to 41.7% and 48.7% of patients receiving biphasic insulin and prandial insulin, respectively.

- **The frequency of hypoglycemic events (grade 2 or 3) was inversely correlated with A1c,** and was significantly higher in patients receiving biphasic and prandial insulin preparations. The frequency of grade 2 and 3 hypoglycemic events was 5.7 events per patient per year in patients receiving biphasic insulin, compared to 12.0 events in patients receiving prandial insulin and 2.3 events in patients receiving basal insulin. In patients who achieved target A1c levels with biphasic or prandial insulin, hypoglycemic events were quite common, occurring in 47.5% and 56.1% of patients, respectively. In contrast, only 21.1% of patients achieving target A1c using basal insulin experienced significant hypoglycemic episodes. Grade 3 hypoglycemic events were apparently not observed in any of the three groups.

- **Substantial weight gain occurred in patients treated with biphasic (4.7 kg or 10 pounds) or prandial (5.7 kg or 12.5 pounds) insulin, with significantly less weight gain in patients receiving basal insulin (1.9 kg or 4 pounds).** Additional adverse events occurred at similar frequencies in all treatment groups. Significant adverse events were rare, but included four deaths due to cardiac disease (three in the biphasic group and one in the prandial group).

- **This one-year interim report from the 4-T study group showed disappointing results, with the majority of patients in all groups failing to reach A1c targets.** As a result, these

findings are unlikely to change current practice, which calls for basal insulin therapy to begin in patients with poor glycemic control who are already receiving maximum doses of oral anti-diabetic therapy. Although insulin detemir, the basal insulin used in this trial, was generally less efficacious than the biphasic or prandial regimens, the side effects of weight gain and hypoglycemia were also significantly lower. In addition, all three insulin regimens were equally effective in patients with baseline A1c < 8.5%. Taken together, these results support the use of a long acting insulin analog at the initiation of insulin therapy.

- **We were surprised more patients on insulin didn't reach goal – this reflects in our view the importance of combination therapy.** A minority of patients in all groups achieved the target A1c of 6.5%, which suggests a need for more sophisticated regimens (basal-bolus) if normal glycemia is the goal. We would also be curious about the effect of adding incretins or Symlin to insulin therapy. Some endocrinologists also use Byetta as add-on therapy to insulin, though this is currently an off-label use.
- **Despite the lack of efficacy in the first phase of this trial, the second phase is likely to provide extremely interesting information, as patients who failed to achieve the 6.5% target with single insulin preparations move to more complicated regimens.** Given the large population of patients who will begin a combination protocol, this trial should be able to test the value of basal-bolus combination insulin analog therapy directly. These results should provide important guidance for insulin prescriptions in patients with persistent hyperglycemia. Regrettably, one drawback of this trial is that newer diabetes treatments, such as GLP-1 analogs, were not included. Since GLP-1 analogs are known to induce weight loss in many patients, the addition of a GLP-1 plus insulin cohort would provide information about the ability of GLP-1 analogs to limit insulin-induced weight gain.

—by John Close, Michael Dougan, Mark Yarchoan, and Kelly Close

7. Conference Report: Cleveland Clinic Obesity Summit 2007

September 27-29 • Cleveland, OH • www.clevelandclinicmeded.com/obesity07

We were delighted to attend the second Obesity Congress at the Cleveland Clinic, co-directed by Dr. Philip Schauer and Dr. William Carey of the Cleveland Clinic and featuring Dr. David Kessler, former Commissioner of the FDA, as keynote speaker. Again this year, the program was extremely well-organized and we found the talks to be of uniformly high quality. With at least 350 drugs in the pipeline, most of the presenters were optimistic about the long-term future of obesity drugs, and underscored that while any single obesity drug is unlikely to cure obesity, combination therapy – lifestyle modification + an expanding "cocktail" of medications – may have a dramatic effect. One of the goals of the meeting was also to demystify bariatric surgery, and attendees were invited to watch two live bariatric surgeries from a satellite viewing area.

- **The conference had at least 200 registered attendees, the majority of whom were clinicians.** Overall, the tone of the conference was very clinically focused and treatment focused, with attendees asking very specific questions about recommendations about treatments and surgical techniques during the various Q&A sessions. There was more optimism this year on drug prospects than last year, though not necessarily more information. Tragically and quite indicative of the extent of the obesity epidemic, many of the attendees were older pediatricians who for the first time were seeing large numbers of obese children. One physician from the Bronx described seeing an explosion of children in the last few years with type 2 diabetes or pre-diabetes, some as young as seven years

old. Those pediatricians who came to learn about what to do with obese children left very distraught by their limited options.

- **Most of the exhibitors were medical device companies but there were a few drug companies in attendance as well.** The main sponsors for the conference were (in order): Ethicon Endo-Surgery (which got approval for its LAP-Band competitor product during the meeting), Covidien, Stryker, Nestle, Sanofi-Aventis, and Allergan. Merck had a table with information about sitagliptin (Januvia) in spite of the fact that Januvia causes no weight loss (though, as the exhibitors pointed out, Januvia is weight neutral whereas some drugs for diabetes cause weight gain).

- **The future of obesity drugs is bright, longer term.** At least 350 obesity drugs are in the pipeline, and some of them are very promising. None of them are likely to far exceed current options in terms of efficacy (about 17% weight loss is the maximum that can be expected), so combination therapy will be necessary. While bariatric surgery can cause 25-40% weight loss and changes a patient's underlying biochemistry, drugs are ultimately going to be the future of obesity treatment. The root cause of obesity is a disturbed underlying biochemistry, and drugs offer the possibility to ameliorate this underlying biochemistry through a less invasive means than surgery.

- **Is the cause of obesity increased energy intake or decreased energy expenditure?** This was a contentious issue at the conference, with Dr. Kessler (former FDA commissioner and keynote speaker) arguing that increased caloric intake is the sole cause of the current obesity epidemic, while Dr. Steven N. Blair argued that the major contributor to obesity is decreased energy expenditure.

- **Dr. Kessler explained that people obtain neurological rewards from highly palatable food (foods high in fat, sugar, and salt).** Comparing obesity to cigarette smoking and alcoholism, he argued that in order to reverse trends in obesity, we need a critical perceptual shift in the way people view large portions of fat, sugar, and salt. He believes that there is "no magic bullet coming" with obesity because our underlying biology for weight gain is so effective. He also explained that he is not optimistic about obesity drugs because any successful obesity drug has to tackle the neurological basis of obesity, and this will cause severe neurological side effects. Speaking specifically about CB1 inhibition, he said "CB1 inhibition is going to have serious side effects on learning, memory, and reward, and other neurological systems."

- **Dr. Blair argued that we instead need to encourage active activities like walking up stairs rather than taking escalators.** Interestingly, physical activity levels (defined as intentionally active activities such as running or other sports) have remained stable for the last few decades. What has not stayed constant is energy expenditure during normal activities. He showed that completing a long set of normal tasks the "active way" burns 10,500 kcal/month compared to only 1,700 kcal/month the "sedentary way." An example is walking up the stairs rather than taking an escalator. Dr. Blair reviewed multiple examples of how our environment is obesogenic, showing pictures of everything from escalators to remote controls. He also suggested that technology could (and should) be used to improve the health environment; for example, with cell phones, it is now possible to walk while you are on the phone.

- **There are three primary types of weight loss surgery (called bariatric surgery)**: gastric bypass surgery, adjustable gastric bending, and biliopancreatic diversion. Of these options, gastric bypass causes the most pronounced effect on type 2 diabetes (over 90% of type 2 diabetes cases are resolved). There are many newer experimental bariatric surgery options, including sleeve gastrectomy, gastric balloon, and "smart devices" such as gastric bands and electrical stimulation. Bariatric surgery cures diabetes through weight loss, decreased nutrient intake, and/or changed GI physiology and signaling (independent of weight loss and decreased nutrient intake). Interestingly, improvements in glycemic control are seen even before significant weight loss occurs; this effect is

limited to bypass-type procedures. This suggests, as we have written before, that gastric bypass surgery may alter GI signals to the brain and other tissues.

- **Drug combinations in the future should mimic bariatric surgery today**. Dr. Lee Kaplan explained that bariatric surgery lowers a patient's energy set-point (the BMI at which caloric intake = energy expenditure) through decreasing hunger and increasing energy expenditure. Diet, by contrast, makes people hungrier and causes a decrease in energy expenditure. Like bariatric surgery, other effective treatments for diabetes will need to affect the weight regulatory system at multiple levels and blunt environmental influences on body weight. These requirements suggest that combination medical therapy will be essential in the future.

- **Obesity is a chronic condition caused by skewed underlying biochemistry**, and like other chronic conditions with biological basis, drugs are ultimately going to be the solution. Dr. Richard Atkinson explained that the current obesity drugs are only modestly effective. He believes that drugs in the pipeline are likely to have similar efficacy as current drugs (up to about 17% weight loss), so combination therapy will be necessary. He stressed that overhype and over-promise by the drug industry and media is detrimental and we have to be realistic about the effectiveness of obesity drugs. However, he also underscored that obesity has a biochemical basis, and because drugs can change biochemistry, the future of obesity treatment is drugs.

- **Dr. Kaplan expressed optimism about the future of obesity treatment, particularly with combination drug therapy.** Clinical trials have indicated that the combination of amylin (pramlintide) + leptin + PYY causes a change of more than 16% weight loss - more than any currently available drug, but not as much as bariatric surgery, which causes about 22% weight loss. In monotherapy, amylin, leptin, and PYY each produce only a modest amount of weight loss. Therefore, combination drug therapy is very promising. Coming soon are new drugs to expand combination therapy options, as well as other novelties - gastric electrical stimulators and balloons. Further in the future there will be new laparoscopic and endoscopic devices, ileal infusion therapy, intestinal electrical stimulators, GI hormone modulators (such as PYY, ghrelin, etc.), and even more combination therapies.

- **Mr. Henry Alder spoke about the promise and perils of evidence based medicine (EBM).** When EBM is properly used, it can stimulate the development of high quality information about treatments and devices. However, EBM can have unintended consequences, such as causing drug coverage decisions to be based purely on cost rather than overall effectiveness of value. Also, EBM may freeze the pace of innovation by discriminating against new products. A new decision making framework is needed that meets the ethical tenets of accountability for reasonableness. In the future, it will be important to design clinical trials to address both regulatory and coverage needs though choosing appropriate comparators in order to show drug superiority, not just non-inferiority. Mr. Alder listed four key questions about new products that help to determine reimbursement: 1) Is the product safe? 2) For whom is the product intended? 3) How does the product compare to others already on the market with regards to efficacy? 4) What is the value of the product? In the future, Mr. Alder said that industry will need to acknowledge the growing "affordability gap" between new and generic drugs, and will need to engage payers directly and constructively. Additionally, it will be important to design clinical trials to address both regulatory and coverage needs through choosing appropriate comparators in order to show drug superiority, not just non-inferiority.

- **In sort of a provocative statement, Dr. David B. Allison urged scientists and politicians to question common assumptions about obesity** before spending billions on physical education in schools and restricting access to certain foods. He underscored that there are many factors that affect obesity, and no single factor seems to account for much variance. He argued that

other "less discussed" explanations may be more important, and may have an enormous cumulative effect in society. Three important explanations that are well described but often ignored are decreased smoking (smoking causes weight loss), demographic changes, and sleep deprivation. Data consistently show that children and adults are sleeping less, and there is a strong association between less sleep and higher BMI. Another interesting possibility is that better temperature control (more air conditioning/heating) is keeping people in the thermo-neutral zone more often, such that people expend less energy. This could also contribute to obesity. He suggested that scientists need to explore the effect of less obvious putative causes, and ask about the evidence for all proposed solutions. He summarized his own talk with the following line: "In the sequence of 'ready, aim, fire', let us not forget 'ready, aim.'"

- **Also arguing against "conventional" explanations for the obesity epidemic, Dr. Atkinson provided some compelling evidence that a virus is contributing to obesity.** He argued that the etiology of obesity is spotty and doesn't follow geographical or developmental patters except that it started all around the world at the same time. Several obesity-causing viruses have been identified, and one virus called AD-36 is actually more prevalent in obese people than lean people.

- **People with metabolic syndrome typically have abnormal fat distribution.** At any given BMI, people with metabolic syndrome have more intraabdominal fat and a decrease in subcutaneous fat. They also have an increase in muscle fat as well as intrahepatic fat. All patients with metabolic derangements should be considered prediabetic and on the way to developing coronary heart disease (CHD). Nearly all patients with metabolic derangements will eventually develop the "full constellation" of metabolic diseases. Early intervention in the form of multiple drugs and lifestyle is critical. The best treatment, of course, is to treat the underlying cause of the problems – obesity.

- **Insulin resistance, hypertension, obesity, and dyslipidemia are all closely related.** Insulin resistance increases free fatty acids. This in turn affects LDL cholesterol, which affects many other things. Metabolic syndrome leads to elevated risk of cardiovascular mortality. The lower a patient's insulin levels, the better off the patient is with regards to numerous risks. Insulin levels aren't routinely checked, which is a shame. You guessed it – hassle factor is a little high.

- **Speaking about the future of obesity therapy, Dr. John Morton believes combination drug therapy will become more important.** Echoing the conclusion of other speakers, he explained that it is unlikely that we will have a single "magic bullet" cure for obesity any time soon. He likened obesity to HIV, which currently is treated quite effectively by a drug "cocktail." Right now, surgery is the most effective treatment for obesity. Some consider bariatric surgery to be primitive; however surgery has been the first line therapy for many other chronic diseases such as cancer and TB, before more selective drugs were introduced. Despite the enormous cultural differences between device and drug companies, drugs and devices should work together to produce a new class of drug/device combination obesity therapies. Dr. Morton believes that minimally invasive devices can be used to administer drugs, especially gut hormones, most effectively. Drugs and devices have already started to merge, and the FDA actually started a new division to regulate these drug/device combinations (an example of a drug/device merging is Pfizer's inhaled insulin, Exubera). Drug/device combinations may become increasingly important in the treatment of obesity.

- **Current obesity drugs cost about $80-130 per month, and consequently many patients cannot afford them.** A study of persistence rates of sibutramine (Meridia, Abbott) and orlistat (Xenical, Roche) in Canada found that more than half of all patients discontinue use after the first prescription, and almost all patients discontinue within two years. This is a much higher attrition rate than other drugs with similar side effects, suggesting that patients have unreasonable weight goals and they quickly become discouraged.

- **All approved obesity drugs have serious side effects.** Orlistat often causes GI adverse events, including fecal incontinence. Sibutramine elevates blood pressure. Rimonabant probably has the most concerning adverse events – psychiatric disorders in 3% of patients, nausea, dizziness, insomnia, and diarrhea. An FDA exploratory meta-analysis found that odds of suicidality increase 1.9-fold with rimonabant. Sanofi-Aventis has pulled its US application for rimonabant, and if it does eventually become approved in the US, it should not be used in patients who suffer from depression.
- **In the final day of the meeting, attendees were invited to watch two live bariatric surgeries from a satellite viewing area.** The attendees watched Dr. Schauer perform gastric bypass surgery and Dr. Bipand Chand perform lap band surgery. Both patients were female and morbidly obese; one patient had several comorbidities, including diabetes, hypertension, depression, and nonalcoholic fatty liver disease. The procedures were exhibited with the intention of "demystifying bariatric surgery," and attendees were so captivated by the demonstration that the session was extended to an hour (about twice the time allocated). The surgery offered attendees a view of the inside of a morbidly obese person, and the audience was shocked by how much visceral fat both patients had. Large masses of visceral fat were stuck between the various organs, and Dr. Schauer and Dr. Chand both explained that the visceral fat made it much harder to perform the surgery. Both doctors had to cut out some visceral fat in order to clear space to perform the bariatric surgery. Patients are asked to go on an intensive diet in the weeks before bariatric surgery is performed in order to make the surgery easier to perform. The quality of the camera feed was impressive. Dr. Schauer explained that it is possible to see much more with a laparoscopic camera than by opening a patient up. The procedure was surprisingly crude - not the precise science some attendees had expected. For example, lengths of incisions and locations were all approximated rather than measured, and during the gastric bypass surgery, the organs were restructured and held together using large staples. At the same time, it was amazing how little blood there was. Dr. Schauer explained that patients generally lose very little blood during bariatric surgery, and oftentimes, no suction is needed during the procedure to remove blood.

—by Mark Yarchoan

8. Conference Report: TCOYD

September 15 • Santa Clara, CA • www.tcoyd.org

The Taking Control of Your Diabetes (TCOYD) Conference was held on September 15th 2007, in Santa Clara, CA. from Hawaii to Minneapolis, Dr. Edelman and his impressive, devoted team hold about a dozen TCOYD meetings every year – the biggest one in San Diego (on December 8 this year). The Santa Clara meeting was labeled by diabetes veterans as providing "reestablished focus in a positive and affirming way" while neophytes said they "learned more today than (they) ever knew was available". About 1,000 people attended and most break-out sessions were filled to capacity and overflowing.

- **Dr. Edelman stressed the importance of learning how to take appropriate actions based on blood glucose data.** In his opening remarks, he asserted that the future of diabetes treatment was "here and now" and called for all patients to work towards an A1cof 7% or lower. Importantly, he discussed the importance of correlating A1c values to average blood glucose readings.
- **He lamented the statistic that 92% of Europeans were using insulin pens compared to only 12% in the U.S. saying "if you are not using a pen, you are in the dark ages".** Sadly we also realized this while attending the European Association for the Study of Diabetes (EASD)

conference in September 2007. We think the main problem is coverage here in the US – whereas many payors say they cover it, they put the co-pays very high on pens compared to syringes.

- **Still on devices, Dr. Edelman characterized continuous glucose monitoring as biggest advance in diabetes therapy since the discovery of insulin**. It will provide, he said, an important step towards the artificial pancreas cure for diabetes. Stem cell research/gene therapy, however, could also provide a cure eventually.
- **Regarding drugs, Dr. Edelman commented that every drug has side effects adding that Avandia was an "excellent" drug despite recent issues**. He advised patients to to find out if the were at risk for heart failure – a logical move, given the FDA black box warning on the drug. See our coverage on Avandia from issue 5 of diaTribe at http://www.diatribe.us/issues/5/conference-pearls.php. He pointed out that diabetes was a poly-pharma condition requiring therapies from glucophage to Viagra and thus, it behooved patients to make a conscious effort engage their healthcare providers in helping them understand as much about their disease and how it affects the body as possible.
- **Dr. Edelman ended his presentation with a wonderful quote:** "If you cannot find time for exercise, you will have to find time for disease." He recommended yearly dilated eye exams (retinopathy) , cholesterol panels (LDL, HDL and triglycerides) and regular visits to the dentist (tooth and gum disease).
- **Dr. Polonsky's presentation was aptly titled "Psychological Secrets for Effective Self-Management"** resounded well with the conference attendees. The bottom-line message was that diabetes is tough and it is not inhuman to make mistakes – patients must be given a break.
- **Dr. Polonsky likened diabetes management to a job that involved a lot of work, with minimal vacation time and poor compensation**. He emphasized the fact that diabetes was not a death sentence and corrected the notion that diabetes is the leading cause of blindness, amputation and kidney failure. He pointing out that it is poorly controlled diabetes that causes these complications. "Well controlled diabetes is the leading cause of nothing." He quoted Sir William Osler who said, "The easiest way to live well is to develop a chronic disease and take good care of yourself." In Joslin's 50-year Medalist Study of groups of people who were diagnosed with diabetes 50-60, 60-69 or >70 years ago, researchers suggest that individuals with such long duration of type 1 diabetes may be protected from, or show slower progression to diabetic retinopathy. The study showed that about 50% of the 50-60 years diabetic duration had retinopathy – 44% and 27% respectively for the 60-69 and >70 years of diabetes groups. Almost 50% of all groups had no significant microvascular complications. These statistics strongly support the idea that a diabetes diagnosis is not a prediction of inevitable severe complications.

—by Kaku Armah and Kelly Close

9. In the news: Sleep Apnea and Diabetes

A study published in the journal Endocrine Practice found that there is a strong link between obstructive sleep apnea (OSA) and type 2 diabetes. Of the nearly 300 adult type 2 diabetes patients surveyed by the researchers, more than a third of the patients also suffered from OSA. In light of the high incidence of undiagnosed OSA, the high correlation between these conditions suggests that type 2 diabetes patients should be screened for OSA.

- **Obstructive sleep apnea (OSA) is a sleep disorder in which a person has difficulty breathing during sleep due to a collapsed airway.** OSA causes sleep disruption and is associated with a number of other conditions including hypertension, obesity, cardiovascular disease, and insulin resistance. According to the National Sleep Foundation, up to 90 percent of the 18 million Americans who suffer from OSA have not been diagnosed.
- **OSA and type 2 diabetes share similar risk factors, particularly obesity.** Previous studies have indicated that OSA may be pathophysiologically related to insulin resistance and may aggravate other aspects of type 2 diabetes. Further indicating a relationship between OSA and type 2 diabetes, a previous study published in the *Archives of Internal Medicine* entitled "Type 2 Diabetes, Glycemic Control, and Continuous Positive Airway Pressure in Obstructive Sleep Apnea" found that treatment of OSA with continuous positive airway pressure significantly improved interstitial glucose levels and A1c levels.
- **Due to the association between OSA and type 2 diabetes, researchers from UC San Diego assessed the prevalence of OSA in a population of adults with type 2 diabetes.** Of the 279 subjects who completed the study, the overall OSA prevalence rate was 36%. The prevalence rate was much higher for males than females (49% and 21% respectively). Given the remarkably high correlation between type 2 diabetes and OSA, the researchers conclude that screening for OSA should be strongly considered for patients with type 2 diabetes.

—by Mark Yarchoan

10. In the news II: Donation for Diabetes Prevention in New York City

In the U.S., getting insurers to cover diabetes prevention measures such as a visit to a nutritionist can be challenging. A shift in reimbursement policies will be necessary before centers can devote adequate attention to preventative care without losing money. In the short run, diabetes centers must rely on charity donations to fund preventative care measures. With that said, we were heartened to learn about the new Gerald J. Friedman Diabetes Institute at Beth Israel Medical Center in New York City, which is dedicated to providing diabetes education, care, and research of the highest quality in a brand-new facility on the Beth Israel campus. With outreach efforts that span both the city and nation, the Friedman Institute is set to improve the health and quality of life of possibly millions of people living with diabetes. The Friedman Center benefits from a $6 million grant from the Gerald J. and Dorothy R. Friedman New York Foundation for Medical Research.

The credo of the Institute is the acronym "C.A.R.E.," with every program at the center falling under one of the categories "Care," "Awareness," "Research," or "Education." Care includes everything from on site blood glucose monitoring to exercise classes and insulin pump training – the latter is sorely needed as many programs around the country are backed up. The awareness programs are planned towards larger public outreach and the Research programs will be both clinical and basic. Education programs will not only be targeted towards populations at high risk for diabetes but also underserved groups such as the deaf and those living with mental illness. There will also be a freely accessible educational website, which we will report on when we learn more. The new center is expected to receive 9,000 visits or more within the first year of operation, and will probably lose about $15 per patient because of its focus on prevention through the widespread use of diabetes educators and nutritionists. Whew.

The New York City Department of Health and Mental Hygiene reported in July 2007 that there are 500,000 adults living with diabetes in New York City - this is higher on average than most US urban centers. The Friedman Institute appears to understand that diabetes is not a problem of just 500,000 New Yorkers but a major public health crisis that requires much larger community involvement. We at

Close Concerns will be delighted to see the official opening of the Friedman Institute on World Diabetes Day, November 14th –this is a real stride. Thank you so much to the Friedmans for their generosity of time, resources, and spirit.

—by Mark Yarchoan and Kelly Close

11. Conference Preview: NAASO

October 20-24, 2007 • New Orleans, Louisiana • www.naaso.org/annualmeeting07

NAASO takes place in New Orleans, through October 24. This year's sessions will be presented in five thematic tracks - cell and molecular biology; integrative biology; clinical studies; population studies; and for the first time, clinical/professional practice.

Saturday, October 20

The first day of NAASO will not be dry. At 1 pm, there is a session on new developments in obesity pharmacotherapy, chaired by Dr. Steven R. Smith. This session will include a discussion of combination drug treatments for obesity – something we heard a lot about at the 2007 Cleveland Clinic Obesity Summit – as well as a lecture on neurohormonal treatments to obesity (particularly amylin, leptin, and PYY). The NAASO opening session will take place in the evening, and will feature a lecture by Dr. Andrew Prentice entitled, "The Evolutionary Context of the Modern Obesity Epidemic." A reception will follow.

Sunday, October 21

morning will begin with two key lectures: "Genetic Dissection of Neuronal Pathways Controlling Energy Homeostasis," given by Dr. Joel Elmquist, and "The Individualistic Approach to Obesity Care; Chair: Richard Atkinson," given by Dr. Robert Kushner. Oral abstracts will follow, split into the five previously mentioned thematic tracks.

In the afternoon, one session not to miss is on the role of sirtuins in mediating obesity and the complications of obesity. Sirtuins are a set of genes that may be involved in regulating the effects of aging, and the company Sirtris hopes to capitalize on sirtuins with their phase 2 drug, SRT-501. Sirtuins have come into focus very recently, and this session will provide some important background information and highlight some of the very exciting results that have been published on this class of genes. Simultaneously, in the "integrative biology" track there will be a lecture on gut hormones and obesity, yet another area of great excitement at the current time. As with much of the conference, it will be difficult to decide which session to attend. Later in the afternoon, there is a session about strategies for weight loss maintenance. This is an area where many patients struggle, and we're looking forward to learning about what works, and what doesn't work. We're hoping that there will be a discussion about the use of leptin and other hormones to keep weight off.

In the evening, a symposium sponsored by Amylin will cover the role of neurohormones in weight regulation, and will review the basic physiology of obesity. Interestingly, the session will also evaluate how metabolic hormones affect cardiac function.

Monday, October 22

Prepare for an early wake up to catch either the Allergan or the Sanofi-Aventis corporate symposium. Allergan's symposium will review the various bariatric surgery options for severely obese patients. There will be an additional focus on ways to improve bariatric surgery patient outcomes. The Sanofi-Aventis

symposium will cover the topic of the endocannabinoid system (ECS), the target of rimonabant (approved only in Europe). Although rimonabant is approved in the EU, earlier this year, an FDA Advisory Committee voted unanimously against recommending the approval of rimonabant because of its neurological side effects (most notably, the drug was found to have a strong association with depression and suicide).

Later in the day, a session in the integrative biology track will cover the chicken and the egg question for leptin and obesity (which is the cause, and which is the effect?). In the population studies track, there will be an interesting lecture about novel technologies for measuring physical activity and diet, given by Dr. Audie Atienza. Feedback for patients about their behavior could have significant and positive effects, and we expect to hear about all sorts of ideas, such as cell phones that measure total daily movement.

In the afternoon, the clinical/professional practice track will feature an important lecture about obesity management entitled, "Obesity Management: Lessons from Clinical Practice." This session will likely provide an up-to-date and realistic assessment of the current treatment options for obese patients. Within this session, we are most excited for Dr. Richard Atkinson's lecture about pharmacotherapy. Dr. Atkinson's lecture at the Cleveland Conference Obesity Summit on the topic of pharmacotherapy was incredible, and we expect nothing less of his lecture at NAASO.

Tuesday, October 23

The morning will begin with a corporate symposium from Merck about the endocannabinoid system (ECS) entitled "The Next Generation Approach to Long-Term Management of Obesity: Selective Modulation of the Endocannabinoid System: The Next Generation." The symposium will review the causes of obesity and the role of the ECS in weight management. Merck has a CB1 drug (named taranabant, or MK0364) under development, and the title suggests that Merck is hoping that its candidate is the next generation of CB1 drug after rimonabant.

Later in the program, there will be a session about childhood and adolescent obesity. This is a serious growing problem and we're glad to see a session dedicated to the topic even if the options for dealing with the problem are not ideal. The session will touch upon the government's role in managing childhood obesity, and will specifically discuss improvements that should be made in schools to reduce childhood obesity rates. In the afternoon, the integrative biology and clinical studies tracks will merge for an important lecture on sleep and obesity. The topic was discussed briefly at the Cleveland Clinic Obesity Summit, and many feel that a decrease in average sleep is one of the many causes of the current obesity epidemic. This session should explain at length the connection between sleep and obesity.

Wednesday, October 24

This last half-day of NAASO is full of key lectures. Two of the lectures will focus on infant or childhood obesity, and implications for adulthood – an important topic that did not get much attention at the Cleveland Clinic Obesity Summit. Later in the morning, there will be a session about improving outpatient management chaired by Dr. Kenneth Storch. Within this session, Dr. Louis J. Aronne, who gave an amazing lecture at the Cleveland Clinic Obesity Summit, will be discussing the medical management of the obese patient in a multidisciplinary setting. The session will close with a discussion of reimbursement for obesity treatment, given by Dr. Jarol Boan.

—by Mark Yarchoan and Kelly Close

12. Close Concerns Market Index, Diabetes Comings and Goings, and Random Thoughts

Here's an interesting thing. GSK stock is actually versus a year ago only down 4%. That was way before the whole Avandia debacle. It had been a strong market for many small diabetes companies, since their IPOs, with Insulet, Sirtris, and Orexigen all up double digits since their debuts. Let us know what other companies you'd like to see on this chart!

	12-Oct-07	12-Sep-07		3-Jan-07		12-Oct-06		IPO		Market Cap
GSK	52.22	53.72	-3%	53.81	-3%	54.27	-4%	-	-	146.06B
NVO	115.63	116.20	0%	83.46	39%	76.74	51%	-	-	38.96B
AMLN	47.62	48.58	-2%	36.32	31%	47.45	0%	14	240%	6.29B
MNKD	10.91	9.55	14%	16.16	-32%	20.74	-47%	14	-22%	801.86M
PODD	25.77	20.29	27%	-	-	-	-	15	72%	678.08M
SIRT	17.76	14.37	24%	-	-	-	-	10	78%	509.67M
OREX	17.58	14.34	23%	-	-	-	-	12	47%	473.08M
BIOD	15.92	18.00	-12%	-	-	-	-	15	6%	320.96M
DXCM	10.07	9.55	5%	9.88	2%	11.54	-13%	12	-16%	285.69M
HDIX	9.32	9.07	3%	10.61	-12%	-	-	12	-22%	169.60M

Diabetes Comings and Goings

- Mirasol Panlilio has joined VeraLight as Vice President of Marketing. She was previously at Abbott Diabetes Care and LifeScan.
- Kim Blickenstaff has joined Phluid as CEO. He was previously CEO of Biosite.
- Kirsten Rebrin has joined MicroCHIPS as Vice President of R&D. She was previously at Abbott Diabetes Care and Medtronic.
- Steve Bubrick has joined Insulet as Vice President of Customer Care. He was previously at Abbott Diabetes Care and LifeScan.
- Mary Bauman has joined Amylin as Vice President of New Product Commercialization. She has previously worked at Bayer and Joslin
- Kay Cox has joined Amylin as Vice President of Government Affaris. He was previously at Ameripath.
- Harry Leonard has joined Amylin as Vice President and Chief Intellectual Property Counsel. He was previously at Sanomix.
- Roseanne Burhenne has joined M2 Medical as Vice President of Marketing. She was previously at Cholestech and Metrika.
- Deborah Rupport has joined DexCom as Director of Marketing. She was previously at M2 Medical.
- Abi Basu has joined Seattle Medical as VP of Marketing. He was previously at Medtronic Diabetes and TheraSense.
- Tom Peyser has joined GluMetrics as VP of Clinical Affairs. He was previously at Abbott Diabetes Care.

Please send news for Diabetes Comings and Goings to us at mark.yarchoan@closeconcerns.com. Thank you!

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. 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 clients of Close Concerns include Abbott, Amylin, Bayer, Becton Dickinson, Insulet, Johnson & Johnson, Medtronic, Novo Nordisk, Roche and a number of private firms.